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Reactions of Dicarbonyl Compounds with Dimethyl β-Ketoglutarate. 4. Formation of 1:1 Adducts[1a]

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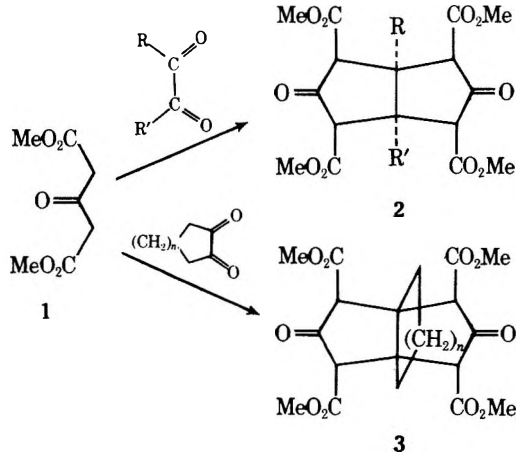
Many aliphatic 1,2-dicarbonyl compounds react at room temperature with dimethyl β-ketoglutarate (1) in aqueous or dilute methanolic solution to furnish 1:2 adducts of type **2**; cyclic 1,2-diketones similarly give the propellane derivatives of type **3**. In contrast, camphorquinone (**14**) and aromatic 1,2-diketones such as benzil (**18**) and phenanthrenequinone (**19**) yield only 1:1 adducts with **1**. The 1,2-glycol (**17**) resulting from simple aldolization followed by hemiketal formation, was isolated in the case of **14**, whereas 4-hydroxycyclopent-2-enones **20** and **23** were obtained in the case of the two fully aromatic dicarbonyl compounds. Ninhydrin gave only the 1:2 adduct (**31**) when reacted with **1**, while phenylglyoxal (**27**) yielded both a stable 1:2 adduct of type **2** and a very unstable 1:1 adduct (not isolated). The significance of these findings for the interpretation of the course of such reactions is discussed.

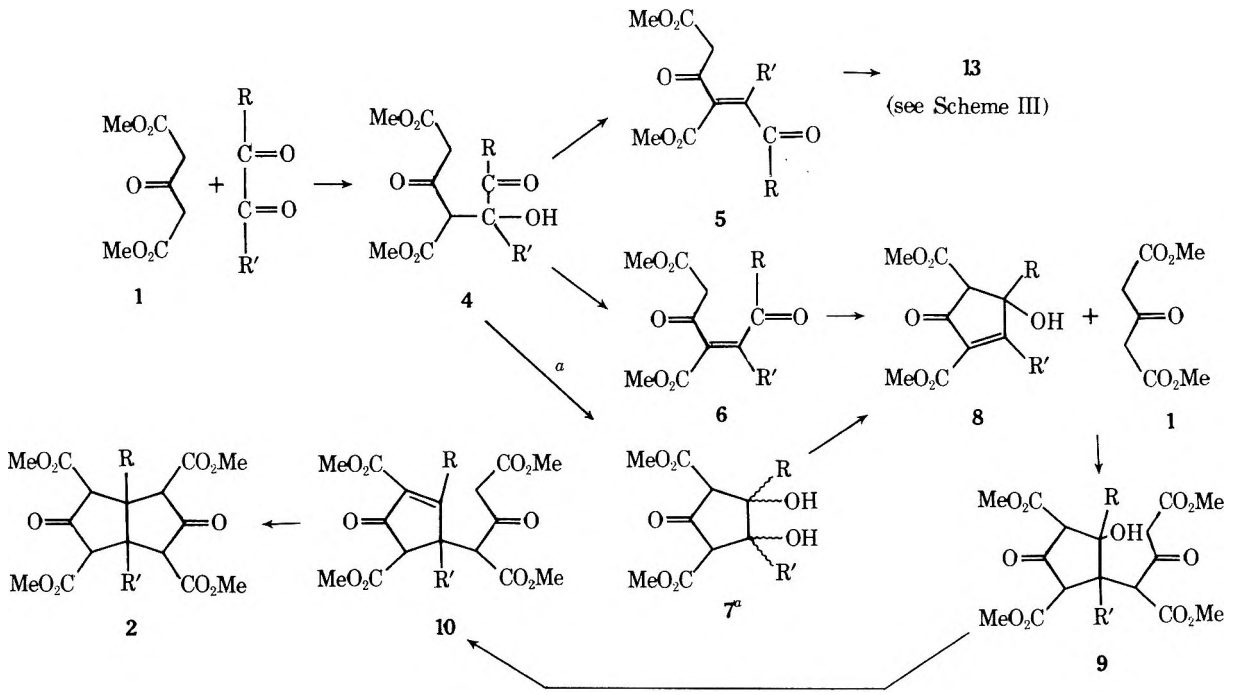
Dimethyl β-ketoglutarate (**1**) has been found[3] to react with aliphatic 1,2-dicarbonyl compounds in aqueous or aqueous/methanolic[4] solution at neutral or slightly acidic pH to provide β-keto esters (**2**)[5] derived from bicyclo[3.3.0]octane-3,7-dione. Alicyclic 1,2-diones in similar fashion yield esters (**3**) of [*n*.3.3]propellanediones.[3,4] From the reaction of **1** with glyoxal, more complex products (see below) have been isolated[3,6] in addition to **2**, R = R′ = H.



It seemed probable a priori that the 1:2 adducts **2** and **3** would be formed stepwise by reaction of one molecule each of **1** and the 1,2-dicarbonyl compound to yield a primary 1:1 adduct, capable of adding a second molecule of **1** to furnish the β-keto esters **2** and **3** actually isolated. A plausible sequence, shown in Scheme I, can be formulated, which is consistent with all information available to date. Simple aldolization of **1** and the dicarbonyl compound in equimolar amounts would generate the adducts **4**, **5**, or **6**. Of these, **4** and **6** could easily be converted to the 4-hydroxycyclopent-2-enone **8**. Michael addition of a second molecule of **1** to **8** would furnish the intermediate **9** which, as a β-hydroxy ketone, would readily eliminate water to form the α,β-unsaturated ketone **10**. A second Michael addition (intramolecular) would then lead to the product **2**.[7] This sequence also can be readily extended to provide an explanation for the origin of the more complex β-keto esters **11**, **12**, and **13** which are obtained from glyoxal[3,6] (see Scheme II). The endo[6a] and exo[6b] isomers **11** and **12** can be assumed to arise through reaction of **2** (R = R′ = H) with intermediate **8** in a sequence of reactions which is perfectly analogous to formation of **2** itself from **8** and **1** via intermediates **9** and **10**. In addition, the hexacarbomethoxy derivative **13**[6c] could similarly originate from **2** by reaction with the α,β-unsaturated aldehyde **5** (R = R′ = H), the *E* isomer of **6**. The formation of the entire series of compounds can thus be explained in a uniform and consistent manner through a sequence of aldolizations and Michael additions.

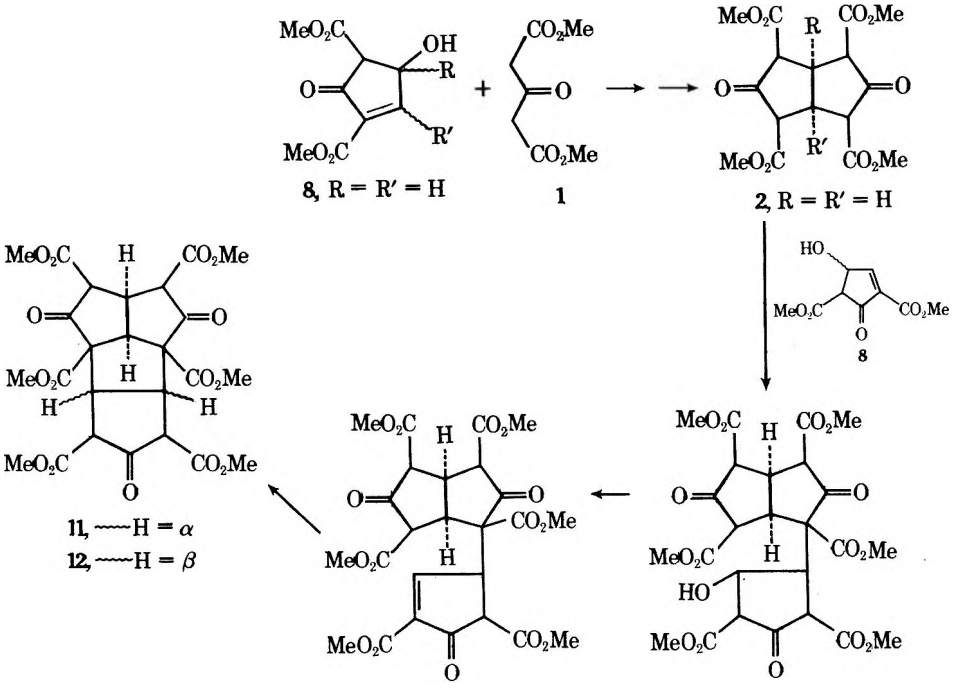
Since all the reactions outlined in Schemes I, II, and III are undoubtedly reversible, there would seem to be little hope for direct experimental verification. However, use of suitable 1,2-dicarbonyl compounds has now permitted the actual isolation of a 1:1 adduct (**17**, see below) derived from the monoaldolization product **4**, and of several 4-hydroxycyclopent-2-enones of type **8**. Several substances related to this latter type[8,9] have been isolated by Japp and his associates long before our work (see below). While none of these compounds can qualify as an actual intermediate in the formation

Scheme I



[a] The sequence 4 → 7 → 8 is plausible but at present highly conjectural; we have so far not encountered any diol of type 7.

Scheme II

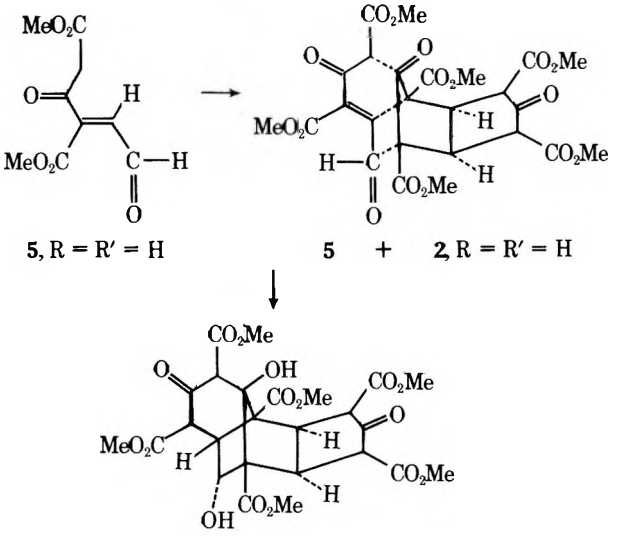


of substances of type **2, 3, 11, 12,** or **13,** their isolation lends definite support to our interpretation of the course of the reactions illustrated in Schemes I–III.

Initial attempts to demonstrate the intermediate formation of 1:1 adducts of type **4, 5, 6,** or **8** in reactions of **1** with aliphatic or alicyclic 1,2-diketones were uniformly unsuccessful. For instance, when the reaction was carried out with a tenfold excess of the 1,2-dicarbonyl compound, cyclododecane-1,2-dione, in a citrate/phosphate buffer (pH 6.8) in the presence of methanol, the only product isolated or observed by TLC was the 1:2 adduct (**3,** n = 10).[4] Moreover, reaction of cyclododecane-1,2-dione (tenfold excess) and **1** with sodium methoxide in methanol similarly provided only the 1:2 adduct (**3,** n = 10).[4]

It seemed likely, however, that a 1,2-dicarbonyl compound with bulky groups adjacent to the keto functions might react to give a 1:1 intermediate unable, for steric reasons, to add a second molecule of **1** (step 8 → **9** in Scheme I). Camphorquinone (**14**) appeared to be a suitable α-diketone for this purpose. Reaction of **14** at room temperature with 1 equiv of **1** in citrate/phosphate buffer (pH 6.8)[10] for 1 week furnished a new compound which was obtained in pure, crystalline form by column chromatography in 20% yield, mp 138–140 °C. The empirical formula $C_{17}H_{24}O_7$, established by microanalysis and mass spectrometry (mol wt calcd and found 340), showed that the substance was a simple 1:1 adduct of **14** ($C_{10}C_{14}O_2$) and **1** ($C_7H_{10}O_5$). On heating with sodium methoxide in methanol, the adduct reverted to **14** and **1,** indicating that no rear-

Scheme III



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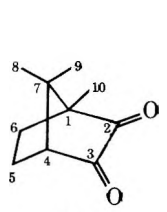
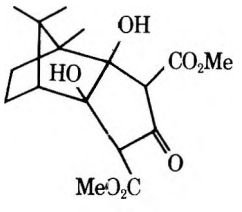
rangement had taken place during the formation of the C_{17} compound. These data are compatible with an aldol-type structure analogous to intermediates 4 or 7 in Scheme I, i.e., with formulas such as **15, 16,** or **17.**



14



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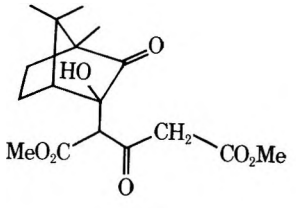

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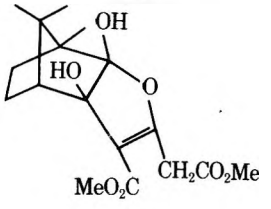


17

Spectroscopic findings excluded the possibility of structure **15.** The symmetry of such a 1,2-glycol, formed through aldolization of *both* carbonyls of **14,** would cause hydroxyl signals to appear at very similar chemical shifts in the NMR spectrum. In fact, the 220-MHz spectrum of the adduct exhibited two signals (singlets, 1 H each) but at very *different* locations (δ 3.35 and 4.48), indicative of a nonsymmetrical structure. The ^{13}C NMR spectrum (see below) is likewise quite incompatible with **15,** as are the ir and uv spectra.

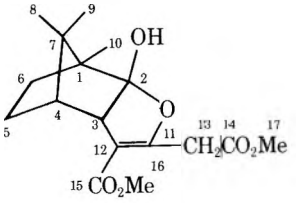
However, it would also be difficult to reconcile the various spectroscopic data with formula **16.** While the presence of *two* hydroxyl signals in the NMR spectrum could be rationalized as being due to enolization of the β-keto ester grouping,[5] the occurrence of a pair of doublets (1 H each) with J = 17.5 Hz, centered at δ 3.56 and 3.92, points clearly to a methylene group with nonequivalent protons, subject to geminal coupling.[11] These findings, and other spectroscopic observations to be discussed, however, can be readily accommodated by formula **17,** the hemiketal of the enol form of **16.** Here, the adjacent carbomethoxy group would interfere somewhat with the rotation of the side chain methylene group; this fact, together with influences from the endo protons of the methylenes of the norbornane system, would create the observed nonequivalence.

Formula **17** also finds strong support from the ir spectrum, which shows hydroxyl stretching bands at 3480 and 3410 cm^{-1}, a band at 1740 cm^{-1} (nonconjugated ester group), and, significantly, bands at 1695 and 1630 cm^{-1}. These latter two absorptions agree well with those reported for other compounds containing the chromophore $MeO_2C-C=C-O$; the iridoids genipin (ν 1695, 1630 cm^{-1})[12] and daphylloside (ν 1700, 1635 cm^{-1})[12] and the indole alkaloids mayumbine[13a] and serpentinine[13b] are pertinent examples.

The uv of **17** (λ_{max} 250.8 nm) is likewise compatible with the spectra of iridoids carrying a carbomethoxy group at C-4 (cf. inter alia, genipin and verbenalin, 240 nm, loganin, 237 nm, and daphylloside, 235 nm).[14] The plausible assumption can be made that the difference in size of the unsaturated heterocyclic ring, six membered in the iridoids, five membered in **17,** is responsible for the bathochromic shift of ~10 nm in the latter case.

Additional support for structure **17** can be obtained from examination of the ^{13}C NMR spectrum (see Table I). Signals from all 17 carbon atoms can be identified, but the spectrum definitely does not contain any resonance ascribable to a free carbonyl in a five-membered ring; this fact eliminates structures **15** and **16.** In contrast, the assignments of the observed signals are entirely compatible with formula **17.** The spectrum

Table I. ^{13}C NMR Chemical Shifts of 1:1 Adduct 17



17

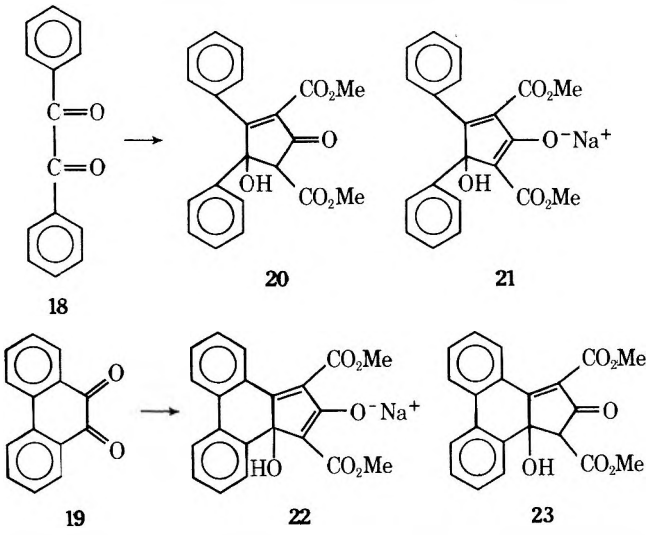
ppm[a]	Sford[b]	Carbon atom		ppm[a]	Sford[b]	Carbon atom	
168.3	s	14	a[c]	52.3	q	16	d[c]
165.2	s	15	a	51.3		17	d
162.9	s	11	a	49.7	s	1	c
117.3	s	12	b	34.6	t	13	
109.2	s	2	b	29.6	t	5	e
86.9	s	3		24.9	t	6	e
54.7	d	4		22.1	q	9	f
53.1	s	7	c	21.5	q	8	f
				9.8	q	10	f

[a] Measured from $(CH_3)_4Si$ standard. [b] Multiplicites observed on angle frequency off-resonance decoupling. [c] Assignments within lettered groups may be interchanged.

contains signals from two fully substituted vinylic carbon atoms [C-11, 162.852 ppm; C-12, 117.259 ppm (see Table I)], one of which is deshielded due to the bond to an oxygen atom. Furthermore, the resonances from two fully substituted carbon atoms are located downfield; one of these is bound to hydroxyl (C-3), while the other is attached to two oxygen atoms (C-2). The formulation of **17** with the stereochemistry shown is based on analogous reactions of **14** with lithium aluminum hydride[15] and Grignard reagents.[16] The assignment[17] was further corroborated by the lanthanide-induced shifts of the "carbon-bound" methyl functions of **17**, which are similar to ones described in analogous systems recently reported by Burgstahler.[18]

As mentioned previously, reaction of cyclododecane-1,2-dione with **1** in methanolic sodium methoxide gave the propellanedione (**3**, $n = 10$)[4] as the only isolable product, although traces of another compound were observed by TLC. However, reaction of **14** with **1** under the same conditions yielded exclusively the 1:1 adduct **17**.

In contrast to the behavior of the aliphatic and alicyclic 1,2-dicarbonyl compounds, fully aromatic α-diketones (Ar–CO–CO–Ar) such as benzil (**18**) and phenanthrenequinone

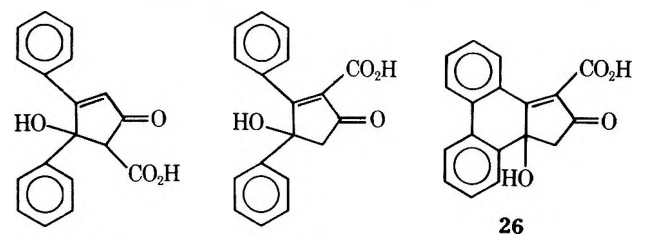


18 20 21

19 22 23

(**19**) failed to react with **1** in aqueous methanol (buffer added, either pH 6.8 or 8.4). In more strongly alkaline media, 1:1 adducts **20** and **23** of the type **8** were readily obtained.

Some related 4-hydroxycyclopent-2-enones have been prepared in the 1890's during the classical studies of Japp and co-workers. Japp and Lander, e.g., reported that they obtained the dicarboxylic acid corresponding to **20** by reaction of benzil (**18**) with free β-ketoglutaric acid in alcoholic KOH.[8] In addition, the acid[8] **24**[8,19] was reported by Japp and co-workers



24 25 26

to result from loss of CO_2 from the diacid of **20**; however, this structure has recently been revised to **25**.[1] In similar experiments, Japp and Klingemann[20] reported that the reaction of **19** and acetoacetic acid yielded the 1:1 adduct **26**; this was later reinvestigated by Cope and MacDowell and the structure of **26** was confirmed.[21]

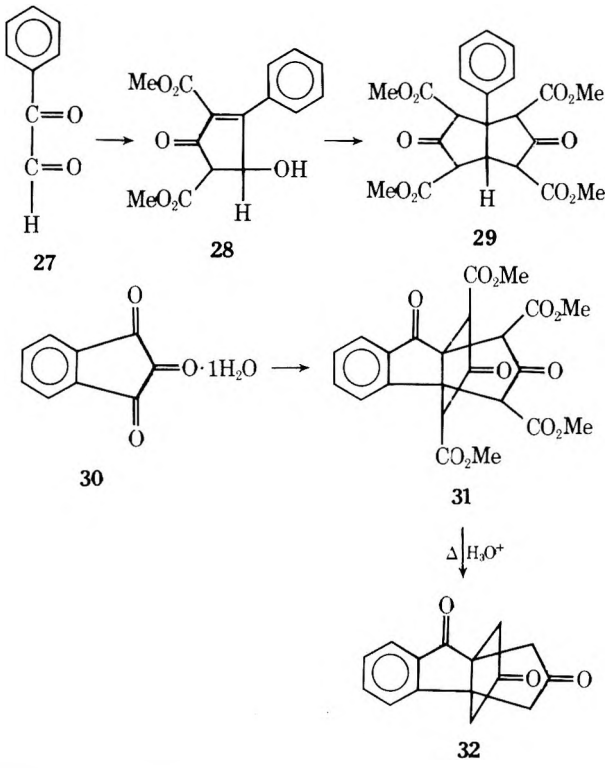
We had previously obtained the 4-hydroxycyclopent-2-enone **20** by reaction of **18** and **1** in alcoholic KOH[4] under conditions similar to those described in the literature.[9a-c] When this same procedure was employed in the reaction of **19** and **1**, a compound (M^+ at m/e 364) corresponding to the alcohol **23** was isolated. However, it was contaminated with impurities of high molecular weight and was not obtained completely pure. In the course of the investigation of the reactions of **18** and **1**, we had carried out this condensation in methanolic sodium methoxide, from which yellow crystals precipitated in 50% yield. The same compound (mp 227–235 °C dec) was obtained by stirring the cyclopent-2-enone **20** with sodium methoxide in either methanol or ethanol. This new compound is therefore **21**, the sodium enolate of **20**. Spectroscopic data were in agreement with this assignment; treatment of the salt **21** with cold, dilute hydrochloric acid (0.1 N) converted it back to **20**. Reaction of **20** with potassium methylate in methanol at room temperature did not produce an analogous enolate; however, heating the solution and subsequent removal of most of the solvent produced a yellow, crystalline potassium salt in amounts too small for study. While our work was in progress a brief mention of a similar sodium compound generated by Harris and co-workers appeared and confirmed our assignment.[22]

Alkali enolates, often colored, have been obtained repeatedly from cyclic β-keto esters related to **2**; cf. e.g., the red mono- and yellow disodium enolates of a derivative of **2** (R = R′ = H) which were discovered by Vossen[23] and studied more recently by Yates et al.[24] Because the enolate salts crystallize rapidly from methanol, it was felt that reaction of **19** with **1** in methanolic sodium methoxide would generate the methanol-insoluble salt **22**, so that further reaction would be stopped. Production of high molecular weight impurities found in ethanolic potassium hydroxide would thus be held to a minimum. This was found to be the case. The sodium enolate **22** precipitated in 68% yield as red-orange crystals (mp 263–270 °C) when **19** and **1** were stirred for 4 h in methanolic sodium methoxide. Acidification with cold hydrochloric acid (0.1 N) furnished the pure 4-hydroxycyclopent-2-enone **23** as a yellow powder (mp 175 °C dec).

The tendency of **18** and **19** to provide 1:1 adducts with **1** and related compounds (e.g., the corresponding free acid)[1] appears to be quite typical of fully aromatic (Ar–CO–CO–Ar) α-dicarbonyl compounds, although strongly alkaline conditions seem to be required. This behavior contrasts with that of aliphatic and alicyclic 1,2-diones which furnish 1:2 adducts in weakly acidic,[3,4,6] neutral,[6] weakly alkaline, or strongly alkaline media.[4,25] The formation of the 1:1 adduct **17** from **14** is the exception rather than the rule and is undoubtedly due to steric factors.

Surprisingly, compounds (Ar–CO–CO–R) in which the 1,2-dicarbonyl system is bound to only one aromatic ring seem not to occupy an intermediate position but to resemble their aliphatic or alicyclic congeners more than **18** or **19**. Two such compounds have been studied to date: phenylglyoxal (**27**) and ninhydrin (**30**).

Reaction of **27** with **1** in bicarbonate buffer (pH 8.4) at room temperature for 60 h produced a yellow solution, which furnished a copious precipitate when it was acidified to pH 1 with sulfuric acid (6 M). Recrystallization from methanol gave the pure 1:2 adduct [**29** (**2**, R = C_6H_5; R′ = H)], mp 147–148 °C. The yield of recrystallized product was 65%. The same reaction was carried out in citrate/phosphate buffer (pH 6.8) for 3 days and furnished an oil which was extracted into chloroform. Column chromatography on silica gel gave a 27% yield of **29**; however, both TLC and mass spectrometry revealed the presence of another, more polar substance in the crude oil. The molecular weight (mass spectrometry) of this product, m/e 290, is that expected for the 1:1 adduct **28**, and the fragment corresponding to the loss of methanol ($M^+ - 32$), typical of these β-keto esters,[4] was present. Unfortunately, this com-



pound proved to be very elusive; all attempts at isolation so far yielded only **29** or material of higher molecular weight. The lability of **28** can be understood by assuming reversion to **27** and **1** by retroaldolization, or loss of the second molecule of water to give the unstable cyclopentadienone. In the first case, the compounds formed would recombine to give **29,** while dimerization of the intermediate cyclopentadienone would lead to products of high molecular weight.

In the case of ninhydrin (**30**), only the 1:2 adduct, the propellane derivative (**31,** mp 95–98 °C) has been observed; it was converted readily into the trione (**32,** mp 172.5–174 °C) by acid hydrolysis.[26]

It would seem plausible that the fully aromatic α-diketones do not add a second molecule of glutarate **1,** for the enone system is stabilized by overlap with the π bonds of the phenyl ring; however, this effect would also be expected to occur in the monoaromatic cases (Ar–CO–CO–R), but apparently does not. Work is in progress at present to explain the difference in reactivity of these closely related systems.

Experimental Section

Microanalyses were performed on an F & M Scientific Corp. Carbon, Hydrogen, Nitrogen Analyzer Model 185; some analyses were also performed at the National Institutes of Health, Bethesda, Md. Melting points were taken on a Thomas-Hoover melting point apparatus; they are uncorrected. Nuclear magnetic resonance spectra were recorded on Varian T-60 and 220 MHz spectrometers. Infrared spectra were taken on a Beckman Acculab-1 instrument. The ultraviolet spectra were recorded on a Cary 17 spectrophotometer, and mass spectra on Finnigan 1015 and AEI MS-902 instruments.

Analytical TLC plates used were E. Merck Brinkmann uv active silica gel on plastic. The citrate/phosphate buffer (pH 6.8) was prepared by dissolving disodium hydrogen phosphate heptahydrate (11.67 g) and citric acid (3.68 g) in water (900.00 ml). The bicarbonate buffer (pH 8.4) was prepared by dissolving $NaHCO_3$ (1.40 g) in water (100.00 ml). Camphorquinone, benzil, phenanthrenequinone, phenylglyoxal, ninhydrin, and dimethyl β-ketoglutarate were purchased from Aldrich Chemical Co.

Reaction of Camphorquinone (14) with Dimethyl β-Ketoglutarate (1) to Produce the 1:1 Adduct (17). Camphorquinone (**14,** 5 g, 0.030 mol) was dissolved in methanol (70 ml). Citrate/phosphate buffer (pH 6.8) was added until the solution became turbid, whereupon small amounts of methanol were added to clarify the solution. To this solution, dimethyl β-ketoglutarate (**1,** 10.5 g, 0.060 mol) was added and the liquid stirred at room temperature for 1 week. It was next extracted with ether (5 × 100 ml); and the combined extracts were washed with water and dried (Na_2SO_4). Removal of solvent at reduced pressure afforded 8.1 g of a solid shown by TLC to consist of **17** and starting materials. The adduct **17** was isolated by column chromatography (silica gel) using petroleum ether (bp 30–60 °C)/benzene as eluent. Recrystallization from methanol furnished white needles (2.1 g, 20%) of mp 138–140 °C: uv λ_{max} (MeOH) 250.8 nm; R_f 0.19 (10% ethyl acetate in benzene); ir (KBr) 3480 and 3410 (OH absorptions), 1740 (saturated ester), 1687 (conjugated ester), and 1630 cm^{-1} (>C=C<); NMR ($CDCl_3$) δ 0.94 (3 H, s), 1.0 (3 H, s), 1.28 (3 H, s), 1.30–1.70 (4 H, broad multiplet), 2.1 (1 H, d, J = 4 Hz), 3.35 (1 H, s, OH) 3.56 (1 H, d, J = 17.5 Hz), 3.71 and 3.73 (6 H, 2 OCH_3 singlets), 3.92 (1 H, d, J = 17.5 Hz), and 4.48 (1 H, s, OH). The singlets at δ 3.35 and 4.48 disappeared on treatment with D_2O. Mass spectrum (electron impact): m/e at 340 (5.5), 322 (5.5 $M^+ - 18$), 310 (30.3, $M^+ - 30$), 308 (10, $M^+ - 32$), 291 (36), 280 (100), 275 (17.2), 252 (38), 249 (56).

Anal. Calcd for $C_{17}H_{24}O_7$: C, 60.00; H, 7.10. Found: C, 60.14; H, 7.18.

Retroaldolization of 17 by Treatment with Base. The hemiketal (1 g) was dissolved in methanol (25 ml) and sodium methoxide (100 mg) was added. The solution was heated gently for 0.5 h. TLC showed the presence of two compounds with R_f values identical with those of **14** and **1.** These two compounds were separated by preparative TLC (silica gel) and were identified by comparison of their mass spectra with those of authentic samples.

Reaction of Benzil (18) and Dimethyl β-Ketoglutarate (1) in Sodium Methoxide and Methanol. Sodium Enolate (21) of Alcohol 20. Benzil (**18,** 2.1 g, 0.010 mol) was dissolved in methanol (125 ml) and sodium methoxide (1.0 g, 0.020 mol) was added. To the resulting solution, dimethyl β-ketoglutarate (**1,** 1.74 g, 0.0100 mol) was added and the mixture was stirred at room temperature for 24 h. Yellow crystals (**21,** 2.0 g, 50%) were filtered from the solution. They were identical with the product obtained by treating **20** with sodium methoxide in methanol or ethanol: mp 227–235 °C dec; ir (KBr) 3500 (s, OH), 3600–3300 (broad OH), 1695 (C=O), 1655 (C=C), and 1005 cm^{-1} (C–O); NMR (pyridine-d_5) δ 3.7 (6 H, s, 2 OCH_3) and 7.0–8.0 (10 H, broad multiplet). Tests indicated the presence of sodium in the salt.

Treatment of the enolate salt **21** with cold aqueous hydrochloric acid (0.1 N) yielded the 4-hydroxycyclopent-2-enone **20** whose properties were identical with those reported previously by several groups.[4,9]

Reaction of Benzil (18) with Dimethyl β-Ketoglutarate in Potassium Methoxide/Methanol. Reaction of benzil (**18**) with **1** in the same proportions as before but with potassium methoxide (0.02 mol) in place of sodium methoxide yielded no crystals on stirring at room temperature. After heating for several hours, followed by evaporation of most of the solvent, a yellow, crystalline potassium salt of **20** was isolated in very low yield. Acidification of this solid gave the previously characterized alcohol **20.**

Reaction of Phenanthrenequinone (19) with Dimethyl β-Ketoglutarate (1) in Sodium Methoxide and Methanol to Provide the Sodium Enolate (22) of 23. Phenanthrenequinone (**19,** 1.0 g, 0.0048 mol) was suspended in methanol (50 ml). Dimethyl β-ketoglutarate (**1,** 0.84 g, 0.0048 mol) and sodium methoxide (0.52 g, 0.0095 mol) were added to the mixture in that order. The phenanthrenequinone dissolved gradually, and red-orange crystals of **22** (1.3 g, 68%) precipitated from the solution during 4 h. They were filtered off and dried: mp 263–270 °C dec; ir (KBr) 3600–3350 (broad OH peak), 1705 (C=O, intense), 860 (s), 840 (s), and 825 cm^{-1} (s); NMR (Me_2SO-d_6) δ 3.60 (3 H, s, OCH_3), 3.64 (3 H, s, OCH_3), 7.1–8.3 (8 H, aromatic multiplet). Tests for sodium were positive.

The red-orange crystals (**22**) were treated with cold aqueous hydrochloric acid (0.1 N). The red color disappeared and a yellow powder (**23**) precipitated from the solution: mp 175 °C dec; ir (KBr) 3440 (sharp, OH), 1750 (C=O, ester), 1725 (cyclopentenone), 1710 (unsaturated ester), 760 (s), and 732 cm^{-1} (s); NMR (Me_2SO-d_6) δ 3.70 (3 H, s, OCH_3), 3.76 (3 H, s, OCH_3), 4.8 (1 H, s), 6.45 (1 H, s, OH), 7.10–8.30 (8 h, broad multiplet). The peak at δ 6.45 disappeared on treatment with D_2O. Mass spectrum: m/e 364 (80, M^+), 348 (30), 346 (15), 332 (50). 316 (90), 305 (50), 273 (95), 257 (100).

Anal. Calcd for $C_{21}H_{16}O_6$: C, 69.20; H, 4.39. Found: C, 69.21; H, 4.52.

Reaction of Phenanthrenequinone (19) with Dimethyl β-Ketoglutarate (1) and Potassium Hydroxide in Ethanol to Furnish 4-Hydroxycyclopentenone (23). Phenanthrenequinone (**19,** 0.7 g, 0.0033 mol) was placed in ethanol (25 ml) and dimethyl β-ketoglutarate (**1,** 0.64 g 0.0036 mol) was added. To the slurry, potassium hydroxide (0.1 g) was added and the reaction mixture was stirred for

24 h. A yellow solid was filtered from the reaction; its ir spectrum was very similar to that of product **23**. The mass spectrum indicated the presence of the alcohol (M^+, 364); however, other products with mass numbers in the 500–600 region were present. The yellow solid **23** had the same R_f as that of the alcohol **23** obtained by acidification of the red-orange salt **22** above.

Tetramethyl 1-Phenylbicyclo[3.3.0]octane-3,7-dione-2,4,6,8-tetracarboxylate (29). Phenylglyoxal monohydrate (**27**, 2.50 g, 0.0164 mol) was dissolved in aqueous sodium bicarbonate (100 ml, pH 8.4). After the solution was stirred for 2 min, dimethyl β-ketoglutarate (**1**, 5.71 g, 0.0328 mol) was added in one portion, whereupon the solution immediately turned yellow. After stirring for 60 h, the reaction was acidified to pH 1 with aqueous sulfuric acid (6 N); a pink solid precipitated from the solution. This solid was recrystallized from methanol to furnish white crystals of **29** (4.79 g, 65.6%): mp 147–148 °C; ir (KBr) 3015 (C–H, aromatic) and 1740 cm^{-1} (broad ester carbonyl); NMR ($CDCl_3$) δ 3.50–3.80 (14 H, 4 overlapping singlets of unequal intensity), 4.36 (1 H, s), 7.28 (5 H, s, aromatic), 10.02 (1 H, s, enol proton), and 10.82 (1 H, s, enol proton). The signals at δ 10.02 and 10.82 disappeared on treatment with D_2O. Mass spectrum: *m/e* 446 (13, M^+), 414 (57, $M^+ - 32$), 383 (36), 382 [100, $M^+ - (2 \times 32)$], 351 (36), 350 [100, $M^+ - (3 \times 32)$], 323 (46), 322 (29), 318 (26), 292 (46), 282 (24), 276 (38).

Anal. Calcd for $C_{22}H_{22}O_{10}$: C, 59.18; H, 4.97. Found: C, 58.93; H, 4.94.

Preparation of Tetramethyl 1-Phenylbicyclo[3.3.0]octane-3,7-dione-2,4,6,8-tetracarboxylate (29) at pH 6.8. Phenylgloxal monohydrate (**27**, 2.50 g, 0.0164 mol) was dissolved in citrate/phosphate buffer (70 ml, pH 6.8). Dimethyl β-ketoglutarate (**1**, 5.71 g, 0.0328 mol) was added all in one portion to the solution. After 3 days, an oil had formed at the bottom of the flask. The mixture was extracted with chloroform (3 × 60 ml). The organic layer was dried (Na_2SO_4) and the solvent removed under reduced pressure to yield an oil which was shown by TLC to be composed of two compounds (R_f 0.10 and 0.86; 2:98 acetic acid/ethyl acetate). This oil (6.25 g) was purified by column chromatography (gradient elution with benzene/ethyl acetate) and yielded a white, crystalline solid (**29**, 2.00 g, 27%) identical in all respects with the 1:2 adduct (**29**) from the previous experiment. The R_f of the 1:2 adduct was 0.86, while the compound of R_f 0.10 has tentatively been assigned structure **28**. The molecular ion of the 1:1 adduct (M^+, 290) was observed in the mass spectrum of the crude oil. In addition a peak at *m/e* 258 could be attributed[4] to the loss of methanol from the parent ion (290) of the 1:1 adduct (**28**). Neither the peak at *m/e* 290 nor the one at *m/e* 258 was found in the spectrum of the 1:2 adduct **27** or the starting materials. Many attempts to isolate the 1:1 adduct **28** were made; however, only decomposition products and **29** were obtained.

Tetramethyl Benzo[3,4]tricyclo[3.3.3.0^{1,5}]undeca-2,7,10-trione-6,8,9,11-tetracarboxylate (31). Dimethyl β-ketoglutarate (**1**, 3.90 g, 0.022 mol) was added to aqueous sodium bicarbonate solution (100 ml, pH 8.4) and the resulting mixture was stirred until the glutarate dissolved. Ninhydrin monohydrate (**30**, 2.00 g, 0.0110 mol) was added to the reaction in one portion and the mixture was stirred for 72 h. The reaction was then acidified to pH 1 with aqueous sulfuric acid (6 M). A white solid precipitated from the solution, which was crystallized from methanol to furnish a 59.2% yield of **31** (2.13 g): mp 95–98 °C; ir (KBr) 2955, 1750–1720 (broad carbonyl), and 1665 cm^{-1} (enol form of β-keto ester); NMR ($CDCl_3$) δ 3.27 (3 H, m), 3.50 (12 H, overlapping singlets), 7.20–7.67 (4 H, m, aromatic protons), and 8.58 (2 H, broad band, enolic protons); mass spectrum *m/e* 472 (2, M^+), 440 (6), 414 (7), 408 (2), 382 (13), 340 (13), 323 (13), 280 (26), 82 (100).

Anal. Calcd for $C_{23}H_{20}O_{11}$: C, 58.48; H, 4.27. Found: C, 58.76; H, 4.22. High-resolution mass spectrum, calcd for $C_{23}H_{20}O_{11}$, 472.1005; found, 472.1027.

Benzo[3,4]trieyclo[3.3.3.0^{1,5}]undeca-2,7,10-trione (32). The tetracarbomethoxy propellanetrione (**31**, 4.5 g, 0.0095 mol) was added to a mixture of glacial acetic acid (55 ml), concentrated hydrochloric acid (40 ml), and water (20 ml). The mixture was refluxed for 10 h and a portion of the excess acid was removed under reduced pressure. The resulting solution was made alkaline with sodium hydroxide/sodium bicarbonate solution and extracted with chloroform (3 × 100 ml). The organic layer was washed with water and dried over sodium sulfate and the solvent removed under reduced pressure to furnish an oil, which crystallized after dissolution in methanol to furnish yellow crystals (**32**, 1.47 g, 70%): mp 172.5–174 °C; ir (KBr) 3060 (aromatic C–H), 1735 (cyclopentanone carbonyl), and 1700 cm^{-1} (conjugated carbonyl); NMR ($CDCl_3$) δ 2.62 (2 H, d, J = 20 Hz), 2.83 (4 H, s) 3.05 (2 H, d, J = 20 Hz), and 7.23–7.93 (4 H, m, aromatic protons). One of the peaks of the AB quartet overlapped with the singlet at δ 2.83. Mass spectrum: *m/e* 240 (26, M^+), 212 (19), 199 (24), 198 (100), 184 (10), 171 (16), 170 (81), 156 (26).

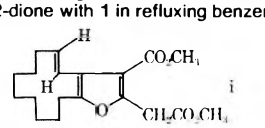
Anal. Calcd for $C_{15}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.67; H, 5.17.

Acknowledgments. We wish to thank Mr. Paul Karges, Mr. William E. Comstock (NIH), and Mr. William R. Landis (NIH) for mass spectra and Dr. Robert J. Highet (NIH) for the ^{13}C NMR spectrum of **17**. One of us (D.W.) wishes to thank the NSF for an Undergraduate Research Participation Summer Fellowship. We also wish to thank Ms. Delpfine Welch for technical assistance.

Registry No.—**1**, 1830-54-2; **14**, 465-29-2; **17**, 60428-14-0; **18**, 134-81-6; **19**, 84-11-7; **20**, 16691-78-4; **21**, 60428-15-1; **22**, 60428-16-2; **23**, 60428-17-3; **27**, 1074-12-0; **29**, 60428-18-4; **30**, 938-24-9; **31**, 60428-19-5; **32**, 60428-20-8.

References and Notes

(1) (a) J. Oehldrich and J. M. Cook, *Can. J. Chem.*, in press. Part 3 in this series. (b) Undergraduate research participants.
(2) This paper also constitutes part 6 in the series "Reactions of Dimethyl β-Ketoglutarate with 1,2-Dicarbonyl Compounds", by U. Weiss and coworkers. Part 5: K. C. Rice and U. Weiss, in press.
(3) U. Weiss and J. M. Edwards, *Tetrahedron Lett.*, 4885 (1968).
(4) D. Yang and J. M. Cook, *J. Org. Chem.*, **41**, 1903 (1976).
(5) For convenience, these esters are written in the keto form; actually, P. Camps [*Tetrahedron Lett.*, 4067 (1974)] has shown that **2** (R = R′ = H) exists as one of the possible dienols in chloroform solution.
(6) (a) J. M. Edwards, I. H. Qureshi, U. Weiss, T. Akiyama, and J. V. Silverton, *J. Org. Chem.*, **38**, 2919 (1973); (b) K. C. Rice, N. E. Sharpless, U. Weiss, and R. J. Highet, *Tetrahedron Lett.*, 3763 (1975); (c) K. C. Rice, U. Weiss, T. Akiyama, R. J. Highet, T. Lee, and J. V. Silverton, *ibid.*, 3767 (1975).
(7) This sequence could easily be formulated with fewer steps, if it were assumed that intermediate **8** lost a second molecule of water to give the corresponding cyclopentadienone, which could produce **2** directly by double Michael addition of another molecule of **1**. However, such cyclopentadienones (other than those stabilized by aromatic rings, see below), if formed at all under the mild conditions of our reaction, would undoubtedly dimerize at once by Diels–Alder reactions, yielding the corresponding endocarbonyl cyclohexenes. These dimerizations have been studied by C. F. H. Allen, *Chem. Rev.*, **37**, 709 (1945). No compounds of this type have been encountered in any part of our work.
(8) F. B. Japp and G. D. Lander, *J. Chem. Soc.*, **71**, 139 (1897).
(9) (a) R. C. Cookson, J. B. Henstock, J. Hudec, and B. R. D. Whitear, *J. Chem. Soc. C*, 1989, 1992 (1967); (b) B. Eistert and A. Thommen, *Chem. Ber.*, **104**, 3048 (1971); (c) D. White, *J. Org. Chem.*, **39**, 1951 (1974).
(10) Methanol was added to the reaction to help solubilize the camphorquinone.
(11) R. M. Silverstein, G. C. Bassler, and C. Morrill, "Spectrometric Identification of Organic Compounds", 3d ed, Wiley, New York, N.Y., 1974, p 226.
(12) J. M. Bobbitt and K.-P. Segebarth in "Cyclopentanoid Terpene Derivatives", W. I. Taylor and A. R. Battersby, Ed., Marcel Dekker, New York, N.Y., 1969, pp 101–104.
(13) (a) M. M. Janot, R. Goutarel, and J. Massonneau, *C. R. Acad. Sci.*, **234**, 850 (1952); (b) C. Djerassi, J. Fishman, M. Gorman, J. P. Kutney, and S. C. Pakrashi, *J. Am. Chem. Soc.*, **79**, 1217 (1957).
(14) Reference 12, pp 98–100.
(15) S. J. Angyal and R. J. Young, *J. Am. Chem. Soc.*, **81**, 5467 (1959).
(16) M. O. Forster, *J. Chem. Soc.*, **87**, 232, 241 (1905).
(17) Structure **17** is assumed here to result by initial aldolization at the more accessible carbonyl function: carbon 3 in the bornane-2,3-dione (camphorquinone) skeleton [K. M. Baker and B. R. Davis, *Tetrahedron*, **24**, 1655 (1968)]. However, our data do not exclude initial attack at position 2 of the bornane-2,3-dione, which would lead to hemiketal formation at position 3 of the bornane molecule. Since, however, only one compound was isolated from this reaction, the latter possibility is considered highly unlikely.
(18) We wish to thank Professor Albert W. Burgstahler for a preprint of his publication.
(19) F. B. Japp and G. D. Lander, *Proc. Chem. Soc., London*, 109 (1896).
(20) F. B. Japp and F. Klingemann, *J. Chem. Soc.*, **59**, 1 (1891).
(21) A. C. Cope and D. W. H. MacDowell, *J. Am. Chem. Soc.*, **80**, 5513 (1958).
(22) F. W. Harris, R. D. Case, and B. A. Reinhardt, paper presented at The First Chemical Congress of the North American Continent, Mexico City, Mexico, Dec 1975, Organic Chemistry Session, Paper No. 12.
(23) G. Vossen, Dissertation, Bonn, 1910.
(24) P. Yates, E. S. Hand, and G. French, *J. Am. Chem. Soc.*, **82**, 6347 (1960).
(25) S. H. Bertz, Harvard University, unpublished work. We wish to thank Mr. Bertz for permission to mention his findings.
(26) A 1:1 adduct representing a novel type, obviously derived from a monoaldolization product analogous to **17**, was obtained through reaction of cyclododecane-1,2-dione with **1** in refluxing benzene in the presence



i

of *p*-toluenesulfonic acid. From spectroscopic evidence, this adduct has a furanoid structure and appears to be **i**. It will be discussed elsewhere: O. Campos and J. M. Cook, manuscript in preparation.

The Direction of Base-Catalyzed Aldol Cyclization of 1,5 Diketones

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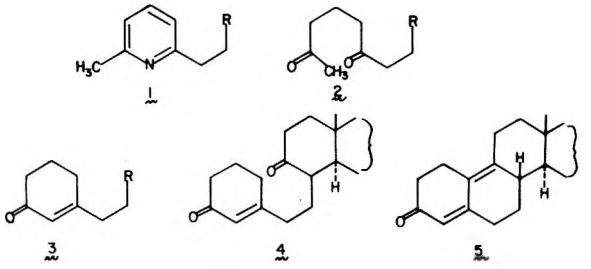
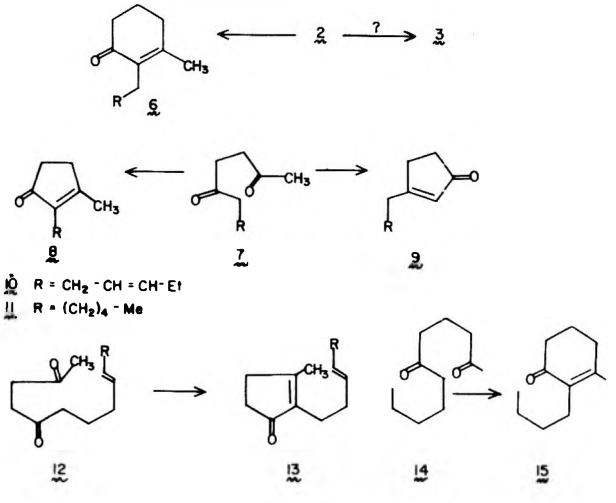
A series of 1,5 diketones of the type $MeC(=O)(CH_2)_3C(=O)CH_2R$ (**2**) has been prepared. The route involves alkylation of 2,6-lutidine via its lithium salt with RX. The resultant pyridine, of the structure $2\text{-}MeC_5H_3N\text{-}6\text{-}CH_2R$, is converted to the diketone of the type **2** by Birch-type reduction followed by hydrolysis. The base-catalyzed cyclodehydration of systems of the type **2** at room temperature has been examined in detail. The relative amounts of the two isomeric cyclohexenones, 3-RCH_2-cyclohex-2-en-1-one (type **3**) and 2-R-3-methylcyclohex-2-en-1-one (type **6**), were determined by product isolation. In the case of R = methyl the type **3**:type **6** ratio is ca. 1:17. When R is straight-chain alkyl, the ratio is close to unity, with a slight preference for the type **3** product. When R is branched alkyl and the branch point is either α or β to the ketone, type **3** product becomes strongly favored. As the branch point is moved γ to the ketone, the ratio veers toward unity. The presence of a dioxolane function in R, δ to the ketone, favors type **6** product. Temperature conditions employed in the base-catalyzed aldol cyclizations are shown to affect the product ratios.

The critical phase in our synthesis of ring A aromatic steroids from 2,6-lutidine involves reduction–hydrolysis of a 6-substituted α-picoline (**1**) to afford a 7-substituted 2,6-octanedione (**2**), which suffers aldol cyclization to provide a 3-substituted cyclohexenone (**3**).[1-4] The R group encompasses the C and D rings of the ultimate steroid. After unmasking the carbonyl group within R, which is α to its center of attachment, the resultant B seco steroid **4**, is susceptible to vinylogous aldolization to yield the tetracyclic system **5**.



At the time the feasibility of this approach was being studied, there was little decisive information bearing on a key issue, i.e., the aldol cyclization **2** → **3**. Clearly there existed, a priori, an alternative aldol cyclization mode, **2** → **6**, whose occurrence to any serious extent would have been deleterious to the scheme set forth above.

The precedents involving the formation of cyclopentenones, from the conceptually related cyclization of 1,4 diketones of the type **7**, might have been viewed to be discouraging in this connection. An imposing collection of syntheses of *cis*-jasmone (**10**) and *cis*-dihydrojasmone (**11**) have involved base-catalyzed cyclization of the type **7** → **8** in which the tetrasubstituted enone is produced to the apparent exclusion of trisubstituted product **9**.[5] Furthermore, the well-known synthesis of steroids of the Johnson school involved the base-catalyzed conversion of **12** → **13**, with apparent exclusion of interference from the cyclization mode, **7** → **9**.[6]



In the case of cyclohexenone formation from 1,5 diketones, we could find only one clearcut example which was relevant[7] to the question of the aldol cyclization course of **2**. Stork and Borch had obtained compound **14** by their elegant directed acetylene hydration, and had reported that this compound cyclizes under basic catalysis (KOH/ethanol, reflux) to yield **15**, to the apparent exclusion of a product of type **3**, R = propyl.[8]

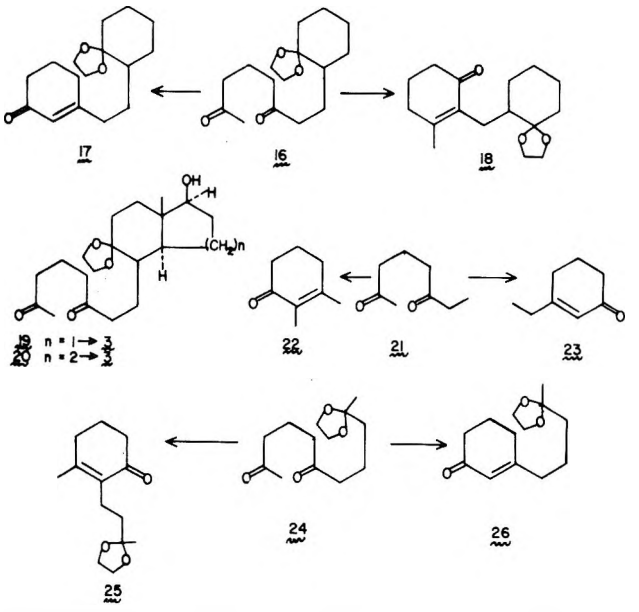
Undeterred by this prior art, we prepared compound **16** by methods which we have previously described and studied its cyclization[2,9] to cyclohexenones under basic conditions. It should be emphasized that for synthetic purposes there is no reason to isolate the intermediate 1,5 diketones since one achieves substantially the same result, in terms of cyclohexenone formation, in much higher yield by directly converting the lutidine system **1** to the product. However, in some cases there are real differences in the ratio of cyclohexenones produced directly from the dihydropyridine and from the 1,5 diketone.[9] Accordingly, all of the reults discussed in this report involve cyclizations of isolated homogeneous 1,5 diketones.

Cyclization of **16** in aqueous ethanolic alkali *under reflux* gave a 1:3.4 ratio of **17**:**18**. However, by the simple expedient of conducting the cyclization at room temperature, the ratio of **17**:**18** was dramatically and favorably reversed to the level of 3.8:1. It was further demonstrated[2] that under these conditions of reflux, **17** is converted to **18** presumably by hydration and retro-aldol followed by aldol cyclization.[10-12]

As we continued to the synthetically crucial substrate **20**, the only cyclohexenone obtained was the desired trisubstituted system (**3**).[2,9] This was the case either at room temperature or under conditions of reflux. Furthermore, the trisubstituted product did not suffer transformation to the tetrasubstituted system (**6**) even under forcing alkaline conditions.

After the viability of the total synthesis had thus been established, some preliminary studies of the aldol cyclization of simpler 1,5 diketones were reported.[9] Birch-type reduction of 6-ethyl-α-picoline followed by careful hydrolysis gave diketone **21**. Alkali-induced cyclodehydration of **21** at room temperature afforded a 19:1 ratio (determined by GLC) of **22**:**23**. This result seemed to be very much in keeping with those expected on the basis of the precedents arising from the cyclization of 1,4 diketones discussed above.[5]

We also prepared the diketone ketal **24** by alkylation of the lithium salt of 2,6-lutidine with the dioxolane of 4-chloro-2-



butanone followed by reduction and hydrolysis. Base-catalyzed cyclization of **24** at room temperature gave a 3:1 ratio of **25:26** (determined by GLC). When this reaction was conducted in refluxing aqueous ethanolic base, the ratio of **25:26** was 10:1.[9]

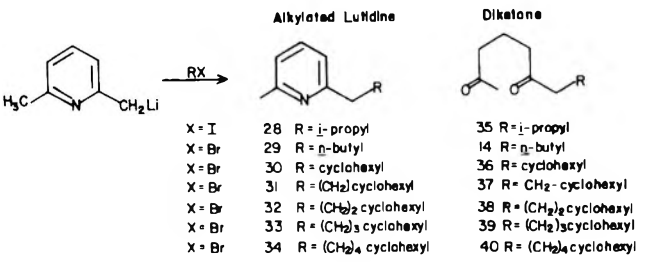
One could thus discern several general effects. Branching in the group R in structure **2** seems to be a factor favoring type **3** (trisubstituted) products. Higher reaction temperatures appear to favor type **6** (tetrasubstituted) products by equilibration. With heavily encumbered R groups such as those found in **19** and **20**, trisubstituted products are favored, exclusively, even at higher temperatures. Whether this reflects an inability to achieve equilibration of the trisubstituted products, or whether in these cases the trisubstituted product is actually thermodynamically more stable, is not known. Since no studies of cyclization of 1,4 diketones similar to **16**, **19**, or **20** had ever been described, there was no reason to suspect any basic differences in the behavior of systems **2** and **7**.

Below we report the results of experiments undertaken to generalize these findings. Except for **21**, the diketones thus far studied under structure **2** were rather special in that the R group contained a ketal. Any specific directive influences of this group could not be readily discerned from our data. Furthermore, it was necessary to define with greater precision the effect of branching on the direction of aldol cyclization and the consequences of varying the distance between the branch point and the ring being produced.

In pursuing this line of study, we have found that there are major differences in the aldol cyclization of 1,5 and 1,4 diketones such as **2** and **7**, respectively. Furthermore, it was found that the ketal does exert a directing effect but the effect favors tetra- rather than trisubstituted products. The findings are summarized below.

Preparation of the 1,5 Diketones. The route which was followed for the preparation of all the 1,5 diketones used in this study involved Birch reduction of 2,6-disubstituted pyridines followed by hydrolytic opening of the dihydropyridines. While the overall yield for the two steps was only in the order of 20–40%, this route was the most convenient for the purposes of this study.

The required pyridines **28** → **34** were prepared by the monoalkylation of 2,6-lutidine via its lithium salt. The latter was generated from the action of the tar base with either phenyl- or butyllithium. The products, obtained in 20–60% yields, were readily separated from the starting material and polyalkylated materials by distillation.



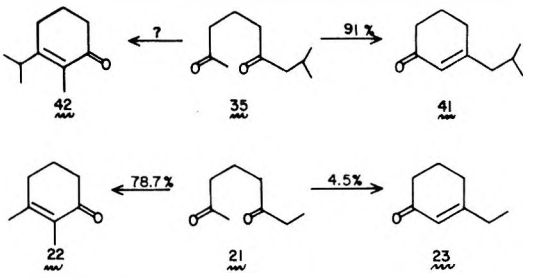
Each pyridine was subjected to Birch-type reduction with sodium in ammonia containing ethanol.[13] After removal of the ammonia, the residue was treated with 10% aqueous sulfuric acid to provide the diketone.[14] Under these conditions, there is no appreciable cyclization to cyclohexenone and the diketone is obtained as the neutral product. This method was of course not feasible for the preparation of diketone ketals **16**, **19**, and **24** since the ketal would have been cleaved.[15] Rapid alkaline hydrolysis of the dihydropyridine intermediate was used to avoid cyclization in these cases.

Starting pyridine compound and overreduction products are easily removed by acidic extraction.

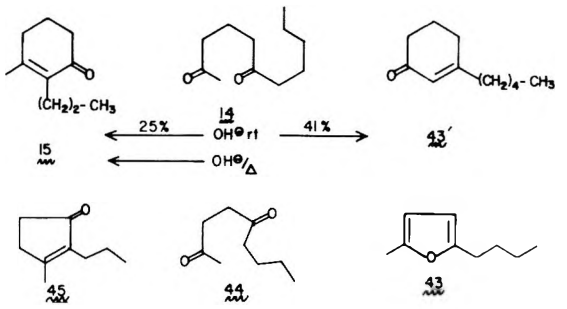
Cyclization of the 1,5 Diketones. The cyclohexenones obtained by base-catalyzed aldol cyclization of the 1,5 diketones were purified by chromatography on silica gel. Elutions were conducted with benzene containing varyingly small amounts of ethyl acetate depending on the ease of the separation. In each case, the tetrasubstituted isomer was eluted first and this was followed by elution of the trisubstituted system. The separations were clean and there seems no reason to doubt that the yield ratio, as determined by isolation, accurately reflects the ratio produced in the reaction.

The structural assignments of the cyclohexenones follow unambiguously from their NMR spectra. The type **3** (trisubstituted) products all exhibit a broad (long range coupling) 1 H singlet in the region δ 5.8 ppm. The NMR spectra of type **4** (tetrasubstituted) enones, of course, contain no such signal but do contain a 3 H singlet in the region δ 1.9 ppm. The assignments were supported by infrared and mass spectra, though these measurements are not useful for purposes of differentiation.

The effects of branching are dramatically een in the comparison of the results of base-catalyzed aldol cyclization of diketones **21** and **35** at room temperature. Although the cy-



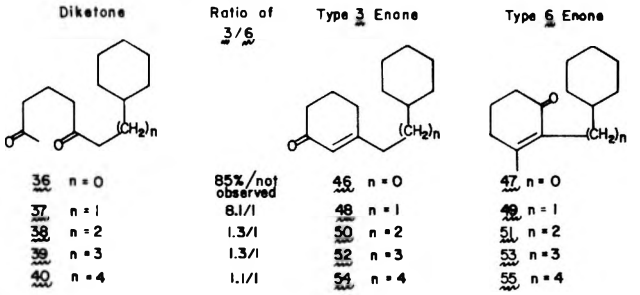
clization of **21** under these conditions had been studied before,[9] this was repeated. The 17:1 ratio of cyclohexenones **22:23** produced in this work, as ascertained by product isolation, compared quite closely with the 19:1 ratio previously reported on the basis of GLC analysis. These results stand in sharp contrast to the virtually exclusive isolation of **41** from cyclization of **35** under identical conditions. TLC analysis leaves open the possibility of the presence of some tetrasubstituted enone **42** but the amount, if any, was too small for isolation. It was now of interest to study the room temperature base-catalyzed aldol cyclization of diketone **14**. As noted above, Stork and Borch[7] had obtained only compound **15** from more forcing alkaline cyclization conditions. *Under our conditions at room temperature, a 1.5:1 ratio of cyclohexenones* **43:15** *was obtained.* When diketone **14** was subjected to the condi-



tions of Stork and Borch, we found, as was reported,[7] that compound **15** was the only isolated product. In a separate experiment it was shown that cyclohexenone **43** could be isomerized to **15** in aqueous ethanolic alkali under reflux.[10,11] This situation is similar to our findings in the case of enone **17** which could be isomerized to **18** under the same conditions.[2] These results leave open the possibility of some difference in the kinetic distribution of cyclohexenones in the room temperature vs. forcing conditions, but the simplest interpretation is that the formation of tetrasubstituted products at elevated temperatures is the consequence of thermodynamic equilibration. In any case, it is seen that in the cyclization of 1,5 diketones of the type **2** where R is straight chain, the kinetic distribution of products is near unity and, in fact, tends to favor type **3** product. Diketone **21** (i.e., **2**, R = H) is actually the exception in that even kinetically (room temperature), the type **6** product is overwhelmingly favored.

We also examined the analogous cyclization of the 1,4 diketone **44**, readily obtained by hydrolysis of 2-methyl-5-*n*-butylfuran. Cyclization of **44** even at room temperature gives cyclopentenone **45** as the only isolated product. *Apparently, there is a major difference in the directionality of base-catalyzed cyclization of 1,5 and 1,4 diketones under identical conditions.* This difference had previously been obscured by our own report of the room temperature cyclization of **21** which gives overwhelmingly **22** product and by the previous report that **14** affords **15** under high temperature conditions. The former case is seen to be the exception at the kinetic level. The later case reflects thermodynamic, rather than kinetic, control.

Analysis of the results of cyclization of diketones **36** → **40**



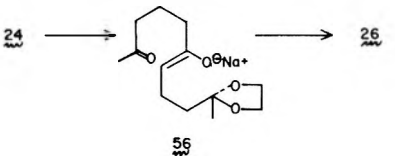
at room temperature indicates the effect of the distance between the carbon branching and the ring to be formed on the distribution of cyclohexenones. It is seen that as the cyclohexyl group is placed further from the C_6 ketone, the ratio of cyclohexenones moves in the direction of unity. In the case of $n = 0$ (**36**), only type **3** product is isolated. This is the analogue of compound **35**. Again it is seen that formation of type **6** product is seriously discouraged where the branched carbon would be adjacent to the ring.

In the cyclohexyl series, the consequence of branching is largely dissipated in passing from compound **37** to compound **38**. In the tetrasubstituted (type **6**) product, this corresponds to changing from a cyclohexylmethyl to a 2-cyclohexylethyl substituent at the α carbon of the β-methylenone system. The stage at which this effect is lost as "n" increases may well vary from system to system.

It will be noted that the case of $n = 1$ is the analogue of **16** which was the model case for the steroid work.[2] The ratio of type **3**/type **6** product obtained from cyclization of **37** at room temperature is 8.1:1 whereas in the case of **16** these products are produced in a ratio of 3.8:1. Thus it appears that in this case the ketal linkage, in fact, exerts a small but distinct directing effect in favor of the type **6** mode of cyclization.

The same tendency is seen in more pronounced form in comparison of the cyclization of **24** [type **6** (**25**)/type **3** (**26**) = 1:4] relative to **14** [type **3** (**43**)/type **6** (**15**) = 1.5:1]. A closer model for the expected result for a carbon branched analogue of **24** would be diketone **39** where the type **3** (**52**)/type **6** (**53**) ratio is 1.3:1. Thus the preponderance of type **6** product (4:1) in the case of **14** is clearly ascribable to the ketal which is exerting a decisive influence in favor of the tetrasubstituted enone at the kinetic level.

While the structural reasons for the effect are not known, it seems possible that the ketal oxygens serve to stabilize that enolate which is the precursor to tetrasubstituted product by bonding to the metal counterion (cf. **56**). The possibility of



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controlling the course of aldol cyclization of systems such as **2** by the placement of remote groups which might influence the course of enolization is a potential consequence of this work.

The nature of the effect of carbon branching in promoting formation of the tetrasubstituted enone is not known in detail. It may be operative, on steric grounds, by retardation of the formation of the β-aldol precursor of the type **6** product. Alternatively, it may be operative by retardation of the final dehydration step.

In the light of these data, the cyclization of **19** and **20** in the direction of type **3** products, which was critical to the steroid total synthesis, is by no means anomalous. The apparent anomaly arose from an inadequate data base since there is virtually no correlation in the cyclization of systems such as **2** and **7**.

Experimental Section

Preparation of 2-Isobutyl-6-methylpyridine (28). To a mixture of 100 ml of anhydrous ether containing 1.4 g (0.2 mol) of lithium metal under a nitrogen atmosphere was added dropwise 15.7 g (0.1 mol) of bromobenzene. The mixture was heated under reflux until the lithium had completely disappeared (approximately 1.5 h). To this mixture was added 9.3 g (0.087 mmol) of 2,6-lutidine. The mixture was stirred under reflux for 30 min. To this mixture was added 6.15 g (0.036 mmol) of isopropyl iodide in an equal volume of anhydrous ether. The mixture was heated under reflux for 30 min. The reaction mixture was then diluted with water and extracted with methylene chloride. The organic layers were dried over anhydrous Na_2SO_4. Evaporation of the volatiles afforded 4.95 g of a brown residue. Distillation of the crude oil at 10 mm yielded 3.21 g (60%)[17] of **28** as a pale yellow liquid, boiling at 70–75 °C; λ_{max} ($CHCl_3$) 1580, 1595 cm^{-1}; δ ($CDCl_3$) 7.28–7.57 (m, 1), 6.77–7.0 (m, 2), 1.88–2.73 (m, 6 containing s ca. 3 at δ 2.52), 0.87, 0.98 (d, 6); *m/e* 149 (P), 107.

Preparation of 8-Methyl-2,6-nonanedione (35). To a solution of 1.00 g (6.7 mmol) of **28**, 1.23 g (26.8 mmol) of absolute ethanol, and 5.0 ml of anhydrous ether in 60 ml of anhydrous liquid ammonia (freshly distilled from sodium) was slowly added 354 mg (15.4 mmol) of sodium metal. The solution was stirred for 15 min and the volatiles were evaporated under a stream of nitrogen. To the residue was added 10 ml of aqueous 10% H_2SO_4, and the solution was stirred at room temperature for 15 min. The reaction mixture was diluted with 10 ml of water and extracted with three 50-ml portions of methylene chloride. The organic layers were dried over anhydrous Na_2SO_4 and the

solvent was removed to afford a residue (612 mg). This was washed with three 15-ml portions of aqueous 10% HCl to afford 305 mg (27%) of diketone **35** as a yellow oil: λ_{max} ($CHCl_3$) 1718 cm^{-1}; δ ($CDCl_3$) 1.5–2.6 (m, 12 H containing s ca. 3 H at δ 2.12). 0.85, 0.97 (d, 6 H); *m/e* 170 (P), 85.

Anal. Calcd for $C_{10}H_{18}O_2$: *m/e* 170.13068. Found: *m/e* 170.13035.

Neutralization of the combined acidic layers, extraction with chloroform, and drying (Na_2SO_4) afforded 523 mg of basic material.

Room Temperature Cyclization of Diketone 35. Formation of 3-Isobutylcyclohex-2-en-1-one (41). To a solution of 936 mg (5.5 mmol) of diketone **35** in 22 ml of ethanol was added a solution of 550 mg (13.75 mmol) of sodium hydroxide in 11 ml of water. The solution was stirred at room temperature under nitrogen for 2.5 h. The solution was acidified with 10% aqueous HCl and extracted with three 100-ml portions of chloroform. The organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded 929 mg of a yellow oil. Chromatography of the oil on 100 g of silica gel using 10:1 benzene–ethyl acetate as eluent yielded 759 mg (91%) of cyclohexenone **41** as an oil: λ_{max} ($CHCl_3$) 1660 cm^{-1}; δ ($CDCl_3$) 0.88, 0.98 (d, 6), 1.93–2.5 (m, 9), 5.88 ppm (s, 1); 2,4-DNP mp 136–138 °C (lit.[18] 135 °C).

Anal. Calcd for $C_{10}H_{16}O$: *m/e* 152.120115. Found: *m/e* 152.120149.

Preparation of 2-Pentyl-6-methylpyridine (29). To a solution of 147 ml of *n*-BuLi (1.6 M in hexane), maintained under a nitrogen atmosphere, was added dropwise 25.0 g (0.234 mol) of 2,6-lutidine in 50 ml of anhydrous ether. The mixture was stirred at reflux for 30 min. To this mixture was added 16.03 g (0.117 mmol) of *n*-butyl bromide in an equal volume of anhydrous ether. The solution was heated under reflux for 30 min. This was followed by dilution with water and extraction with ether. The organic layers were combined and dried over anhydrous Na_2SO_4. Evaporation and solvent removal afforded 18.5 g of a yellow oil. Vacuum distillation of the crude oil yielded 13.2 g (69%)[17] of compound **29:** bp 42–45 °C (22 mm); λ_{max} ($CHCl_3$) 1582, 1597 cm^{-1}; δ ($CDCl_3$) 7.17–7.47 (m, 1), 6.68–6.88 (m, 2), 2.48–2.82 (m, 2), 2.38 (s, 3), 0.77–1.85 ppm (m, 9).

Anal. Calcd for $C_{11}H_{17}N$: *m/e* 163.13609. Found: *m/e* 163.13609.

Preparation of 2,6-Undecanedione (14). To a solution of 1.00 g (6.1 mmol) of **29,** 1.13 g (24.4 mmol) of absolute ethanol and 6 ml of anhydrous ether in 60 ml of anhydrous liquid ammonia (freshly distilled from sodium) was slowly added 323 mg (14 mmol) of sodium metal. The solution was stirred for 15 min and the volatiles were evaporated under a stream of nitrogen. To the residue was added 10 ml of aqueous 10% H_2SO_4 and the solution was stirred at room temperature for 15 min. The reaction mixture was diluted with 10 ml of water and extracted with three 50-ml portions of ether. The organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed to afford 701 mg (62%) of diketone **14** as tan crystals: mp 46–48 °C; λ_{max} ($CDCl_3$) 1712 cm^{-1}; δ ($CDCl_3$) 0.9–2.6 ppm (m, 20 containing s ca. 3 at 2.13).

Anal. Calcd for $C_{11}H_{20}O_2$: *m/e* 184.14633. Found: *m/e* 184.14619.

Neutralization of the acidic layer, extraction with chloroform, and drying (Na_2SO_4) yielded 232 mg of basic material.

Room Temperature Cyclization of Diketone 14. Formation of 2-Butyl-3-methylcyclohex-2-en-1-one (15) and 3-Pentylcyclohex-2-en-1-one (43′). To a solution of 172 mg (0.94 mmol) of diketone **14** in 3.74 ml of ethanol was added a solution prepared from 94 mg (2.35 mmol) of sodium hydroxide and 1.87 ml of water. The solution was stirred at room temperature under nitrogen for 2.5 h. The solution was acidified with 10% aqueous HCl and was extracted with three 250-ml portions of chloroform. The organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded 143 mg of a yellow oil. Chromatography of the oil on 30 g of silica gel using 40:1 benzene–ethyl acetate as eluent yielded 39 mg (25%) of **15** as an oil: λ_{max} ($CHCl_3$) 1656 cm^{-1}; δ ($CDCl_3$) 1.8–2.5 (m, 11 containing s ca. 3 at 1.93), 0.83–1.42 ppm (m, 7); 2,4-DNP mp 147–148 °C (lit.[19] 144 °C).

Anal. Calcd for $C_{11}H_{18}O$: *m/e* 166.13577. Found: *m/e* 166.13561.

Continued elution with the same solvent system afforded 64 mg (41%) of cyclohexenone **43′** as an oil: λ_{max} ($CHCl_3$) 1661 cm^{-1}; δ ($CDCl_3$) 0.7–2.5 (m, 17), 5.88 ppm (s, 1); 2,4-DPN mp 125–126 °C.

Anal. Calcd for $C_{11}H_{18}O$: *m/e* 166.13577. Found: *m/e* 166.13546.

Preparation of 2,6-Octanedione (21). To a solution of 1.01 g (8.3 mmol) of 2-methyl-6-ethylpyridine, 1.52 g (0.33 mmol) of absolute ethanol, and 5.0 ml of anhydrous ether in 50 ml of anhydrous ammonia (freshly distilled from sodium) was slowly added 440 mg (20 mmol) of sodium metal. The solution was stirred for 15 min and the volatiles evaporated under a stream of nitrogen. To the residue was added 10 ml of aqueous 10% H_2SO_4 and the solution was stirred at room temperature for 15 min. The reaction mixture was diluted with 10 ml of water and extracted with three 50-ml portions of ether. The organic layers were combined and dried over anhydrous Na_2SO_4 and the solvent was evaporated at the water pump to yield 755 mg (64%) of diketone **21** as an oil: λ_{max} ($CHCl_3$) 1712 cm^{-1}; δ $CDCl_3$) 1.67–2.63 (m, 11 containing s ca. 3 at 2.12), 0.92–1.17 ppm (t, 3); *m/e* 142 (P).

Neutralization of the acidic layer, extraction with chloroform, and drying (Na_2SO_4) afforded 200 mg of basic material.

Room Temperature Cyclization of Diketone 21. Formation of 2,3-Dimethylcyclohex-2-en-1-one (22) and 3-Ethylcyclohex-2-en-1-one (23). To a solution of 306 mg (2.2 mmol) of diketone **21** in 8.6 ml of ethanol was added a solution of 215 mg (5.38 mmol) of sodium hydroxide in 4.3 ml of water. The solution was stirred at room temperature under nitrogen for 2.5 h. The solution was acidified with 10% aqueous HCl and then stirred for 15 min at room temperature. The solution was extracted with three 50-ml portions of chloroform and the organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded 250 mg of a yellow oil. Chromatography of the oil on 40 g of silica gel using chloroform as eluent yielded 124 mg of pure **22** and 131 mg of a mixture of **22** and **23.** The mixture was rechromatographed on 20 g of silica gel using 95:5 hexane–ether as eluent. This chromatography yielded 86 mg (210 mg total, 78.7%) of the tetrasubstituted isomer **22** as an oil: λ_{max} ($CHCl_3$) 1645 cm^{-1}; δ ($CDCl_3$) 2.17–2.5 (m, 6), 2.0 (s, 3), 1.77 ppm (s, 3); *m/e* 124 (P). 2,4 DNP mp 198–200 °C (lit.[20] 198–199 °C).

Continued elution with chloroform as eluent afforded 12 mg (4.5%) of the isomeric cyclohexenone **23** as an oil: λ_{max} ($CHCl_3$) 1658 cm^{-1}; δ ($CDCl_3$) 6.07 (s, 1), 2.0–2.5 (m, 8), 1.12–1.37 ppm (t, 3); *m/e* 124 (P). 2,4 DNP mp 163–164 °C (lit.[21] 160–161 °C).

Preparation of 2-Cyclohexylmethyl-6-methylpyridine (30). To a solution of 30 ml of *n*-BuLi (1.6 M in hexane), maintained under a nitrogen atmosphere, was slowly added 4.6 g (0.043 mol) of 2,6-lutidine in 5 ml of anhydrous ether. The mixture was stirred at reflux for 1 h. To this mixture was added 7.0 g (0.043 mol) of cyclohexyl bromide in an equal volume of anhydrous ether. Addition required 15 min. The solution was heated under reflux overnight to ensure complete reaction. The solution was hydrolyzed and extracted with three 100-ml portions of ether and the organic layers dried over anhydrous Na_2SO_4. Solvent evaporation yielded 8.12 g of a brown oil. Vacuum distillation of the crude liquid yielded 2.4 g (29%) of **30:** bp 73–75 °C (0.15 mm); λ_{max} ($CHCl_3$) 1577, 1592 cm^{-1}; δ ($CDCl_3$) 7.32–7.57 (m, 1), 6.78–6.98 (m, 2), 2.48–2.70 (m, 5 containing s ca. 3 at δ 2.53), 0.98–1.95 ppm (m, 11); *m/e* 189 (P), 107.

Anal. Calcd for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.47; H, 10.18; N, 7.31.

Conversion of 30 to 7-Cyclohexyl-2,6-heptanedione (36). To a solution of 997 mg (5.27 mmol) of compound **30** and 970 mg (21 mmol) of absolute ethanol in 5.0 ml of anhydrous ether in 50 ml of anhydrous liquid ammonia (freshly distilled from sodium) was slowly added 279 mg (12 mmol) of sodium metal. The solution was stirred for 15 min and the volatiles evaporated under a stream of nitrogen. To the residue was added 10 ml of 10% H_2SO_4 and the solution was stirred at room temperature for 15 min. The reaction mixture was diluted with 10 ml of water and extracted with three 50-ml portions of ether. The organic layers were dried over anhydrous Na_2SO_4 and the solvent evaporated to yield 944 mg of a yellow oil. Chromatography of the oil on 100 g of silica gel using 10:1 benzene–ethyl acetate as eluent afforded 545 mg (49%) of diketone **36:** λ_{max} ($CHCl_3$) 1715 cm^{-1}; δ ($CDCl_3$) 1.0–2.6 ppm (m, 22 containing s ca. 3 at δ 2.13).

Anal. Calcd for $C_{13}H_{22}O_2$: *m/e* 210.16198. Found: *m/e* 210.16173.

Room Temperature Cyclization of Diketone 36. Formation of 3-Cyclohexylmethylcyclohex-2-en-1-one (46). To a solution of 320 mg (1.52 mmol) of diketone **36** in 6.2 ml of ethanol was added a solution of 152 mg (3.8 mmol) of sodium hydroxide in 3.1 ml of water. The solution was stirred under nitrogen at room temperature for 2.5 h. The solution was then acidified with 10% aqueous HCl and extracted with three 50-ml portions of chloroform. The organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded 288 mg of a yellow oil. Chromatography of the oil on 20 g of silica gel using 10:1 benzene–ethyl acetate as eluent afforded 250 mg (85%) of cyclohexenone **46** as an oil: λ_{max} ($CHCl_3$) 1658 cm^{-1}; δ ($CDCl_3$) 1.0–2.5 (m, 19), 5.87 ppm (s, 1); 2,4-DNP mp 150–153 °C.

Anal. Calcd for $C_{13}H_{20}O$: *m/e* 192.15151. Found: *m/e* 192.15060.

Preparation of 2-(2-Cyclohexyl)ethyl-6-methylpyridine (31). To a solution of 30 ml of *n*-BuLi (1.6 M in hexane), maintained under a nitrogen atmosphere, was slowly added 4.6 g (0.043 mol) of 2,6-lutidine in 5 ml of anhydrous ether. The mixture was stirred at reflux for 1 h. To this mixture was added 7.0 g (0.040 mol) of cyclohexylmethyl bromide in an equal volume of anhydrous ether. The solution was heated under reflux for 5 h. The solution was diluted with water and extracted with ether. The organic extracts were combined and

dried over anhydrous Na_2SO_4 and the solvent removed to afford 9.96 g of a yellow oil. Vacuum distillation of the crude oil afforded 4.14 g (52%) of **31:** bp 92–93 °C (0.29 mm); λ_{max} ($CHCl_3$) 1582, 1592 cm^{-1}; δ ($CDCl_3$) 7.33–7.58 (m, 1), 6.87–6.98 (m, 2), 2.65–2.93 (m, 2), 2.53 (s, 3), 1.0–1.95 ppm (m, 13); *m/e* 203 (P).

Anal. Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.66; H, 10.40; N, 6.87.

Conversion of 31 to 8-Cyclohexyl-2,6-octanedione (37). To a solution of 1.01 g (4.9 mmol) of compound **31,** 902 mg (19.6 mmol) of absolute ethanol, and 5.0 ml of anhydrous ether in 50 ml of anhydrous liquid ammonia (freshly distilled from sodium) was slowly added 260 mg (11.3 mmol) of sodium metal. The solution was stirred for 15 min and the volatiles evaporated under a stream of nitrogen. To the residue was added 10 ml of 10% H_2SO_4 and the solution was stirred at room temperature for 15 min. The reaction mixture was diluted with 10 ml of water and extracted with three 50-ml portions of ether. The organic layers were combined and dried over anhydrous Na_2SO_4 and the solvent removed to yield 220 mg (20%) of crystalline diketone **37:** mp 52–54 °C; λ_{max} ($CHCl_3$) 1712 cm^{-1}; δ ($CDCl_3$) 1.0–2.6 (m, 24 containing s ca. 3 at δ 2.13); *m/e* 244, 128 (P).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.80; H, 10.76.

Neutralization of the acidic layer, extraction with chloroform, and drying (Na_2SO_4) yielded 431 mg of unreacted **31** (42%).

Room Temperature Cyclization of Diketone 37. Formation of 3-(2-Cyclohexyl)ethylcyclohex-2-en-1-one (48) and 3-Cyclohexylmethyl-3-methylcyclohex-2-en-1-one (49). To a solution of 202 mg (0.91 mmol) of diketone **37** in 3.6 ml of ethanol was added a solution prepared from 91 mg (2.3 mmol) of sodium hydroxide in 1.8 ml of water. The solution was stirred at room temperature under nitrogen for 2.5 h. The solution was acidified with 10% aqueous HCl and extracted with three 50-ml portions of chloroform, and the organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded 170 mg of a yellow oil. Chromatography of the oil on 17 g of silica gel using 10:1 benzene–ethyl acetate as eluent yielded 11 mg (6.1%) of **49** as an oil: λ_{max} ($CHCl_3$) 1658 cm^{-1}; δ ($CDCl_3$) 0.8–2.5 ppm (m, containing s ca. 3 at δ 1.93).

Anal. Calcd for $C_{14}H_{22}O$: *m/e* 206.16706. Found: *m/e* 206.16711.

Continued elution with the same solvent system gave **48** (92 mg, 50%) as an oil: λ_{max} ($CHCl_3$) 1658 cm^{-1}; δ ($CDCl_3$) 1.0–2.5 (m, 21), 5.87 ppm (s, 1); 2,4-DNP mp 149–151 °C.

Anal. Calcd for $C_{14}H_{22}O$: *m/e* 206.16706. Found: *m/e* 206.16650.

Preparation of 2-(3-Cyclohexyl)propyl-6-methylpyridine (32). To a solution of 15 ml of *n*-BuLi (1.6 M in hexane), maintained under a nitrogen atmosphere, was slowly added 2.3 g (0.021 mol) of 2,6-lutidine in 2.5 ml of anhydrous ether. The mixture was stirred under reflux for 1 h. To this mixture was added 3.8 g (0.020 mol) of 2-cyclohexylethyl bromide in an equal volume of anhydrous ether. The solution was heated under reflux for 5 h. The solution was diluted with water and extracted with ether. The organic layers were dried over anhydrous Na_2SO_4. Solvent removal afforded 5.11 g of a yellow oil. Vacuum distillation of the crude oil yielded 2.55 g (59%) of **32:** bp 101–103 °C (0.17 mm); λ_{max} ($CHCl_3$) 1582, 1600 cm^{-1}; δ ($CDCl_3$) 7.4–7.6 (m. 1), 6.9–7.0 (m, 2), 2.62–2.88 (m, 2), 2.53 (s, 3), 0.83–1.92 ppm (m, 15); *m/e* 217 (P).

Anal. Calcd for $C_{15}H_{23}N$; C, 82.89; H, 10.67; N, 6.44. Found: C, 82.70; H, 10.66; N, 6.59.

Conversion of 32 to 9-Cyclohexyl-2,6-nonanedione (38). To a solution of 1.02 g (4.7 mmol) of compound **32,** 865 mg (18.8 mmol) of absolute ethanol, and 5.0 ml anhydrous ether in 50 ml of anhydrous liquid ammonia (freshly distilled from sodium) was slowly added 249 mg (10.8 mmol) of sodium metal. The solution was stirred for 15 min and the volatiles were evaporated under a stream of nitrogen. To the residue was added 10 ml of 10% H_2SO_4 and the solution was stirred for 15 min at room temperature. The reaction mixture was diluted with 10 ml of water and extracted with three 50-ml portions of ether. The organic layers were dried over anhydrous Na_2SO_4 and the solvent evaporated to yield 469 mg of a yellow oil. Chromatography of the oil on 50 g of silica gel using 10:1 benzene–ethyl acetate as eluent afforded 382 mg (34%) of diketone **38:** λ_{max} ($CHCl_3$) 1715 cm^{-1}; δ ($CDCl_3$) 1.0–2.6 ppm (m, cntaining s ca. 3 at δ 2.13).

Anal. Calcd for $C_{15}H_{26}O_2$: *m/e* 238.19328. Found: *m/e* 238.19320.

Neutralization of the acidic layer, extraction with chloroform, and drying (Na_2SO_4) afforded 660 mg of basic material.

Room Temperature Cyclization of Diketone 38. Formation of 3-(3-Cyclohexyl)propylcyclohex-2-en-1-one (50) and 2-(2-Cyclohexyl)methyl-3-methylcyclohex-2-en-1-one (51). To a solution of 251 mg (1.06 mmol) of diketone **38** in 4.2 ml of ethanol was added a solution of 106 mg (2.7 mmol) of sodium hydroxide in 2.1 ml of water. The solution was stirred at room temperature under nitrogen for 2.5 h. The solution was acidified with 10% aqueous HCl and stirred at room temperature for 15 min. The solution was extracted with three 50-ml portions of chloroform and the organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded 224 mg of a yellow oil. Chromatography of the oil on 25 g of silica gel using 10:1 benzene–ethyl acetate as eluent yielded 84 mg (36.4%) of 51 as an oil: λ_{max} ($CHCl_3$) 1656 cm^{-1}; δ ($CDCl_3$) 0.9–2.5 ppm (m, containing s ca. 3 at δ 1.93); 2,4-DNP mp 146–148 °C.

Anal. Calcd for $C_{15}H_{24}O$: *m/e* 220.18271. Found: *m/e* 220.18240.

Continued elution with the same solvent system gave cyclohexenone **50** (111 mg, 48.3%) as an oil: λ_{max} ($CHCl_3$) 1664 cm^{-1}; δ ($CDCl_3$) 1.0–2.5 (m, 23), 5.78 (s, 1); 2,4-DNP mp 140–141 °C.

Anal. Calcd for $C_{15}H_{24}O$: *m/e* 220.18271. Found: *m/e* 220.18239.

Preparation of 2-(Cyclohexyl)butyl-6-methylpyridine (33). To a solution of 15 ml of *n*-BuLi (1.6 M in hexane), maintained under a nitrogen atmosphere, was slowly added 2.3 g (0.0215 mol) of 2,6-lutidine in 2.5 ml of anhydrous ether. The mixture was stirred at reflux for 1 h. To this mixture was added 4.1 g (0.020 mmol) of 3-cyclohexylpropyl bromide in an equal volume of anhydrous ether. The solution was heated under reflux overnight. The solution was diluted with water and extracted with three 50-ml portions of ether. The organic layers were dried over anhydrous Na_2SO_4. Solvent removal afforded 5.77 g of a crude liquid. Vacuum distillation of the recovered liquid yielded 2.86 g (62%) of **33:** bp 107–108 °C (0.17 mm); λ_{max} ($CHCl_3$) 1580, 1597 cm^{-1}; δ ($CDCl_3$) 7.35–7.6 (m, 1), 6.87–7.0 (m, 2), 2.65–2.9 (m, 2), 2.52 (s, 3), 0.98–1.88 (m, 17).

Anal. Calcd for $C_{16}H_{25}N$: *m/e* 231.19869. Found: *m/e* 231.19814.

Conversion of 33 to 10-Cyclohexyl-2,6-decanedione (39). To a solution of 516 mg (2.2 mmol) of compound **33,** 405 mg (8.8 mmol) of absolute ethanol, and 3.0 ml of anhydrous ether in 30 ml of anhydrous liquid ammonia (freshly distilled from sodium) was slowly added 116 mg (5.04 mmol) of sodium metal. The solution was stirred for 15 min and the volatiles were evaporated under a stream of nitrogen. To the residue was added 10 ml of 10% H_2SO_4 and the solution was stirred for 15 min at room temperature. The reaction mixture was diluted with 10 ml of water and extracted with three 50-ml portions of ether. The organic layers were combined and dried over anhydrous Na_2SO_4. Solvent removal afforded 360 mg of crude diketone **39.** Chromatography of the oil on 30 g of silica gel using 10:1 benzene–ethyl acetate as eluent yielded 202 mg (36%) of crystalline diketone **39:** mp 43.0–44.5 °C; λ_{max} ($CHCl_3$) 1698 cm^{-1}; δ ($CDCl_3$) 1.0–2.6 ppm (m, containing s ca. 3 at δ 2.13).

Anal. Calcd for $C_{16}H_{28}O_2$: *m/e* 252.20893. Found: *m/e* 252.20908.

Neutralization of the acidic layer, extraction with chloroform, and drying (Na_2SO_4) afforded 190 mg of basic material.

Room Temperature Cyclization of Diketone 39. Formation of 3-(4-Cyclohexyl)butylcyclohex-2-en-1-one (52) and 2-(3-Cyclohexyl)propyl-3-methylcyclohex-2-en-1-one (53). To a solution of 115 mg (0.46 mmol) of diketone **39** in 1.8 ml of ethanol was added a solution prepared from 46 mg (1.15 mmol) of sodium hydroxide in 0.92 ml of water. The solution was stirred under nitrogen at room temperature for 2.5 h. The solution was then acidified with 10% aqueous HCl and extracted with chloroform. The organic layers were dried over anhydrous Na_2SO_4. Solvent evaporation yielded 108 mg of a yellow oil. Chromatography of the oil on 6 g of silicic acid using 30:1 benzene–ethyl acetate as eluent afforded 41.8 mg (40%) of **53** as an oil: λ_{max} ($CHCl_3$) 1664 cm^{-1}; δ ($CDCl_3$) 1.0–2.5 ppm (m, containing s ca. 3 at δ 1.93). 2,4 DNP mp 171–173 °C.

Anal. Calcd for $C_{16}H_{26}O$: *m/e* 234.19837. Found: *m/e* 234.19818.

Continued elution with the same solvent system gave cyclohexenone **52** (57.2 mg, 54%) as an oil: λ_{max} ($CHCl_3$) 1664 cm^{-1}; δ ($CDCl_3$) 1.0–2.5 (m, 25), 5.83 (s, 1). 2,4 DNP mp 118–121 °C.

Anal. Calcd for $C_{16}H_{26}O$: *m/e* 234.19837. Found: *m/e* 234.19819.

Preparation of 2-(5-Cyclohexyl)pentyl-6-methylpyridine (34). To a solution of 38 ml of *n*-BuLi (1.42 M in hexane), maintained under a nitrogen atmosphere, was slowly added 4.6 g (0.043 mol) of 2,6-lutidine in 5 ml of anhydrous ether. The mixture was stirred at reflux for 1 h. To this mixture was added over a 15-min period 9.4 g (0.043 mol) of cyclohexylbutyl bromide in an equal volume of anhydrous ether. The solution was refluxed overnight. The solution was diluted with water and extracted with three 100-ml portions of ether. The organic layers were combined and dried over anhydrous Na_2SO_4. Solvent evaporation yielded 15.17 g of a yellow oil. Vacuum distillation of the crude oil afforded 4.4 g of **34:** bp 120–123 °C (0.20 mm); 42% yield; λ_{max} ($CHCl_3$) 1583, 1596 cm^{-1}; δ ($CDCl_3$) 7.34–7.6 (m, 1), 6.87–7.0 (m, 2), 2.63–2.89 (m, 2), 2.53 (s, 3), 0.98–1.95 ppm (m, 19).

Anal. Calcd for $C_{17}H_{27}N$: *m/e* 245.21434. Found: *m/e* 245.21434.

Conversion of 34 to 11-Cyclohexyl-2,6-undecanedione (40). To a solution of 1.18 g (4.8 mmol) of compound **34,** 883 mg (19.2 mmol) of absolute ethanol, and 5.0 ml of anhydrous ether in 50 ml of anhy-

drous liquid ammonia (freshly distilled from sodium) was slowly added 254 mg (11 mmol) of sodium metal. The solution was stirred for 15 min and the volatiles were evaporated under a stream of nitrogen. To the residue was added 10 ml of 10% H_2SO_4 and the solution was stirred for 15 min at room temperature. The reaction mixture was diluted with 10 ml of water and extracted with three 50-ml portions of ether. The organic layers were combined and dried over anhydrous Na_2SO_4. Solvent removal yielded 615 mg of a yellow oil. Chromatography of the oil on 60 g of silica gel using 10:1 benzene–ethyl acetate as eluent afforded 565 mg (44%) of diketone **40**: λ_{max} ($CHCl_3$) 1704 cm^{-1}; δ ($CDCl_3$) 1.0–2.6 ppm (m, containing s ca. 3 at δ 2.12); *m/e* 266 (P).

Room Temperature Cyclization of Diketone 40. Formation of 3-(5-Cyclohexyl)pentylcyclohex-2-en-1-one (54) and 2-(4-Cyclohexyl)butyl-3-methylcyclohex-2-en-1-one (55). To a solution of 90 mg (0.34 mmol) of diketone **40** in 1.4 ml of ethanol was added a solution of 33.8 mg (0.85 mmol) of sodium hydroxide in 0.71 ml of water. The solution was stirred at room temperature under nitrogen for 2.5 h. The solution was then acidified with 10% aqueous HCl and extracted with three 30-ml portions of chloroform. The organic layers were dried over anhydrous Na_2SO_4. Solvent evaporation afforded 80 mg of a yellow oil. Chromatography of the oil on 19 g of silica gel using 30:1 benzene–ethyl acetate as eluent afforded 37.7 mg (45%) of cyclohexenone **55** as an oil: λ_{max} ($CHCl_3$) 1664 cm^{-1}; δ ($CDCl_3$) 0.9–2.5 ppm (m, containing s ca. 3 at δ 1.93); 2,4-DNP mp 136–137 °C.

Anal. Calcd for $C_{17}H_{28}O$: *m/e* 248.21402. Found: *m/e* 248.21145.

Continued elution with the same solvent system gave **54** (42.2 mg, 51%) as an oil: λ_{max} ($CHCl_3$) 1667 cm^{-1}; δ ($CDCl_3$) 1.0–2.5 (m, 27), 5.87 ppm (s, 1); 2,4-DNP mp 131–133 °C.

Anal. Calcd for $C_{17}H_{28}O$: *m/e* 248.21402. Found: *m/e* 248.21400.

Preparation of 2-Methyl-5-*n*-butylfuran (43).[22] To 59 ml of 1.6 M *n*-BuLi (0.095 mmol) cooled to −20 °C and under a nitrogen atmosphere was slowly added a solution of 7.7 g (0.094 mmol) of 2-methylfuran dissolved in 10 ml of THF. The mixture was stirred at −20 °C for 1.5 h. To this was added slowly a solution of 13.1 g (0.096 mmol) of *n*-butyl bromide in 10 ml of THF. Stirring was continued at −20 °C for 1 h and the solution was warmed to room temperature and allowed to stir overnight. The reaction mixture was poured over ice and thoroughly extracted with chloroform. The organic layers were combined and dried over anhydrous Na_2SO_4 and the solvent removed to afford 6 g (47%) of a crude **43** which was used as such in the next experiment without further purification: λ_{max} ($CHCl_3$) 2895, 1575, 1462 cm^{-1}; δ ($CDCl_3$) 5.77 (s, 2), 2.7–2.43 (t, 2), 2.23 (s, 3), 1.7–0.9 (m, 7).

Preparation of 2,5-Nonanedione (44). Glacial acetic acid (3 ml), water (1 ml), 20% H_2SO_4 (4 drops), and 2.1 g (15.2 mmol) of crude 2-methyl-5-*n*-butylfuran were combined and heated under reflux for 4 h. The resulting solution was poured into water and extracted with chloroform. The organic layers were combined and dried over Na_2SO_4. Solvent evaporation afforded 2 g of a crude product which was distilled to yield 1.5 g (63%) of the desired diketone **44**: bp 110–115 °C (15 mm); λ_{max} ($CHCl_3$) 2941, 1725, 1488 cm^{-1}; δ ($CDCl_3$) 2.75 (s, 4), 2.6–2.3 (t, 2), 2.2 (s, 3), 1.7–0.9 (m, 7).

Room Temperature Cyclization of Diketone 44.[22] Formation of 2-Propyl-3-methylcyclopent-2-en-1-one (45). To 200 mg (1.28 mmol) of diketone **44** was added 2.56 ml of 5% NaOH (3.2 mmol) and 5.1 ml of EtOH. The solution was stirred at room temperature under nitrogen for 20 h. After neutralization with 10% HCl the solution was extracted with three 20-ml portions of $CHCl_3$. The combined organic layers were dried over Na_2SO_4. Solvent removal afforded 150 mg (85%) of a product whose NMR revealed the presence of cyclopentenone **45**:[22] λ_{max} ($CHCl_3$) 1692, 1645, 2743 cm^{-1}; δ ($CDCl_3$) 2.6–2.1 (m, containing s ca. 3 at δ 2.1), 1.7–0.9 ppm (m, 5).

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Registry No.—**14**, 39557-21-6; **15**, 13679-29-3; **21**, 38275-04-6; **22**, 1122-20-9; **23**, 17299-34-2; **28**, 60439-17-0; **29**, 5394-28-5; **30**, 60439-18-1; **31**, 60439-19-2; **32**, 60439-20-5; **33**, 60439-21-6; **34**, 60439-22-7; **35**, 30963-76-9; **36**, 60439-23-8; **37**, 60439-24-9; **38**, 60439-25-0; **39**, 60439-26-1; **40**, 60439-27-2; **41**, 6301-50-4; **43'**, 60439-28-3; **43'** 2,4-DNP, 60439-29-4; **43**, 3857-27-0; **44**, 25234-82-6; **45**, 50397-91-6; **46**, 60439-30-7; **46** 2,4-DNP, 60439-01-2; **48**, 60439-02-3; **48** 2,4-DNP, 60439-03-4; **49**, 60439-04-5; **50**, 60439-05-6; **50** 2,4-DNP, 60439-06-7; **51**, 60439-07-8; **51** 2,4-DNP, 60439-08-9; **52**, 60439-09-0; **52** 2,4-DNP, 60439-10-3; **53**, 60439-11-4; **53** 2,4-DNP, 60439-12-5; **54**, 60439-13-6; **54** 2,4-DNP, 60439-14-7; **55**, 60439-15-8; **55** 2,4-DNP, 60464-14-4; 2,6-lutidine, 108-48-5; isopropyl iodide, 75-30-9; butyl bromide, 109-65-9; 2-methyl-6-ethylpyridine, 1122-69-6; cyclohexyl bromide, 108-85-0; cyclohexylmethyl bromide, 2550-36-9; 2-cyclohexylethyl bromide, 1647-26-3; 3-cyclohexylpropyl bromide, 34094-21-8; cyclohexylbutyl bromide, 60439-16-9; 2-methylfuran, 534-22-5.

References and Notes

(1) S. Danishefsky and P. Cain, *J. Am. Chem. Soc.*, **97**, 5282 (1975).
(2) S. Danishefsky, P. Cain, and A. Nagel, *J. Am. Chem. Soc.*, **97**, 380 (1975).
(3) S. Danishefsky and A. Nagle, *J. Chem. Soc., Chem. Commun.*, 373 (1972).
(4) S. Danishefsky and R. Cavanaugh, *J. Am. Chem. Soc.*, **90**, 2806 (1968).
(5) For a review see T. L. Ho, *Synth. Commun.*, **4**, 265 (1974).
(6) W. S. Johnson, M. F. Semmelhack, M. U. S. Sultanbawa, and L. A. Dolak, *J. Am. Chem. Soc.*, **90**, 2994 (1968).
(7) For purposes of this subject, a relevant example is one in which there are no substituents on the three carbons between the two carbonyl groups and in which the R group is not such as to strongly bias the enolization of the proximate ketone. An interesting case in this regard was recently reported by Rouessac. The significance of the branching effect outlined in this paper is nicely illustrated in the system 8-methylnon-8-ene-2,6-dione. Even though the acidity factor must strongly favor formation of the tetrasubstituted isomer, the ratio is in fact close to unity; see C. Alexander and F. Rouessac, *J. Chem. Soc., Chem. Commun.*, 275 (1975).
(8) G. Stork and R. Borch, *J. Am. Chem. Soc.*, **86**, 935 (1964).
(9) S. Danishefsky, A. Nagel, and D. Peterson, *J. Chem. Soc., Chem. Commun.*, *374* (1972). In this paper the ratio of product formation of compounds XI:XII was inadvertently reversed by the journal personnel in preparing the manuscript for publication.
(10) R. N. Lacey, *J. Chem. Soc.*, 1639 (1960).
(11) R. K. Singh and P. M. McCurry, *J. Org. Chem.*, **39**, 2317 (1974).
(12) For a mechanistic study of aldolization of 1,4 diketones see R. K. Singh and P. M. McCurry, *J. Org. Chem.*, **39**, 2316 (1974).
(13) For reduction of pyridines by metal–ammonia see A. J. Birch, *J. Chem. Soc.*, 1270 (1947).
(14) Under more drastic acidic hydrolytic conditions, Birch[13] had gone directly from dihydropyridines to cyclohexenones.
(15) Loss of the ketal in these cases could be followed by multiple cyclization pathways of the triketo system.
(16) Melting and boiling points are uncorrected. Infrared spectra were measured on a Perkin-Elmer 137 Infracrod spectrophotometer. NMR spectra were obtained from either a Varian Associates T-60 or A-60D spectrometer. Data are reported in δ parts per million from an internal tetramethylsilane reference. Low-resolution mass spectra were measured on an LKB-9000 system by direct insertion. High-resolution spectra were obtained on a Varian Associates CH-5 system. Microanalyses were performed by the Galbraith Laboratories, Knoxville, Tenn.
(17) This yield is based on alkylating agent rather than lutidine.
(18) A. Downes, N. Gill, and F. Lions, *J. Am. Chem. Soc.*, **72**, 3464 (1950).
(19) A. Edgar, S. Harper, and M. Kazi, *J. Org. Chem.*, **22**, 1083 (1957).
(20) E. Adlerova, L. Novak, and M. Protiva, *Chem. Listy*, **51**, 553 (1957).
(21) R. Lukes and A. Fabryova, *Collect Czech. Chem. Commun.*, **25**, 1618 (1960).
(22) For an alternative preparation see R. K. Singh, Thesis, Carnegie-Mellon University, 1974.

Direct Methods for α-Methylene Lactone Synthesis Using Itaconic Acid Derivatives

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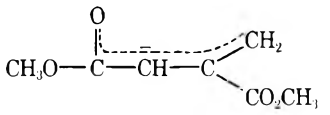
Anions of itaconic acid derivatives [$RO_2C\bar{C}HC(=CH_2)CO_2$] are versatile intermediates for the synthesis of α-methylene lactones. The addition of these anionic species to aldehydes or ketones and subsequent lactonization and hydrolysis have been utilized for the synthesis of a variety of compounds including protolichesterinic acid, nephrosterinic acid, and canadensolide.

α-Methylene lactones have recently attracted much synthetic effort[1] owing to the isolation of several cytotoxic and/or antitumor agents that possess this characteristic system.[2] Although several direct procedures have been developed for the synthesis of α-methylene lactones, the current methodology rests primarily upon techniques for the introduction and subsequent elimination of a heteroatom attached to the β carbon.[1]

Structural analysis of several naturally occurring β-carboxy-α-methylene lactones such as protolichesterinic acid,[3] nephrosterinic acid,[4] and canadensolide[5] suggested that these compounds could be obtained by the addition of an itaconic acid derivative to an aldehyde[6] (Scheme I). This synthesis would offer the advantages of broad scope and the ready availability of starting materials.[7]

Results and Discussion

Stable enolate anions could not be generated from dimethyl itaconate (1, $R_1 = R_2 = CH_3$) even at reduced temperatures (−78 °C).[8] The polymeric products that resulted from such attempts appeared to be derived from a Claisen condensation of the desired anion with the carboxymethyl not directly involved in the resonance stabilized system. Therefore, in order to avoid nucleophilic addition to the affected carbonyl carbon a carboxylate anion was used as a convenient protecting group (1, $R_2 = Li$).[9]



Attempts to generate the trianion of itaconic acid (1, $R_1 = R_2 = Li$) and to add it to carbonyl compounds were only moderately successful. Thus, treatment of itaconic acid with 3 equiv of lithium diisopropylamide[10] (LDA) at −78 °C in tetrahydrofuran (THF) followed by the addition of 1 equiv of aldehyde or ketone gave, upon acidification, low yields (~30%) of the desired α-methylene lactone 2 ($R_1 = H$).[11] The use of higher reaction temperatures and/or hexamethylphosphoramide (HMPA) decreased the yield of 2.

In contrast, the dianions derived from monoesters of itaconic acid 1 ($R_1 = CH_3$, $ArCH_2$; $R_2 = Li$) were generated and observed to be viable nucleophiles in addition reactions to both aldehydes and ketones (Table I). For example, treatment of methyl itaconate (prepared by the addition of methanol to itaconic anhydride[7,12]) with 2 equiv of LDA[10] gave the dianion which upon addition to cyclohexanone and acid-catalyzed cyclization provided a 71% yield of the desired α-methylene lactone 2 [$R_1 = CH_3$; $R_3R_4 = (-CH_2-)_5$]. However, the use of methyl itaconate in the synthesis of protolichesterinic acid and its carboxy analogues 3 was precluded by the inability to hydrolyze the methyl ester without isomerization to the butenolide (Scheme II).

The problem of selective hydrolysis vs. isomerization in this overall scheme was overcome by utilizing the dianion of *p*-methoxybenzyl itaconate (1, $R_1 = ArCH_2$; $R_2 = Li$).[13] Hydrolysis of the ester without concurrent isomerization was then effected with trifluoroacetic acid. The overall sequence of addition, cyclization, and hydrolysis successfully generated a number of α-methylenebutyrolactones 3, including protolichesterinic and nephrosterinic acids (Table I).

Scheme I

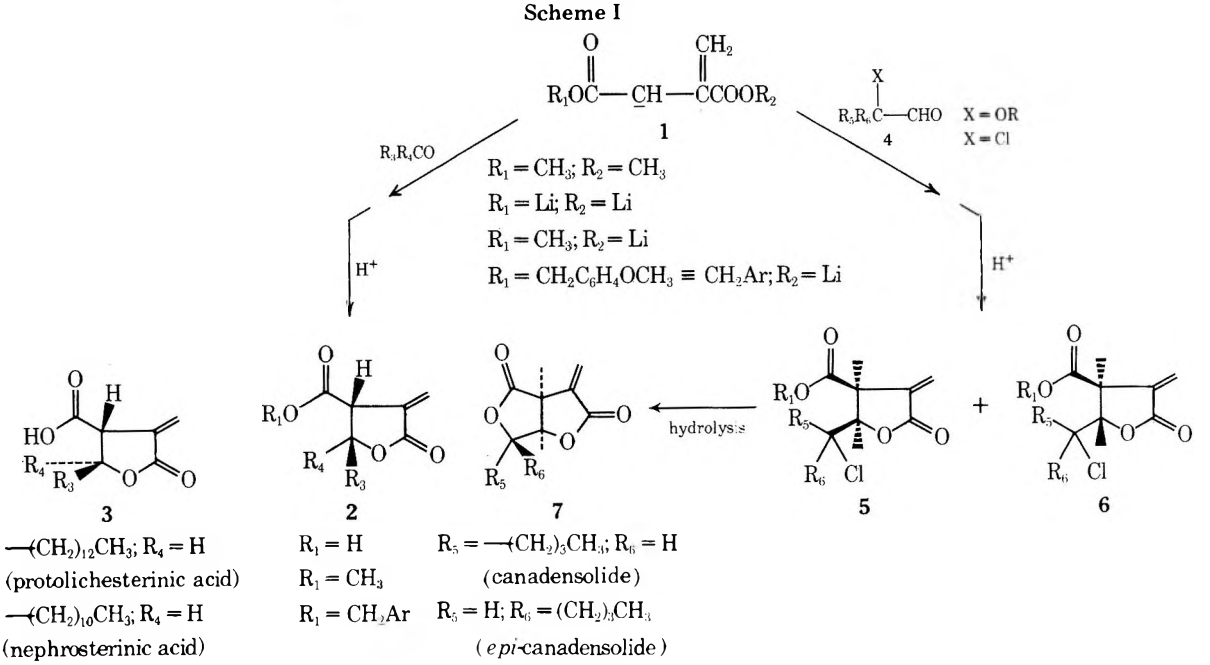
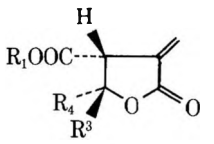


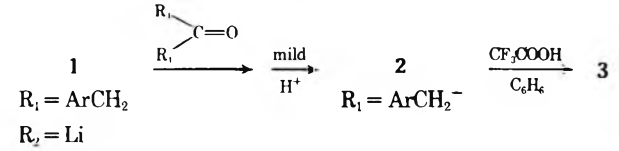
Table I.[a] Compounds Prepared from Monoesters of Itaconic Acid



2 and 3

Compd (registry no.)	R_1	R_4	R_3	% yield	Mp, °C	NMR, δ
2a (60427-56-7)	p-$CH_3OC_6H_4CH_2$	CH_3	CH_3	78[a]	54.5–55.5[b]	1.22 (3 H, s), 1.55 (3 H, s), 3.72 (1 H, t), 3.81 (3 H, s), 5.19 (2 H, s), 5.85 (1 H, d, J = 2.5 Hz), 6.48 (1 H, d, J = 2.5 Hz), 6.95 (2 H, m), 7.32 (2 H, m)[c]
3a (60427-57-8)	H	CH_3	CH_3	69[a]	150–151.8[b]	1.37 (3 H, s), 1.55 (3 H, s), 3.85 (1 H, t), 5.90 (1 h, d, J = 2.2 Hz), 6.05 (1 H, broad), 6.30 (1 H, d, J = 2.8 Hz)[d]
2b (60427-58-9)	p-$CH_3OC_6H_4CH_2$	$-CH_2CH_2CH_2CH_2-$		73[a]	*e*	1.7 (8 H, m), 3.78 (3 H, s), 3.90 (1 H, t), 5.12 (2 H, s), 5.75 (1 H, d, J = 2.2 Hz), 6.32 (1 H, d, J = 2.8 Hz), 6.9 (2 H, m), 7.3 (2 H, m)[c]
3b (60427-59-0)	H	$-CH_2CH_2CH_2CH_2-$		54[a]	107–109[b]	1.9 (8 H, m), 3.92 (1 H, t), 5.90 (1 H, d, J = 2.2 Hz), 6.47 (1 H, d, J = 2.5 Hz), 8.5 (1 H, s)[c]
2c (60427-60-3)	p-$CH_3OC_6H_4CH_2$	CH_3CH_2	CH_3CH_2	30[a]	*e*	0.9 (6 H, m), 1.7 (4 H, m), 3.8 (2 H, s), 3.8 (1 H, m), 5.15 (2 H, s), 5.8 (1 H, d, J = 2.5 Hz), 6.4 (1 H, d, J = 2.5 Hz), 6.9 (2 H, m), 7.28 (2 H, m)[c]
3c (60427-61-4)	H	CH_3CH_2	CH_3CH_2	17[a]	74–75[b]	1.0 (6 H, m), 1.85 (4 H, m), 3.9 (1 H, t), 5.95 (1 H, d, J = 2.5 Hz), 6.52 (1 H, d, J = 2.5 Hz), 8.5 (1 H, s)[c]
2d (60427-62-5)	p-$CH_3OC_6H_4CH_2$	H	$CH_3(CH_2)_{12}$	25[f]	53.5–54.5[b]	0.91 (3 H, t), 1.28 (24 H, m), 3.65 (1 H, m), 3.90 (3 H, s), 4.83 (1 H, m), 5.28 (2 H, s), 5.98 (1 H, d, J = 2.1 Hz), 6.50 (1 H, d, J = 2.5 Hz), 7.1 (2 H, m), 7.4 (2 H, m)[c]
2e (60427-63-6)	p-$CH_3OC_6H_4CH_2$	$CH_3(CH_2)_{12}$	H	16[f]	38–39.5[b]	0.89 (3 H, t), 1.25 (24 H, m), 3.9 (3 H, s), 4.08 (1 H, d, t, J = 8 and 1 Hz), 4.7 (1 H, m), 5.25 (2 H, s), 5.9 (1 H, d, J = 2 Hz), 6.5 (1 H, d, J = 2 Hz), 7.08 (2 H, m), 7.4 (2 H, m)[c]
3d (51260-32-3)	H	H	$CH_3(CH_2)_{12}$	20[g]	91–92[b]	0.9 (3 H, t), 1.3 (24 H, m), 3.7 (1 H, m), 4.85 (1 H, m), 6.1 (1 H, d, J = 2.1 Hz), 6.55 (1 H, d, J = 2.8 Hz), 8.3 (1 H, s)[c]
3e (60478-54-8)	H	$CH_3(CH_2)_{12}$	H	13[g]	87–88[b]	0.9 (3 H, t), 1.25 (24 H, m), 4.08 (1 H, d, t, J = 7.6 and 2 Hz), 4.7 (1 H, m), 6.0 (1 H, d, J = 2 Hz), 6.55 (1 H, d, J = 2 Hz), 9.75 (1 H, s)[c]
2f (60427-64-7)	p-$CH_3OC_6H_4CH_2$	H	$CH_3(CH_2)_{10}$	13[f]	46.8–47[b]	0.88 (3 H, t), 1.25 (20 H, m), 3.58 (1 H, m), 3.8 (3 H, s), 4.75 (1 H, m), 5.13 (2 H, s), 6.83 (1 H, d, J = 2.3 Hz), 6.37 (1 H, d, J = 3 Hz), 6.9 (2 H, m), 7.3 (2 H, m)[c]
2g (60427-65-8)	p-$CH_3OC_6H_4CH_2$	$CH_3(CH_2)_{10}$	H	13[f]	34–35[b]	0.89 (3 H, t), 1.23 (20 H, m), 3.8 (3 H, s), 3.95 (1 H, d, t, J = 7.6 and 2 Hz), 4.55 (1 H, m), 5.12 (2 H, s), 5.78 (1 H, d, J = 2.1 Hz), 6.38 (1 H, d, J = 2.5 Hz), 6.9 (2 H, m), 7.2 (2 H, m)[c]
3f (60427-66-9)	H	H	$CH_3(CH_2)_{10}$	11[g]	83.5–84.5[b]	0.88 (3 H, t), 1.28 (20 H, m), 3.65 (1 H, m), 4.8 (1 H, m), 6.0 (1 H, d, J = 2.7 Hz), 6.49 (1 H, d, J = 2.8 Hz), 9.5 (1 H, s)[c]
3g (60427-10-0)	H	$CH_3(CH_2)_{10}$	H	5[g]	81.5–82.5[b]	0.9 (3 H, t), 1.28 (20 H, m), 4.05 (1 H, d, t, J = 8 and 2.1 Hz), 4.65 (1 H, m), 5.92 (1 H, d, J = 1.9 Hz), 6.5 (1 H, d, J = 2.1 Hz), 9.3 (1 H, s)[c]
2h (60427-67-0)	CH_3	$-CH_2CH_2CH_2CH_2CH_2-$		71[a]	63–65[b]	1.6 (10 H, m), 3.62 (1 H, t, J = 2.1 Hz), 3.88 (3 H, s), 5.86 (1 H, d, J = 2.8 Hz), 6.58 (1 H, d, J = 2.5 Hz)[c]

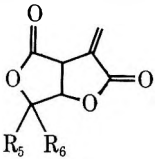
[a] Initial yield based on itaconic acid ester; >90% pure by NMR and/or HPLC. [b] A satisfactory elemental analysis (±0.3%) was obtained for this compound. [c] Solvent: $CDCl_3$. [d] Solvent: acetone-d_6. [e] This compound gave satisfactory mass spectral analysis. [f] Yield of single diastereomer, based on itaconic ester, after separation and purification by HPLC. [g] Yield based on itaconic acid ester; includes separation of intermediate ester diastereomers by HPLC and subsequent hydrolysis. [h] Lit.[3a] mp of (±)-protolichesterinic acid is 92–93.5 °C. [i] (±)-Alloprotolichesterinic acid.[3a,16] [j] "(±)-*trans*-Nephrosterinic acid".[4,16] [k] "(±)-*cis*-Nephrosterinic acid".[4,16]



The synthesis of canadensolide and related bislactones **7** (Table III) could be visualized as emanating from the previously developed synthetic sequence by the use of aldehydes **4** possessing an α-hydroxyl equivalent (Scheme I).

Symmetrically substituted α-chloro aldehydes were found

Table II. Physical Properties of Compounds Prepared from Symmetrical α-Chloro Aldehydes and Methyl Itaconate

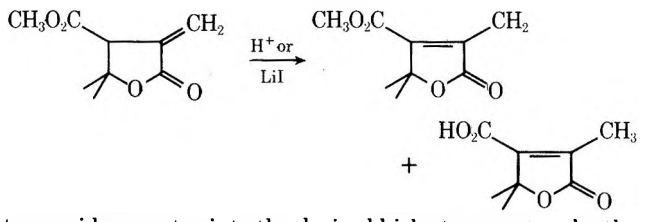


7

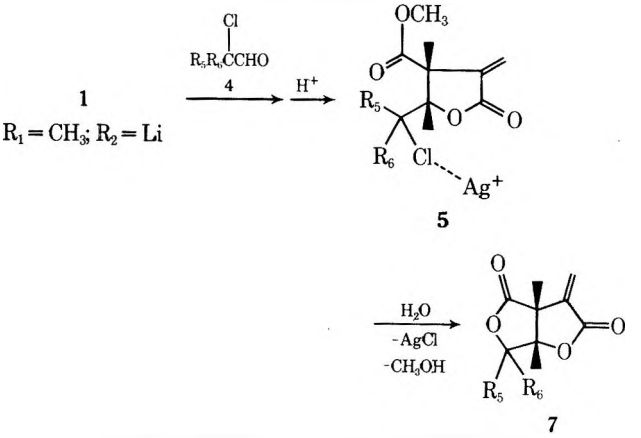
Compd (registry no.)	R_5	R_6	Mp, °C	NMR, δ ($CDCl_3$)
7a (60451-45-8)	$-CH_2CH_2CH_2CH_2CH_2-$		174–175[a]	1.7 (m, 10 H), 4.2 (d, t, 1 H, J = 7, 2 Hz), 5.0 (d, 1 H, J = 7 Hz), 6.4 (d, 1 H, J = 2 Hz), 6.7 (d, 1 H, J = 2 Hz)
7b (60427-68-1)	$-CH_2CH_2CH_2CH_2CH_2CH_2-$		148–151[a]	1.7 (m, 12H), 4.25 (d, t, 1 H, J = 7, 2 Hz), 5.0 (d. 1 H, J = 7 Hz), 6.3 (d, 1 H, J = 2 Hz), 6.65 (d, 1 H, J = 2 Hz)
7c (60427-69-2)	$CH_3CH_2CH_2$	$CH_3CH_2CH_2$	80.5–82[a]	1.0 (t, 3 H), 1.6 (m, 8 H), 4.15 (d, t, 1 H, J = 7, 2 Hz), 5 (d, 1 H, J = 7 Hz), 6.35 (d, 1 H, J = 2 Hz), 6.65 (d, 1 H, J = 2 Hz)

[a] A satisfactory elemental analysis (±0.3%) was obtained for this compound.

Scheme II



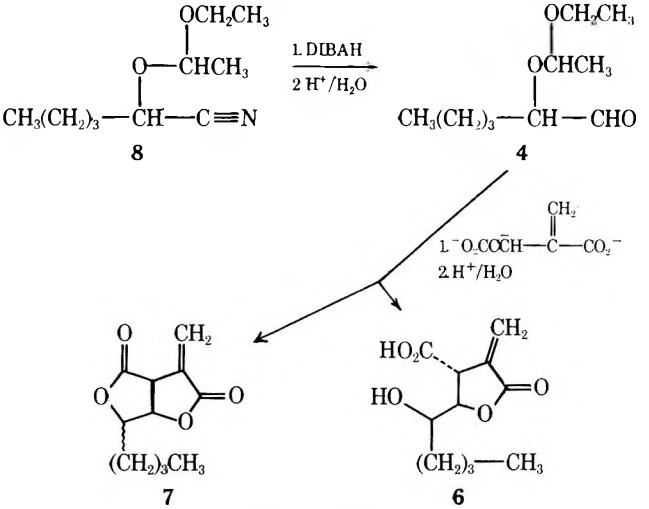
Scheme III



to provide an entry into the desired bislactone system by the addition of methyl itaconate dianion, the formation of the cis chloro lactone **5** (contaminated with 0–20% of the trans lactone **6**) by treatment with acid, and the generation of the bislactone by the silver ion promoted solvolysis of the tertiary halide (Scheme III, Table II).

However, the synthesis of canadensolide itself from α-chlorovaleraldehyde could not be accomplished utilizing this procedure since the requisite cis chloro lactone **5** was not formed during the initial addition step.

The successful synthesis of canadensolide involved the addition of the itaconic acid trianion (**1**, $R_1 = R_2 = Li$)[14] to α-hydroxyvaleraldehyde protected as the ethoxyethyl ether [**4**, $R_5 = CH_3(CH_2)_3$; $R_6 = H$; $X = OCH(OCH_2CH_3)CH_3$]. Moreover, the ease of isolation of the canadensolide isomers by the extraction of the uncyclized acidic products **6** ($R_1 = H$) from the itaconic acid trianion addition provided significant consolation for the relatively low yields. Separation of the isomers by liquid chromatography (HPLC) gave pure samples of canadensolide and *epi*-canadensolide.



Experimental Section

General. Melting points (uncorrected) were obtained on a Thomas-Hoover capillary apparatus. Infrared spectra were recorded on a Beckman IR-33. NMR spectra were obtained with a Varian EM-360 instrument using Me_4Si as an internal standard. Preparative liquid chromatography (HPLC) was carried out on Waters Associates equipment using two 610 × 9.5 mm columns packed with Porasil A. In most cases ether–hexane mixtures were used at a flow rate of 9.9 ml/min.

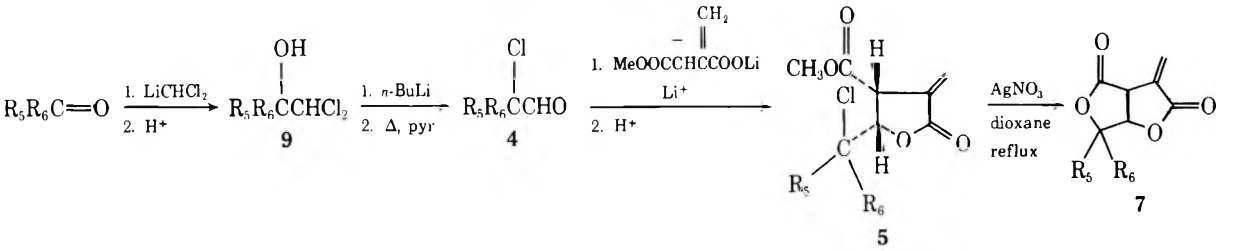
The THF (Aldrich Gold Label, <0.003% H_2O) was maintained under N_2 in septum-capped bottles and removed via syringe. The *n*-butyllithium and the diisobutylaluminum hydride (DIBAH) in hexane were obtained from Alfa Products. The diisopropylamine was distilled from CaH_2 and stored under N_2. The itaconic acid was obtained from Aldrich. The methyl itaconate was prepared by literature methods.[12]

All reactions involving organometallic reagents were carried out under N_2 in septum-capped flasks with introduction of reagents via syringe.

Elemental analyses were performed by Robertson Laboratories, Florham Park, N.J. Mass spectra were run on a Varian CH5 by Mr. Douglas Kuehl, National Water Quality Laboratory, Duluth, Minn.

General Procedure for the Preparation and Addition Reactions of Dianions of Monoesters of Itaconic Acid. The preparation of protolichesterinic acid (**3d**) using *p*-methoxybenzyl itaconate provides a typical example of the experimental procedure for the compounds listed in Table I. LDA[10] was prepared from *n*-butyllithium (4.2 ml of a 2.4 M solution in hexane, 0.010 mol) and diisopropylamine (1.4 ml, 0.010 mol) in 25 ml of THF contained in a septum-capped flask with nitrogen atmosphere at −10 °C. After stirring for 15 min the solution was cooled to −78 °C and *p*-methoxybenzyl itaconate[13] (1.25 g, 0.0050 mol) dissolved in 3 ml of THF was added. After 1.5 h tetradecylaldehyde (1.06 g, 0.0050 mol) in 3 ml of THF was added and the resulting mixture stirred for 7 h at −78 °C before quenching at this temperature with 25 ml of cold 6 M H_2SO_4. Immediate extraction with ether followed by overnight treatment with $MgSO_4$ afforded 2.05 g of a 3:1 mixture (by NMR) of the desired diastereomeric lactones (**2**) and *p*-methoxybenzyl itaconate. After removal of the starting material with a saturated $NaHCO_3$ wash, 1.4 g (64%) of an approximately 1:1 mixture of the two diastereomers remained. Separation of 1.0 g of this mixture by HPLC[15] gave 0.39 g

Table III. Preparation of Bislactones 7. Yield Data



9 4 5 7

	R_5	R_6	9[e]	4[e]	5[e]	7	Overall yield, %
a	$-CH_2CH_2CH_2CH_2CH_2-$		56% (52183-64-9) bp 55–56 °C (0.2 mm)	70% (53627-10-4) bp 56–60 °C[b] (5.5 mm)	65%[c] (60427-72-7)	31%	8
b	$-CH_2CH_2CH_2CH_2CH_2CH_2-$		74% (52183-65-0) bp 75 °C (0.3 mm)	76% (60464-11-1) bp 55–57 °C (1.4 mm)	29% (60427-73-8)	65%	11
c	$CH_3CH_2CH_2$	$CH_3CH_2CH_2$	49% (60427-70-5) bp 65–68 °C (1.3 mm)	64%[d] (60427-71-6) bp 38–42 °C (1.8 mm)	69%[c] (60427-74-9)	48%	10

[a] Yields represent material of 95% purity (by NMR) unless stated otherwise. [b] Lit. bp 47–50 °C (6 mm): G. Stork et al., *J. Am. Chem. Soc.*, 82, 4315 (1960). [c] 60–75% pure. [d] 90% pure. [e] Registry no. in parentheses.

(25% overall) of the *p*-methoxybenzyl ester of protolichesterinic acid[16] (**2d**) and 0.26 g (16% overall) of the *p*-methoxybenzyl ester of alloprotolichesterinic acid[16] (**2e**).

The *p*-methoxybenzyl ester of protolichesterinic acid (**2d**) (0.159 g, 0.357 mmol) and trifluoroacetic acid[17] (0.05 ml, 0.714 mmol) in 2 ml of benzene were stirred for 7 h at 25 °C. The reaction mixture was then extracted with a saturated $NaHCO_3$ solution. The combined aqueous extracts were washed with ether, acidified to ~pH 1 with 6 M H_2SO_4, and extracted with ether to give 0.093 g (80%) of (±)-protolichesterinic acid (**3d**).[3]

General Procedure for the Preparation of the Bislactones (7, R_5 = R_6 = Alkyl). The general procedure for the preparation of the bislactones shown in Table II is illustrated below for the case of the lactone **7b** [R_5, R_6 = $(CH_2)_6$]. In all cases, the intermediates in the reaction sequence were not isolated in an analytically pure form, but rather, they were used in the subsequent step with little or no purification (see Table III).

Modified literature methods were used to prepare the α-chloro aldehyde.[18] Dichloromethane (11.6 ml, 0.18 mol) was dissolved in 300 ml of dry THF at −78 °C under N_2. *n*-Butyllithium (62.5 ml, 0.15 mol of a 2.4 M solution in hexane) was added dropwise from an addition funnel over a 1-h period. After the resulting solution had stirred for 40 min at −78 °C, cycloheptanone (16.3 ml, 0.138 mol) was added over a 5-min period. The reaction mixture was stirred for 2 h at −78 °C and then was allowed to gradually warm to −35 °C before it was poured into a cold solution of 15 ml of sulfuric acid in 600 ml of water. The resulting mixture was immediately extracted with 1 l. of ether in three portions. The combined ether extracts were dried over $MgSO_4$ and evaporated to yield 33 g of oil. Distillation afforded **9b** [20 g, 74%, bp 75–79 °C (0.3 mm); NMR ($CDCl_3$) δ 1.4–2.2 (broad multiplet, 12 H), 2.3 (s, 1 H), 5.7 (s, 1 H)]. A portion of the alcohol (**9b**) (14.5 g, 0.0738 mol) was dissolved in 180 ml of THF at −78 °C under N_2 and *n*-butyllithium (29.5 ml, 0.0738 mol of a 2.5 M solution in hexane) was added dropwise. After stirring for 20 min at −78 °C, 0.06 ml (0.74 mmol) of pyridine was added and the solution was gradually warmed to reflux and maintained at reflux for 18 h. The mixture was cooled, filtered, diluted with 200 ml of water, and extracted three times with 250-ml portions of ether. The combined ether extracts were dried over $MgSO_4$ and evaporated to give 12.6 g of crude α-chloro aldehyde which was distilled to provide a colorless liquid **4b** [bp 55–57 °C (1.4 mm), 9.03 g, 76% based on alcohol or 56% based on cycloheptane].

The addition of methyl itaconate to the α-chloro aldehyde **4b** was carried out as described below. Diisopropylamine (4.61 ml, 0.0329 mol) was dissolved in 125 ml of dry THF under N_2 at −10 °C and *n*-butyllithium (13.2 ml, 0.0329 mol of a 2.5 M solution in hexane) was added dropwise. After stirring for 15 min at −10 °C, the solution was cooled to −78 °C in a dry ice–acetone bath and 2.37 g (0.016 mol) of methyl itaconate[12] dissolved in 6 ml of THF was added slowly. After stirring for 2 h at −78 °C, 2.6 g (0.016 mol) of the α-chloro aldehyde **4b** in 2 ml of THF was added. After stirring for an additional 4.5 h at −78 °C, the reaction mixture was quenched at this temperature with 100 ml of 6 M H_2SO_4. The dry ice–acetone bath was removed, and after stirring for 5 min the mixture was extracted with 650 ml of ether in three portions. The combined ether extracts were dried overnight with $MgSO_4$. Evaporation of the solvent gave 5.5 g of an oil which contained the addition product, the starting aldehyde, and methyl itaconate (by NMR). This mixture was dissolved in ether and washed with saturated $NaHCO_3$ solution. After drying over $MgSO_4$, the organic layer was slowly evaporated to yield a solid which was purified by hexane trituration. The yield of solid amounted to 1.36 g (29%) and gave an NMR spectrum consistent with structure **5b**: NMR ($CDCl_3$) δ 1.65 (m, 8 H), 2.25 (m, 4 H), 3.85 (s, 3 H), 4.25 (d, t, J = 8, 2 Hz, 1 H), 4.8 (d, J = 7 Hz, 1 H), 5.95 (d, J = 2 Hz, 1 H), 6.6 (d, J = 2 Hz, 1 H).

Closure to the bislactone **7b** was effected with silver nitrate. Silver nitrate (0.8 g, 0.0047 mol) was dissolved in 12 ml of water and 20 ml of dioxane and heated to reflux. The product **5b** (0.67 g, 0.00235 mol) dissolved in 5 ml of dioxane was then added and the resulting mixture was maintained at reflux for 15 min. After cooling, the mixture was filtered and concentrated on a rotary evaporator. The residue was diluted with water and extracted three times with methylene chloride. The combined organic extracts were washed twice with brine and dried over $MgSO_4$. Evaporation gave 0.49 g (88%) of white solid of mp 142–146 °C (>85% pure by NMR). Recrystallization from THF gave analytically pure **7b** (0.362 g, 65%, mp 148–151 °C).

Preparation of Canadensolide. To the ethyl vinyl ether adduct[19] of valeraldehyde cyanohydrin[20,21] (8) (18.3 g, 0.099 ml), dissolved in 100 ml of hexane at −78 °C under nitrogen, was added 108 ml (0.105 mol) of a 0.97 M solution of DIBAH in hexane over a period of 40 min. After stirring for an additional 30 min, the reaction mixture was poured into 690 ml (6.9 mol) of 10 M acetic acid cooled to 0 °C. The resulting mixture, after stirring for 30 min at 0 °C, was extracted three times with hexane (1250 ml total). The combined extracts were diluted with 200 ml of a saturated sodium bicarbonate solution and solid sodium bicarbonate was added to the resulting mixture until carbon dioxide ceased to be liberated. The organic layer was separated, washed one time with 200 ml of saturated sodium bicarbonate solution, and dried over $MgSO_4$. The crude yield of product, which amounted to 12.2 g (66%), was shown by NMR to be 75–83% pure. Distillation afforded analytically pure aldehyde 4 [R_5 = $CH_3(CH_2)_3$; R_6 = H; X = $OCH(OCH_2CH_3)CH_3$;[22,23] 8.7 g, 47% yield, bp 46 °C (0.8 mm); NMR ($CDCl_3$) δ 0.8–2.0 (m, 15 H), 3.4–4.2 (m, 3 H), 4.8 (m, 1 H), 9.75 (m, 1 H); ir (neat) 1750 cm^{-1} (C=O)].

LDA[10] in 140 ml of THF was prepared from 6.06 ml (0.0432 mol) of diisopropylamine and 17.3 ml (0.0432 mol) of a 2.5 M *n*-butyllithium solution in hexane at −10 °C under nitrogen. After 15 min the pale-yellow solution was cooled to −78 °C and 1.87 g (0.0144 mol) of itaconic acid in 9 ml of THF was added. After 4 h at −78 °C, the 2-(1-ethoxy)ethoxyvaleraldehyde (4) was added to the finely divided suspension. After an additional 4 h at −78 °C, the reaction mixture was quenched at this temperature with 87 ml of 6 M H_2SO_4. The dry ice–acetone bath was then removed and the reaction mixture stirred vigorously for 25 min before extraction with 400 ml of ether in three portions. The ether extracts were combined and dried overnight with $MgSO_4$.[24] Evaporation yielded 3.5 g of a complex mixture which included itaconic acid, canadensolide (and its epimer), and unidentified

products. In order to remove itaconic acid and uncyclizable trans products 6 (R_1 = H), the mixture was dissolved in ether and washed three times with a saturated solution of sodium bicarbonate. After drying over $MgSO_4$, the ether was evaporated to yield 1.01 g of a mixture containing canadensolide. This mixture was separated by HPLC using 9:1 ether–hexane and columns deactivated as previously described.[15] The first peak, which appeared after 5 min, amounted to 0.48 g of material which presumably was largely derived from the unreacted aldehyde (based on NMR). The second peak, which appeared after 6.9 min, amounted to 0.225 g (7.4% based on starting aldehyde) of slightly impure (±)-*epi*-canadensolide. The third peak, which appeared after 12.5 min, amounted to 0.134 g (4.4% based on starting aldehyde) of impure (±)-canadensolide.

The material derived from the second peak was recrystallized once from ether–hexane to yield (±)-*epi*-canadensolide [0.179 g, 5.9%, mp 47–48 °C (lit.[5b] mp 47.5–48.5 °C); NMR ($CDCl_3$) δ 0.95 (t, J = 6 Hz, 3 H), 1.2–1.9 (m, 6 H), 4.1 (dt, J = 7 and 2 Hz, 1 H), 4.75 (dt, J = 7 and 1 Hz, 1 H), 5.1 (dt, J = 8 and 1 Hz, 1 H), 6.3 (d, J = 2 Hz, 1 H), 6.6 (d, J = 2 Hz, 1 H)].

The material derived from the third peak was recrystallized once from ether to yield (±)-canadensolide [0.071 g, 2.3%, mp 96–96.5 °C (lit.[5b] mp 92.5–93.5 °C); NMR δ 0.92 (t, J = 6 Hz, 3 H), 1.1–2.2 (m, 6 H), 4.05 (dt, J = 7 and 2 Hz, 1 H), 4.7 (m, 1 H), 5.22 (m, 1 H), 6.2 (d, J = 2 Hz, 1 H), 6.51 (d, J = 2 Hz, 1 H)].

Acknowledgment. We wish to express our appreciation to Professor A. Yoshikoshi, Tohoku University, Sendai, Japan, for providing ir and NMR spectra of authentic canadensolide and *epi*-canadensolide and to Professor N. J. McCorkindale, the University of Glasgow, Glasgow, Scotland, for unpublished information on canadensolide and canadensic acid. Technical support for certain aspects of this research effort was provided by Mr. Brian Kobilka and Mr. William Schmidt.

Registry No.—**4** [R_5 = $CH_3(CH_2)_3$; R_6 = H; X = $OCH(OCH_2CH_3)CH_3$], 60427-75-0; **7** [R_5 = H; R_6 = $(CH_2)_3CH_3$], 35093-30-2; **7** [R_5 = $(CH_2)_3CH_3$; R_6 = H], 35093-28-8; **8**, 60427-76-1; *p*-methoxybenzyl itaconate, 60427-77-2; methyl itaconate, 7338-27-4; cyclohexanone, 108-94-1; cycloheptanone, 502-42-1; heptan-4-one, 123-19-3; acetone, 67-64-1; cyclopentanone, 120-92-3; pentan-3-one, 96-22-0; tetradecanal, 124-25-4; dodecanal, 112-54-9.

References and Notes

(1) For reviews see P. A. Grieco, *Synthesis*, 67 (1975); R. B. Gammill, C. A. Wilson, and T. A. Bryson, *Synth. Commun.*, **5**, 245 (1975).
(2) K.-H Lee, E.-S Huang, C. Piantodosi, J. Pagano, and T. A. Geissman, *Cancer Res.*, **31**, 1649 (1971).
(3) (a) J. Martin, P. C. Watts, and F. Johnson, *J. Org. Chem.*, **39**, 1676 (1974); (b) A. Löffler, R. D. Pratt, J. Pucknat, G. Gelbard, and A. Dreiding, *Chimia*, **23**, 413 (1969); (c) P. Boll, *Acta Chem. Scand.*, **22**, 3245 (1968); (d) E. E. van Tamelen and S. Bach, *J. Am. Chem. Soc.*, **80**, 3079 (1958).
(4) (±)-Nephrosterinic acid has been isolated from *Centraria endocrocea* [Y. Asahina and M. Yanagita, *Chem. Ber.*, **7013**, 227 (1937)] but the stereochemistry has not yet been assigned.
(5) (a) N. J. McCorkindale, J. L. C. Wright, P. W. Brian, S. M. Clarke, and S. A. Hutchinson, *Tetrahedron Lett.*, 727 (1968); (b) M. Kato, M. Kageyama, R. Tanaka, K Kuwahara, and A. Yoshikoshi, *J. Org. Chem.*, **40**, 1932 (1975).
(6) A preliminary communication describing portions of this work has been published: R. M. Carlson and A. R. Oyler, *Tetrahedron Lett.*, 4099 (1975).
(7) B. E. Tate, *High Polym.*, **24**, 205 (1970).
(8) C. Katsuta and N. Sugiyama, *Bull. Chem. Soc. Jpn.*, **35**, 1194 (1962).
(9) R. M. Carlson, A. R. Oyler, and J. R. Peterson, *J. Org. Chem.*, **40**, 1610 (1975); P. L Creger, *ibid.*, **37**, 1907 (1972); A. P. Krapcho and E. G. E. Jahngen, *ibid.*, **39**, 1323 (1974); P. E. Pfeffer, L. S. Silbert, and E. Kinsel, *Tetrahedron Lett.*, 1163 (1973).
(10) S. Reiffers, H. Wynberg, and J. Strating, *Tetrahedron Lett.*, 3001 (1971).
(11) The observed products were only those resulting from addition of the β carbon of the itaconic acid derivative to the various aldehydes and ketones; see J. L. Herrmann, G. R. Kieczykowski, and R. H. Schlessinger, *Tetrahedron Lett.*, 2433 (1973); P. E. Pfeffer, L. S. Silbert, and E. Kinsel, *ibid.*, 1163 (1973); G. Cainelli, G. Cardello, M. Contento, and A. U. Ronchi, *Gazz. Chim. Ital.*, **104**, 625 (1974); M. W. Rathke and D. Sullivan, *Tetrahedron Lett.*, 4249 (1972); C. A Henrick, W. E. Willy, D. R. McKean, E. Baggiolini, and J. B. Siddall. *J. Org. Chem.*, **40**, 8 (1975).
(12) B. R. Baker, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **17**, 116 (1952).
(13) This hitherto unknown compound was prepared by a modification of the Baker procedure (ref 12) for methyl itaconate. In the present case, the *p*-methoxybenzyl alcohol was allowed to react with the itaconic anhydride for 30 h at 55–60 °C: mp 86.8–87.2 °C; NMR ($CDCl_3$) δ 3.38 (2 H, s), 3.74 (3 H, s), 5.06 (2 H, s), 5.82 (1 H, m), 7.05 (4 H, m); overall yield, 68%.
(14) The use of dianions **1** (R_1 = CH_3, R_2 = Li; R_1 = $ArCH_2$, R_2 = Li) provided only trace amounts of candensolide and its epimer.
(15) The Porasil A columns were deactivated with a 3:2 mixture of ether–2-propanol before the preparative separation was carried out using a 5:1.5:93.5 ether–2-propanol–hexane mixture. Failure to deactivate the columns resulted in extensive isomerization of the double bond of these α-methylene lactones to form α-methyl butenolides.
(16) Structural assignment based on NMR spectrum. For a discussion of the NMR spectra of methyl esters of protolichesterinic acid and allοprotolichesterinic acid, see ref 3b.
(17) J. Weber, E. VanHeyningen, and R. Vasileff, *J. Am. Chem. Soc.*, **91**, 5274 (1969).
(18) G. Kobrich, J. Grossner, and W. Werner, *Chem. Ber.*, **106**, 2610 (1973); H. Taguchi, S. Tanaka, H. Yamota, and H. Nozaki, *Tetrahedron Lett.*, 2465 (1973).
(19) The procedure for the addition of the cyanohydrin to ethyl vinyl ether was reported by G. Stork and L. Maldonado, *J. Am. Chem. Soc.*, **93**, 5286 (1971).
(20) The general procedure for the preparation of cyanohydrins is discussed by D. Mowry, *Chem. Rev.*, **42**, 189 (1948).
(21) Bp 55 °C (0.2 mm); NMR ($CDCl_3$) δ 0.8–2 (m, 15 H), 3.6 (m, 2 H), 4.4 (m, H), 4.9 (m, 1 H). NMR and HPLC showed the distilled product to be an approximately 1:1 mixture of two diastereomers.
(22) A satisfactory elemental analysis (±0.3%) was obtained for this compound.
(23) NMR showed the distilled product to be an approximately 1:1 mixture of two diastereomers. HPLC analysis was not possible owing to apparent decomposition on "μ Porasil" column.
(24) Traces of acid in the ether apparently account for a substantial amount of ring closure Experiments in which the ether extracts were washed with brine before drying resulted in greatly decreased amounts of ring closed products.

Synthesis of Kavain, Dihydrokavain, and Analogues†[1]

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The synthesis of kavain, dihydrokavain, and a number of new analogues of kava pyrones is described. Kavain and dihydrokavain were synthesized by a modification of the Reformatsky reaction in yields severalfold higher than described before. A novel analogue of kavain was obtained by this procedure. Several new analogues of the naturally occurring kava pyrones were synthesized in 10–60% yields by condensing the appropriate aldehyde with 4-methoxy-6-methyl-2-pyrone. The pyrones dehydrokavain and yangonin were obtained in much improved yields. Catalytic hydrogenation of pyrones gave new analogues of dihydrokavain.

The root, rhizome, and the base of the stem of *Piper methysticum* Forster (Kava)[2] have been used for centuries to prepare an intoxicating beverage.[3] Kava was used in Europe before World War I for the treatment of gonorrhea, cystitis, and gout.[4] The active principle of Kava resin consists of a number of α-pyrones and reduced pyrones (nine lactones and two chalcones)[5-10] which have a variety of pharmacological properties (soporific and sedative, potentiation of barbiturate narcosis, protection against chemo- and electroshock, local anesthetic, spasmolytic and smooth muscle relaxant, analgetic, antimycotic, and antiedemic).[5,8,11-26]

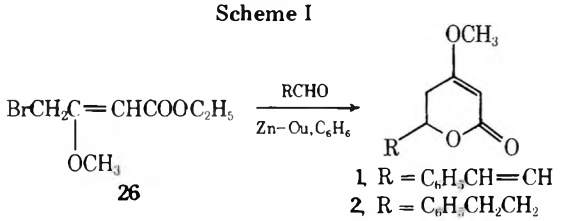
To obtain analogues of the naturally occurring kava lactones we investigated several possible general synthetic methods for the preparation of α-pyrones and reduced pyrones. A number of new analogues of kava lactones were synthesized, and the yield of several known compounds was improved severalfold.

The structures of the kava lactones described here are given in Table I. Only kavain (**1**)[27-31] 7,8-dihydrokavain (**2**),[31] yangonin (**3**),[10,32-35] 5,6-dehydrokavain (**4**),[35] and 7,8-dihydro-5,6-dehydrokavain (**5**)[34] had previously been synthesized (in low yields).

We synthesized kavain, dihydrokavain, and analogues by two methods: (a) modifications of the Reformatsky reaction, and (b) catalytic reduction of the corresponding dehydrokavains.

(a) By using Neuwland and Daly's modification of the Reformatsky reaction,[36] the appropriate aldehydes when condensed with ethyl 4-bromo-3-methoxycrotonate (**26**) gave **1** and **2** in 80 and 50% yield, respectively (Scheme I). This procedure was not successful in the synthesis of the *p*-*N*,*N*-dimethylamino analogue of kavain (**6**). However, when the aldehyde group was activated toward nucleophilic attack (by conversion of the *p*-*N*,*N*-dimethylamino group to a quaternary nitrogen with chloromethyl methyl ether), the activated aldehyde underwent modified Reformatsky reaction to give **6** in 26.5% yield.

Scheme I



26

1, R = $C_6H_5CH{=}CH$
2, R = $C_6H_5CH_2CH_2$

Kavain (**1**) was also obtained (25% yield) by the condensation of the *N*-butylamine Schiff base of cinnamaldehyde under Reformatsky conditions. This approach was also unsuccessful in the synthesis of **6**.

(b) Hydrogenation of dehydrokavains in THF (over Pd/C) resulted in the stepwise reduction of $\Delta^{7,8}$ and $\Delta^{5,6}$ bonds ($\Delta^{7,8}$ reduced faster than $\Delta^{5,6}$) to give the corresponding kavains and dihydrokavains (Table II) in good yields. In EtOH, the reduction products were mainly tetrahydrokavaic acid (**23**) and analogues (obtained by opening of lactone ring and subsequent hydrogenation); however, the model compound 4-methoxy-6-methyl-2-pyrone (**27**) was reduced to the intact lactone 3-methoxy-5-hydroxy-2-hexenoic acid lactone (**28**) in 85% yield.

Reduction of dehydrokavains with $NaBH_4$ (which occurred only when α-pyrones were refluxed in alcoholic KOH for 4–6 h with a 30-fold excess of $NaBH_4$) yielded kavaic acid (**20**) and analogues instead of the expected dihydropyrones.

For the synthesis of dehydrokavains, the procedure of Bu'lock and Smith[33] was modified. Compounds **3** and **4** were obtained in much higher yield than reported previously. A number of new analogues (**10–12, 15–19**) were obtained in yields of 10–60%.

Experimental Section

Melting points were determined on a calibrated Thomas-Hoover melting point apparatus and are corrected. The uv spectra were recorded on a Cary recording spectrophotometer Model 14. The ir spectra were taken on a Beckman IR-8 and IR-10 infrared spectrophotometer. NMR spectra (reported in δ) were recorded on a Varian A-60 and A-60A spectrometer using tetramethylsilane and 3-(trimethylsilyl)propanesulfonic acid sodium salt as internal standards. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., and on a F and M Carbon, Hydrogen and Nitrogen Analyzer Model 185, University of Kansas.[37] Mass spectra were obtained by The Analytical Instrument Division of Varian on a M-66 mass spectrometer. Solvents were removed by evaporation in vacuo by using a Calab Model C rotary evaporator normally at room temperature.

3-Methoxy-5-hydroxy-7-phenyl-2,6-heptadienoic acid Lactone (Kavain, 1). Kavain was synthesized by a modification of the Reformatsky reaction[36] (using Zn–Cu couple instead of Zn). Thus, 13.2 g (0.1 mol) of cinnamaldehyde and 44.4 g (0.2 mol) of ethyl 4-bromo-3-methoxycrotonate (**26**) were condensed in the presence of 19.6 g (~0.3 mol) of Zn–Cu couple (95% Zn) to give 18.5 g (80% yield) of colorless needles (THF), mp 146–147.5 °C (lit.[31] mp 145–146 °C).

3-Methoxy-5-hydroxy-7-phenyl-2-heptenoic acid Lactone (Dihydrokavain, 2). Synthesis was carried out as for **1** using 13 g (0.1 mol) of hydrocinnamaldehyde. The product was isolated by column chromatography (silica gel 0.05–0.2 mm, Et_2O–petroleum ether, bp 55–65 °C) to give 11.6 g (50% yield) of **2**, recrystallized from CCl_4 as colorless needles: mp 69–71 °C (lit.[31] 65–69 °C); NMR (CCl_4) δ 7.15 (s, 5, aromatic), 5.05 (s, 1, –CH=), 4.5–4.0 (complex, 1, methine H), 3.66 (s, 3, $-OCH_3$), and 2.9–1.65 (complex, 6, methylene H).

***p*-(*N*,*N*-Dimethyl-*N*-methoxymethylammonium)cinnamaldehyde Chloride.** *p*-*N*,*N*-Dimethylaminocinnamaldehyde (17.5 g, 0.1 mol) and chloromethyl methyl ether (37.5 ml, 40.5 g, 0.5 mol) were mixed under an atmosphere of N_2 and allowed to stand at room temperature for 48 h. The precipitated solid was collected by filtration, washed several times with C_6H_6, and dried at 80 °C to give 24.7

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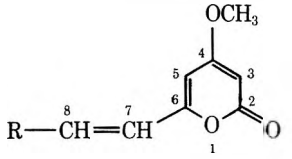
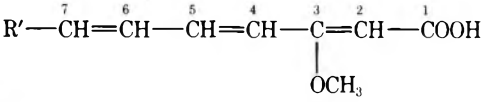
Table I. Structure of Kava Type Lactones and Acids



	R	$\Delta^{5,6}$	$\Delta^{7,8}$	Name
1	Phenyl	Reduced		Kavain[a]
2	Phenyl	Reduced	Reduced	7,8-Dihydrokavain[a]
3	4-Methoxyphenyl			Yangonin[a]
4	Phenyl			5,6-Dehydrokavain[a]
5	Phenyl		Reduced	7,8-Dihydro-5,6-dehydrokavain[a]
6	4-*N*,*N*-Dimethylaminophenyl	Reduced		
7	4-*N*,*N*-Dimethylaminophenyl		Reduced	
8	3,4,5-Trimethoxyphenyl		Reduced	
9	2-Thienyl		Reduced	
10	4-*N*,*N*-Dimethylaminophenyl			
11	3,4,5-Trimethoxyphenyl			
12	2-Thienyl			
13	4-*N*,*N*-Dimethylaminophenyl	Reduced	Reduced	
14	3,4,5-Trimethoxyphenyl	Reduced	Reduced	
15	2-Pyridyl			
16	3-Pyridyl			
17	4-Pyridyl			
18	Styryl			
19	Phenylethyl			



	R′	$\Delta^{4,5}$	$\Delta^{7,8}$	Name
20	Phenyl			Kavaic acid[a]
21	4-Methoxyphenyl			
22	3,4,5-Trimethoxyphenyl			
23	Phenyl	Reduced	Reduced	Tetrahydrokavaic acid
24	4-*N*,*N*-Dimethylaminophenyl	Reduced	Reduced	
25	3,4,5-Trimethoxyphenyl	Reduced	Reduced	

[a] Known compounds.

g (97% yield) of a brownish powder which was used without further purification. The product absorbs moisture very quickly upon exposure.

3-Methoxy-5-hydroxy-7-(4-*N*,*N*-dimethylaminophenyl)-2,6-heptadienoic Acid Lactone (6). Compound **6** was synthesized by a further modification of the Reformatsky reaction: Zn–Cu couple (4.0 g, 0.06 mol) was suspended in thiophene-free C_6H_6 (150 ml) and about 30 ml of C_6H_6 was distilled through the Dean-Stark trap. A crystal of iodine was added followed by 6 ml of a mied solution of the above described quaternary compound (4.6 g, 0.018 mol) in Me_2SO (20 ml) and **28** (13.2 g, 0.06 mol) in C_6H_6 (20 ml). The greenish brown reaction mixture was heated under reflux with stirring for 10 min after which the remainder of the aldehyde–ester mixture was added dropwise in 1 h maintaining a gentle reflux. After the addition was over the reaction mixture was stirred under reflux for 4 h and then for another 2.5 h at room temperature. A saturated solution of NH_4Cl (75 ml) was added and the stirring continued for 20 min. The organic layer was separated and combined with four 100-ml C_6H_6 extracts[38] of the H_2O layer and the combined C_6H_6 solution was washed with H_2O four times and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was taken in 50 ml of C_6H_6 and diluted with Et_2O (150 ml). The yellow precipitate which formed (300 mg) was removed by filtration and the filtrate was concentrated under reduced pressure. On cooling in an ice bath the residue deposited light colored crystals. The product was recrystallized from C_6H_6 as pale yellow needles: 1.2 g (26.5% yield) as hydrobromide, mp 172–172.5 °C; ν_{CO} (KBr) 1705 cm^{-1}; NMR ($DCCl_3$) δ 7.78–6.65 (complex, 6, aromatic and –CH=CH–), 5.26 (s, 1, –CH=), 5.2–4.9 (complex, 1, methine H), 3.78 (s, 3, $-OCH_3$), 3.0 (s, 6, NCH_3), and 2.95–2.5 (complex, 2, $-CH_2-$): mass spectrum *m/e* (rel intensity) parent peak 273 (7), base peak 133 (100). Anal. ($C_{16}H_{19}NO_3$·HBr) C, H, N. H: calcd, 5.65; found, 5.10.

***n*-Butylamine-*N*-cinnamalydine.** The Schiff base was prepared by a procedure similar to that of Robertson.[39] A mixture of *n*-butylamine (8.05 g, 0.11 mol) and cinnamaldehyde (13.2 g, 0.1 mol) in thiophene-free C_6H_6 (50 ml) was heated under reflux (1 h). The H_2O (2 ml) which formed during the reaction was removed by using a Dean-Stark trap. The solvent and the excess amine were removed under vacuum. The residue, 20.6 g (89% yield), was used without further purification.

Modified Reformatsky Condensation of *n*-Butylamine-*N*-cinnamalydine with 26. The procedure for the synthesis of kavain described earlier was followed. The above described Schiff base (11.2 g, 0.05 mol) and **26** (22.2 g, 0.1 mol) were condensed in the presence of Zn–Cu couple (10 g, 0.15 mol) to give light colored crystals, 2.2 g (22% yield), of **1**, mp 145–147 °C (THF).

3-Methoxy-7-phenyl-2,4,6-heptatrienoic Acid (Kavaic Acid, 20). Dehydrokavain (**4**, 340 mg) was dissolved in warm MeOH (50 ml) containing 1 g of KOH. $NaBH_4$ (340 mg) was added and the mixture was heated under reflux for 4 h. After cooling, the mixture was acidified (20% HOAc) and the precipitate was collected by filtration. The precipitate was washed with H_2O and Et_2O and recrystallized from hot acetone to give colorless neeles of **20** (40% yield): mp 180–182 °C (lit. 184,[27] 178–178.5 °C[40]); ν_{CO} (KBr) 1675 cm^{-1}; NMR (CD_3COCD_3) δ 7.15–6.25 (complex, 9, aromatic and –CH=CH–), 4.62 (s, 1, –CH=), and 3.18 (s, 3, $-OCH_3$).

3-Methoxy-7-(4-methoxyphenyl)-2,4,6-heptatrienoic Acid (21). Yangonin (**3**) was converted to the acid **21** by the method used for **20**: light yellow crystals ($CHCl_3$, 60% yield); mp 164–165 °C; ν_{CO} (KBr) 1659 cm^{-1}; NMR (CD_3COCD_3) δ 7.3–6.4 (complex, 8, aromatic and –CH=CHCH=CH–), 4.8 (s, 1, –CH=), 3.4 and 3.35 (s, 6, $-OCH_3$). Anal. ($C_{15}H_{16}O_4$), C, H. C: calcd, 69.22; found, 68.72.

3-Methoxy-7-(3,4,5-trimethoxyphenyl)-2,4,6-heptatrienoic Acid (22). The acid was obtained from pyrone **11** by the procedure described for **20**: yellow needles from $CHCl_3$ (64% yield); mp 174.5–175.5 °C; ν_{CO} (KBr) 1670 cm^{-1}; NMR ($DCCl_3$) δ 7.9–6.8 (complex, 4, –CH=CHCH=CH–), 6.75 (s, 2, aromatic), 5.22 (s, 1, –CH=), 3.97 (s, 9, aromatic $-OCH_3$), and 3.8 (s, $-OCH_3$); mass spectrum *m/e* (rel intensity) parent peak 320 (0.5), base peak 181 (100). Anal. ($C_{17}H_{20}O_5$), C, H.

General Procedure for the Catalytic Hydrogenation of Pyrones. The compound was dissolved in the appropriate solvent and exposed to H_2 in a microhydrogenator at room temperature in the presence of palladium on charcoal (Table II). After a certain time period the catalyst was removed by filtration and the filtrate was

Table II Catalytic Hydrogenation of Pyrones[a]

Starting material	Registry no.	Product[b]	Registry no.	Yield, %	Mp, °C (solvent)	Analyzed for		Reaction conditions[c]
1		2		92	69.5–71.5 (Et_2O–petroleum ether) (lit.[31] 65–69)	d		THF/0.1/15/1.3
4		5		60	94.5–95.5 (Et_2O) (lit.[34] 96–97[31])	d		THF/0.1/50/6.5
10	60427-78-3	7	60427-82-9	97	92.5–94.5 (Et_2O–CCl_4)	$C_{16}H_{19}NO_3$	C, H, N	THF/0.1/50/48
11	60427-79-4	8	60427-83-0	30	128–130 (Et_2O–petroleum ether)	$C_{17}H_{20}O_6$	C, H	THF/0.12/15/0.2
12	60427-80-7	9	60427-84-1	52	69.5–71.5 (CCl_4)	$C_{12}H_{12}O_3S$	C, H	THF/0.3/15/40
10		13	60427-85-2	90	76.5–78.5 (petroleum ether)	$C_{16}H_{21}NO_3$	C, H, N	THF/0.2/50/72
11		14	60427-86-3	90	75.3–76.2 (Et_2O–CCl_4)	$C_{17}H_{22}O_6$	C, H	THF/0.2/50/16
27	672-89-9	28	3791-79-5	85	62–64 (Et_2O–petroleum ether) (lit.[41] 68)	$C_{13}H_{10}O_3$	C, H	EtOH/0.12/15/6.5
1	1635-33-2	23	60427-87-4	13	108–109 (CCl_4)	$C_{14}H_{18}O_3$	C, H	EtOH/0.1/15/24
10		24	60427-88-5	4	102.5–105.5 (Et_2O–petroleum ether)	e		EtOH/0.2/15/19
22	60427-81-8	25	60427-89-6	83	120.5–121 (CCl_4)	$C_{17}H_{24}O_6$	C, H	THF/0.1/15/1

[a] The catalyst was 10% Pd/C except in the case of products 24 and 28, where 30% Pd/C was used. [b] All products were obtained as colorless crystals except 9 which was yellow. Compound 14 was obtained as rhombic crystals. [c] The reaction conditions employed are indicated as solvent/catalyst:substrate (w/w) ratio/H_2 pressure (psi)/time (h). [d] Known compounds. [e] Identification based on spectral data only.

concentrated in vacuo. The residue was recrystallized. The reaction conditions, yields, and physical properties of the products are given in Table II. The spectroscopic properties are listed below.

3-Methoxy-5-hydroxy-7-phenyl-2,4-heptadienoic Acid Lactone (5): ν_{CO} (KBr) 1730 cm^{-1}; NMR (CCl_4) δ 7.17 (s, 5, aromatic) 5.58 (d, 1, J = 2 Hz, –CH=), 5.28 (d, 1, J = 2 Hz, –CH=), 3.75 (s, 3, $-OCH_3$), and 2.83 (sym m, 4, $-CH_2CH_2-$).

3-Methoxy-5-hydroxy-7-(4-*N,N*-dimethylaminophenyl)-2,4-heptadienoic Acid Lactone (7): ν_{CO} (KBr) 1730 cm^{-1}; NMR (CCl_4) δ 6.78 (doublet of d, 4, J = 8.5 Hz, aromatic), 5.57 (d, 1, J = 2 Hz, –CH=), 5.27 (d, 1, J = 2 Hz, –CH=), 3.73 (s, 3, $-OCH_3$), 2.89 (s, 6, $-NCH_3$), and 2.72 (sym m, 4, $-CH_2CH_2-$).

3-Methoxy-5-hydroxy-7-(3,4,5-trimethoxyphenyl)-2,4-heptadienoic Acid Lactone (8): ν_{CO} (KBr) 1705 cm^{-1}; NMR ($DCCl_3$) δ 6.78 (s, 2, aromatic), 6.08 (d, 1, J = 2 Hz, –CH=), 5.75 (d, 1, J = 2 Hz, –CH=), 4.06 and 4.00 (s, 12, $-OCH_3$), and 3.00 (sym m, 4, $-CH_2CH_2-$).

3-Methoxy-5-hydroxy-7-(2-thienyl)-2,4-heptadienoic Acid Lactone (9): ν_{CO} (KBr) 1720 cm^{-1}; NMR (CCl_4) δ 7.45–6.67 (complex, 3, aromatic), 5.68 (d, 1, J = 2 Hz, –CH=), 5.34 (d, 1, J = 2 Hz, –CH=), 3.76 (s, 3, $-OCH_3$), and 3.0 (sym m, 4, $-CH_2CH_2-$).

3-Methoxy-5-hydroxy-(4-*N,N*-dimethylaminophenyl)-2-heptenoic Acid Lactone (13): ν_{CO} (KBr) 1710 cm^{-1}; uv λ_{max} (CH_3OH) 246 nm (log ϵ 5.26), 301 (4.26); NMR (CCl_4) δ 6.79 (doublet of d, 4, J = 9 Hz, aromatic), 4.25 (broad, 1, methine H), 3.69 (s, 3, $-OCH_3$), 2.86 (s, 6, $-NCH_3$), and 2.95–1.75 (complex, 4, $-CH_2-CH_2-$).

3-Methoxy-5-hydroxy-7-(3,4,5-trimethoxyphenyl)-2-heptenoic Acid Lactone (14): ν_{CO} (KBr) 1695 cm^{-1}; NMR (CCl_4) δ 6.35 (s, 2, aromatic), 5.02 (s, 1, –CH=), 4.25 (broad, 1, methine H), 3.77 and 3.69 (s, 12, $-OCH_3$), and 2.9–1.65 (complex, 6, $-CH_2-$).

3-Methoxy-5-hydroxy-2-hexenoic Acid Lactone (28): ν_{CO} (KBr) 1700 cm^{-1}; NMR (CCl_4) δ 5.05 (s, 1, –CH=), 4.47 (sym m, 1, –CH<), 3.74 (s, 3, $-OCH_3$), 2.48–2.22 (m, 2, $-CH_2-$), and 1.4 (d, 3, J = 6 Hz, $-CH_3$).

3-Methoxy-7-phenyl-2-heptenoic Acid (23): ν_{CO} (KBr) 1690 and 1655 cm^{-1}; NMR (CCl_4) δ 11.93 (broad s, 1, –COOH), 7.1 (s, 5, aromatic), 4.95 (s, 1, –CH=), 3.65 (s, 3, $-OCH_3$), 3.00–2.33 and 1.95–1.35 (broad complex, 8 and 2, $-CH_2-$).

3-Methoxy-7-(4-*N,N*-dimethylaminophenyl)-2-heptenoic Acid (24): ν_{CO} (KBr) 1665 cm^{-1}; NMR (CCl_4) δ 10.86 (broad s, 1, –COOH), 6.74 (doublet of d, 4, J = 7 Hz, aromatic), 4.93 (s, 1, –CH=), 3.63 (s, 3, $-OCH_3$), 2.85 (s, 6, $-NCH_3$), 3.0–2.28 and 1.75–1.25 (broad complex, 8, $-CH_2-$).

3-Methoxy-7-(3,4,5-trimethoxyphenyl)-2-heptenoic Acid (25): ν_{CO} (KBr) 1690 cm^{-1}; NMR (CCl_4) δ 11.66 (broad s, 1, –COOH), 6.28 (s, 2, aromatic), 4.99 (s, 1, –CH=), 3.78 (s, 9, aromatic $-OCH_3$), 3.68 (s, 3, $-OCH_3$), 3.00–2.32 (complex, 4, $-CH_2CH_2-$), and 1.7–1.4 (complex, 4, $-CH_2CH_2-$).

3-Methoxy-5-hydroxy-7-(3,4,5-trimethoxyphenyl)-2,4,6-heptatrienoic Acid Lactone (11). A solution of 3,4,5-trimethoxybenzaldehyde (19.6 g, 0.1 mol) and 4-methoxy-6-methyl-2-pyrone (**27**, 16.8 g, 0.12 mol) in absolute MeOH (40 ml) was added dropwise with stirring to a suspension of magnesium methoxide (prepared from 7.5 g of Mg turnings) in MeOH (100 ml) in 45 min, maintaining a gentle reflux and an atmosphere of N_2. After the addition was complete, the reaction mixture was stirred under gentle reflux for 6 h. The solvent was removed under reduced pressure at 40 °C and the residue was treated with dilute HOAc (45 g of glacial HOAc diluted to 225 ml) and extracted with CH_2Cl_2 (500 ml). The CH_2Cl_2 extract was washed with H_2O (80 ml), dried (Na_2SO_4), and filtered. The filtrate was evaporated under reduced pressure and the residue was triturated with Et_2O (150 ml) and filtered. The yellow, crystalline solid was washed with Et_2O followed by a small amount of MeOH, and then dried in vacuo at 80 °C: 19.1 g (60% yield), recrystallized from MeOH, shiny yellow plates; mp 196.5–197.5 °C; uv λ_{max} 345 nm (log ϵ 4.38), 362 (4.36), 224 (4.29); ν_{CO} (KBr) 1710 cm^{-1}; NMR ($DCCl_3$) δ 7.02 (doublet of d, 2, J = 15.5 Hz, –CH=CH–), 6.8 (s, 2, aromatic), 6.02 (d, 1, J = 2 Hz, –CH=), 5.50 (d, 1, J = 2 Hz, –CH=), 3.93 (s, 9, aromatic $-OCH_3$), and 3.85 (s, 3, $-OCH_3$); mass spectrum m/e 318, parent peak. Anal. ($C_{17}H_{18}O_6$), C, H.

3-Methoxy-5-hydroxy-7-(4-methoxyphenyl)-2,4,6-heptatrienoic Acid Lactone (Yangonin) (3). This compound was synthesized by the procedure described for **11**. Anisaldehyde (6.8 g, 0.05 mol), **27** (8.5 g, 0.06 mol), and magnesium methoxide (from 1.2 g of Mg) gave 5.3 g (41.5%) of the product, recrystallized from MeOH as yellow needle clusters, mp 156–157 °C (lit.[35] 155–157 °C).

3-Methoxy-5-hydroxy-7-phenyl-2,4,6-heptatrienoic Acid Lactone (5,6-Dehydrokavain) (4). The procedure for the synthesis of pyrone **11** was followed using benzaldehyde (6.2 g, 0.06 mol), **27**

(10.2 g, 0.07 mol), and magnesium methoxide (from 2.5 g of Mg). The product, 6.1 g (44% yield), was recrystallized from MeOH as colorless, fine needles, mp 134–136 °C (lit.[35] yellow needles, mp 139–141 °C). Anal. ($C_{14}H_{12}O_3$), C, H.

3-Methoxy-5-hydroxy-7-(4-*N,N*-dimethylaminophenyl)-2,4,6-heptatrienoic Acid Lactone (10). This compound was synthesized by a modified procedure of that described for the synthesis of the pyrone **11**. A solution of *p*-*N,N*-dimethylaminobenzaldehyde (36 g, 0.24 mol) and **27** (40.8 g, 0.29 mol) in absolute MeOH (200 ml) was added dropwise with stirring to a suspension of magnesium methoxide (prepared from 10 g of Mg) in MeOH (200 ml) in 2 h, while maintaining a gentle reflux under an atmosphere of N_2. The reddish brown reaction mixture was stirred under reflux for an additional 15 h, after which period it was cooled and treated with 15% HOAc (60 g of glacial HOAc diluted to 400 ml) and extracted exhaustively with C_6H_6 (ten portions of 150 ml each). The C_6H_6 extract was washed with H_2O, dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure at 40 °C and the residue triturated with Et_2O. The solid was filtered, washed with MeOH and Et_2O, and then dried in vacuo, 26.5 g (40% yield). The product was recrystallized (MeOH) to give silky yellow, shiny plates: mp 201–202 °C; uv (CH_3OH) λ_{max} 408 nm (log ϵ 5.58), 245 (5.21), 232 (5.2); ν_{CO} (KBr) 1705 cm^{-1}; NMR ($DCCl_3$) δ 7.62–6.25 (groups of multiplets, 3, aromatic and –CH=CH–), 5.86 (d, 1, J = 2 Hz, –CH=), 5.45 (d, 1, J = 2 Hz, –CH=), 3.82 (s, 3, $-OCH_3$), and 3.01 (s, 6, $-NCH_3$). Anal. ($C_{16}H_{17}NO_3$), C, H, N. C: calcd, 70.85; found, 70.38.

3-Methoxy-5-hydroxy-7-(2-pyridyl)-2,4,6-heptatrienoic Acid Lactone (15). The procedure for the synthesis of the pyrone **11** was followed using 2-pyridinecarboxaldehyde (5.4 g, 0.05 mol), **27** (8.5 g, 0.06 mol), and magnesium methoxide (from 2.8 g of Mg). The crude product, 1.5 g (13.1% yield), was obtained as a brown powder, ν_{CO} (KBr) 1705 cm^{-1}. The modified procedure as described for the synthesis of the pyrone **10** did not give the product.

3-Methoxy-5-hydroxy-7-(3-pyridyl)-2,4,6-heptatrienoic Acid Lactone (16). The procedure for the synthesis of the pyrone **11** was followed using 3-pyridinecarboxaldehyde (6.5 g, 0.06 mol), **27** (10.1 g, 0.07 mol), and magnesium methoxide (from 2.5 g of Mg). The product, 1.4 g (10% yield), was recrystallized (MeOH) to give pale yellow needles: mp 180.5–182 °C; ν_{CO} (KBr) 1735 cm^{-1}; NMR ($DCCl_3$) δ 8.8–6.58 (complex, 6, aromatic and –CH=CH), 6.09 (d, 1, J = 2 Hz, –CH=), 5.59 (d, 1, J = 2 Hz, –CH=), and 3.89 (s, 3, $-OCH_3$). Anal. ($C_{13}H_{11}NO_3$), C, H, N.

3-Methoxy-5-hydroxy-7-(4-pyridyl)-2,4,6-heptatrienoic Acid Lactone (17). The procedure for the synthesis of the pyrone **11** was followed, using 4-pyridinecarboxaldehyde (5.4 g, 0.05 mol), **27** (8.5 g, 0.06 mol), and magnesium methoxide (from 2.8 g of Mg). The crude product, 2.0 g (17.5% yield), was obtained as a pinkish brown powder.

The modified procedure as described for the synthesis of the pyrone **10** gave the product in 5% yield, recrystallized from MeOH–Et_2O: light brown needles; mp 146–150 °C dec; ν_{CO} (KBr) 1735 cm^{-1}; NMR ($DCCl_3$) δ 8.88 and 7.58 (pair of d, 4, J = 6 Hz, aromatic), 7.3 (doublet of d, 2, J = 16.5 Hz, –CH=CH–), 6.22 (d, 1, J = 2 Hz, –CH=), 5.59 (d, 1, J = 2 Hz, –CH=), and 3.87 (s, 3, $-OCH_3$). Anal. ($C_{13}H_{11}NO_3$) C, H, N.

3-Methoxy-5-hydroxy-7-(2-thienyl)-4,6-heptatrienoic Acid Lactone (12). The procedure for the synthesis of the pyrone **10** was followed, using 2-thiophenecarboxaldehyde (6.7 g, 0.06 mol), **27** (10.1 g, 0.07 mol), and magnesium methoxide (from 2.5 g of Mg). The product, 6.0 g (42.8% yield), was recrystallized (MeOH) to give yellow crystals mp 176.5–177.5 °C; ν_{CO} (KBr) 1735 cm^{-1}; NMR ($DCCl_3$) δ 7.8–6.28 (complex, 5, aromatic and –CH=CH–), 5.94 (d, 1, J = 2 Hz, –CH=), 5.52 (d, 1, J = 2 Hz, –CH=), and 3.83 (s, 3, $-OCH_3$). Anal. ($C_{12}H_{10}O_3S$) C, H.

3-Methoxy-5-hydroxy-9-phenyl-2,4,6,8-nanotetraenoic Acid Lactone (18). The procedure for the synthesis of the pyrone **11** was followed, using 6.6 g (0.05 mol) of cinnamaldehyde, 8.4 g (0.06 mol) of **27**, and magnesium methoxide (from 2.5 g of Mg). The product, 2.0 g (15.7% yield), was recrystallized (MeOH) to give bright yellow plates: mp 188.5–190 °C; ν_{CO} (KBr) 1730 cm^{-1}; NMR ($DCCl_3$) δ 7.02–6.02 (complex, 9, aromatic and –CH=CHCH=CH–), 5.86 (d, 1, J = 2 Hz, –CH=), 5.46 (d, 1, J = 2 Hz, –CH=), and 3.8 (s, 3, $-OCH_3$). Anal. ($C_{16}H_{14}O_3$) C, H. C: calcd, 75.59; found, 75.14.

3-Methoxy-5-hydroxy-9-phenyl-2,4,6-nanotrienoic Acid Lactone (19). The procedure for the synthssis of the pyrone **11** was followed using hydrocinnamaldehyde (6.7 g, 0.05 mol), **27** (8.4 g, 0.06 mol), and magnesium methoxide (from 2.5 g of Mg). The crude product obtained was a syrupy liquid. The modified procedure as that employed for the synthesis of the pyrone **10** also gave the same product, ν_{CO} (neat) 1730 cm^{-1}.

Acknowledgment. We wish to thank Dr. Peter G. Dayton for reviewing this manuscript.

Appendix

The following new compounds were synthesized as intermediates, by-products, or model compounds (for details see ref 1). 3,4,5-Trimethoxycinnamaldehyde, mp 106–108.5 °C (Et_2O–petroleum ether). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.99; H, 6.38. Methyl 5-keto-7-phenylheptanoate, bp 144–146 °C (0.95 mm). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.54; H, 7.68. 2,6-Diketo-4-(2-phenylethyl)heptane-1,3,5,7-tetracarboxylic acid tetramethyl ester, mp 184–185 °C (EtOAc). Anal. Calcd for $C_{23}H_{28}O_{10}$: C, 59.48; H, 6.08. Found: C, 59.12; H, 6.10. 2,6-Diketo-4-styrylheptane-1,3,5,7-tetracarboxylic acid tetramethyl ester, mp 180.5–181.5 °C (EtOAc). Anal. Calcd for $C_{23}H_{26}O_{10}$: C, 59.74; H, 5.67. Found: C, 59.86; H, 5.72.

Registry No.—**2**, 587-63-3; **3**, 500-62-9; **4**, 1952-41-6; **5**, 3155-51-9; **6**, 60427-90-9; **15**, 60427-94-3; **16**, 15317-59-6; **17**, 15317-60-9; **18**, 60427-92-1; **19**, 60427-95-4; **20**, 501-73-5; **21**, 60427-93-2; **26**, 1116-51-4; $C_{16}H_{19}NO_3 \cdot CH_2Cl_2$; 60427-91-0; cinnamaldehyde, 104-55-2; hydrocinnamaldehyde, 104-53-0; *p*-(*N,N*-dimethyl-*N*-methoxymethylammonium)cinnamaldehyde chloride, 60427-96-5; butylamine-*N*-cinnamalydine, 15286-55-2; 3,4,5-trimethoxybenzaldehyde, 86-81-7; anisaldehyde, 123-11-5; benzaldehyde, 100-52-7; *p*-*N,N*-dimethylaminobenzaldehyde, 100-10-7; 2-pyridinecarboxaldehyde, 1121-60-4; 3-pyridinecarboxaldehyde, 500-22-1; 4-pyridinecarboxaldehyde, 872-85-5; 2-thiophenecarboxaldehyde, 98-03-3; 3,4,5-trimethoxycinnamaldehyde, 34346-90-2; methyl 5-keto-7-phenylheptanoate, 60427-97-6; 2,6-diketo-4-(2-phenylethyl)heptane-1,3,5,7-tetracarboxylic acid tetramethyl ester, 60427-98-7; 2,6-diketo-4-styrylheptane-1,3,5,7-tetracarboxylic acid tetramethyl ester, 60427-99-8.

References and Notes

(1) Taken in part from the dissertation presented by Z. H Israili, Sept 1968, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree. Available from University Microfilms, Ann Arbor, Mich., Order No. 69-12,680 [*Diss. Abstr. Int. B*, **30**, 581–582 (1969)].
(2) Also known as kava-kava, ava-ava, kavae, karae, keu, kawaka, yangona, hoi, and wati.
(3) E. F. Steinmetz, "*Piper methysticum* (kava), Famous Drug Plant of the South Sea Islands", Elsevier, Amsterdam, 1960.
(4) E. F. Steinmetz, *Q. J. Crude Drug Res.*, **1**, 72 (1961).
(5) R. Haensel, *Pac. Sci.*, **22**, 293 (1968).
(6) W. Borsche and B. K. Blount, *Chem. Ber.*, **66B**, 803 (1933).
(7) O. R. Gottlieb and W. B. Mors, *J. Org. Chem.*, **24**, 1614 (1959).
(8) M. W. Klohs F. Keller, R. E. Williams, M. I. Tockes, and G. E. Cronheim, *J. Med. Pharm. Chem.*, **1**, 95 (1959).
(9) W. B. Mors, M. T. Magalhaes, and O. R. Gottlieb in "Progress in the Chemistry of Organic Natural Products", Vol. 20, L. Zechmeister, Ed., Springer-Verlag, West Berlin, 1962.
(10) R. Haensel and L. Klaproth, *Arch. Pharm. (Weinheim, Ger.)*, **299**, 503 (1966).
(11) A. G. van Veen, *Ned. Tijdschr. Geneeskd.*, **78**, 1941 (1938).
(12) R. Haensel and H. U. Beiersdorff, *Naturwissenschaften*, **45**, 573 (1958).
(13) R. Haensel and H. U. Beiersdorff, *Arzneim.-Forsch.*, **9**, 581 (1959).
(14) D. H. Canham, Ph.D. Thesis, "A Reinvestigation of Some Constituents of Piper Methysticum", University of Wisconsin, 1959.
(15) F. Keller and M. W. Klohs, *Lloydia*, **26**, 1 (1963).
(16) H. J. Meyer, *U.S/ Public Health Serv. Publ.*, **No. 1645**, 133 (1967).
(17) J. P. Buckley, A. R. Furgiuele and M. J. O'Hara, *U.S. Public Health Serv. Publ.*, **No. 1645**, 141 (1967).
(18) H. J. Meyer, A. Oberdorf, and E. Seifen, *Arch. Exp. Pathol. Pharmakol.*, **238**, 124 (1960).
(19) H. J. Meyer, *Arch. Int. Pharmacodyn. Ther.*, **138**, 505 (1962).
(20) H. J. Meyer, *Arch. Int. Pharmacodyn. Ther.*, **150**, 118 (1964).
(21) H. J. Meyer and J. Meyerburg, *Arch. Int. Pharmacodyn. Ther.*, **148**, 97 (1964).
(22) H. J. Meyer and H. U. May, *Klin. Wochenschr.*, **42**, 407 (1964).
(23) H. J. Meyer, *Arch. Int. Pharmacodyn. Ther.*, **154**, 449 (1965).
(24) F. von Bruggenmann and H. J. Meyer, *Arzneim.-Forsch.*, **13**, 407 (1963).
(25) R. Haensel, D. Weiss, and B. Schmidt, *Planta Med.*, **14**, 1 (1966).
(26) H. J. Meyer, *Klin. Wochenschr.*, **43**, 469 (1965).
(27) E. M. E. Fowler and H. B. Henbest, *J. Chem. Soc.*, 3642 (1950).
(28) D. Kostermans, *Nature (London)*, **166**, 788 (1950).
(29) D. Kostermans, *Recl. Trav. Chim. Pays-Bas*, **70**, 79 (1951).
(30) C. Piantadosi and V. G. Skulason, *J. Pharm. Sci.*, **53**, 902 (1964).
(31) K. Viswanathan and S. Swaminathan, *Proc. Indian Acad. Sci., Sect. A*, **52**, 63 (1960).
(32) W. Borsche, C. K. Bodenstein, and M. Lewinsohn, *Chem. Ber.*, **62B**, 2515 (1929).

(33) J. B. Bu'lock and H. G. Smith, *J. Chem. Soc.*, 502 (1960).
(34) Y. Kimura, M. Takido, K. Nakano, and M. Takishita, *Yakugaku Zasshi*, **86**, 1184 (1966); *Chem. Abstr.*, **67**, 21775e (1967).
(35) R. Haensel, H. Sauer, and H. Rimpler, *Arch. Pharm. (Weinheim, Ger.)*, **229**, 507 (1966).
(36) J. A. Nieuwland and S. F. Daly, *J. Am. Chem. Soc.*, **53**, 1842 (1931).
(37) Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.
(38) If CH_2Cl_2 was used for extraction, the product was obtained as yellow needles with a molecule of CH_2Cl_2 of crystallization, mp 169–172 °C. Anal. ($C_{16}H_{19}NO_3$-CH_2Cl_2) C, H, N.
(39) D. N. Robertson, *J. Org. Chem.*, **25**, 47 (1960).
(40) E. E. Smissman and A. N. Voldeng, *J. Org. Chem.*, **29**, 3161 (1964).
(41) R. Haensel, H. Rimpler, and L. Langhammer, *Z. Anal. Chem.*, **218**, 346 (1966).

Synthesis of *C*-Glycosyl Thiazoles

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Condensation of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosylthiocarboxamide (**1**) with α-chloroketo compounds yielded the corresponding 2-*C*-glycosyl thiazole nucleosides (**4a** and **7**) as the major products along with the 2-(thiazol-2-yl)-5-benzoyloxymethylfuran derivatives (**5a** and **8**). Reaction of **1** with ethyl bromopyruvate gave as the only resulting compound the 2-*C*-glycosyl thiazole nucleoside **12**. A similar series of reactions was carried out with 5-benzoyloxymethylfuran-2-thiocarboxamide (**2**) and α-halo ketones. Finally, treatment of methyl 6-deoxy-6-diazo-2,3-*O*-isopropylidene-β-D-*ribo*-hexofuranosid-5-ulose (**24**) with thiourea afforded the 4-*C*-glycosyl thiazole **26**.

Of the several synthetic procedures described in the literature for obtaining thiazole derivatives, the reaction of thioamides and related compounds with α-halocarbonyl derivatives has been the most extensively used.[1] By application of this method, some acyclic sugar 2- and 4-thiazolyl nucleoside analogues have been prepared starting from suitable aldonic acid thioamides[2] or α-haloketoses,[3] respectively. More recently Tronchet et al.[4] have described the synthesis of 4-*C*-glycosyl thiazoles by reacting thiourea or thioacetamide with an α-halocarbonyl sugar derivative, namely 6-*S*-benzyl-6-chloro-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-6-thiohexofuranos-5-ulose.

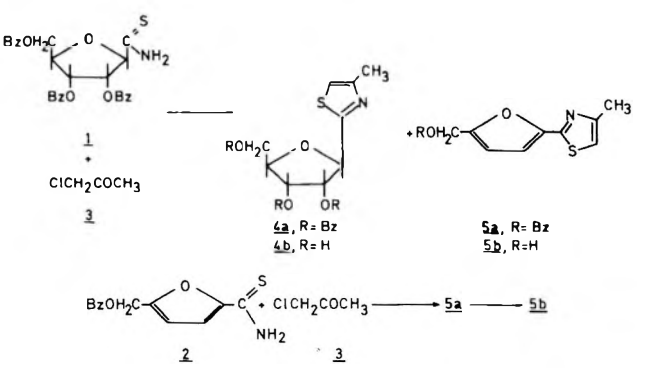
In a recent preliminary communication[5] we have reported on the synthesis of a 2-*C*-glycosyl thiazole nucleoside and also the synthesis of several acyclic sugar 4-thiazolyl nucleoside analogues. Now we wish to give a full account of this and related work.

The starting material in our synthesis of 2-glycosyl thiazole nucleosides, the hitherto unknown 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosylthiocarboxamide[5,6] (**1**), was obtained in 20% yield as an amorphous solid by reaction of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide[7] with hydrogen sulfide. It should be noted that the furan derivative **2** resulting from the elimination of two benzoyloxy groups was also separated from the reaction. Similar base-catalyzed eliminations of these protecting groups have been already reported.[8]

The assignment of the anomeric configuration of **1** was made on the basis of the known configuration of the nitrile used as starting material, since the doublet corresponding to the anomeric proton of **1** (τ 4.92) showed a coupling constant larger than 1 Hz ($J_{1,2}$ = 5 Hz). This assignment was further supported by the consistent application of Imbach's criterion[9] on the 2′,3′-*O*-isopropylidene-β-D-ribofuranosyl nucleoside **14**, obtained from **1** as described below.

Reaction of the thiocarboxamide **1** with chloroacetone in ethanol afforded a mixture of 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-4-methylthiazole (**4a**) in 32% yield and the furan derivative **5a** in 15% yield. Debenzoylation of these products with methanolic ammonia gave the deblocked compounds **4b** and **5b**, respectively (Scheme I). Similarly, reaction of the furan thiocarboxamide **2** with chloroacetone gave a 35% yield of **5a** identical with the compound obtained in the foregoing reaction.

Scheme I



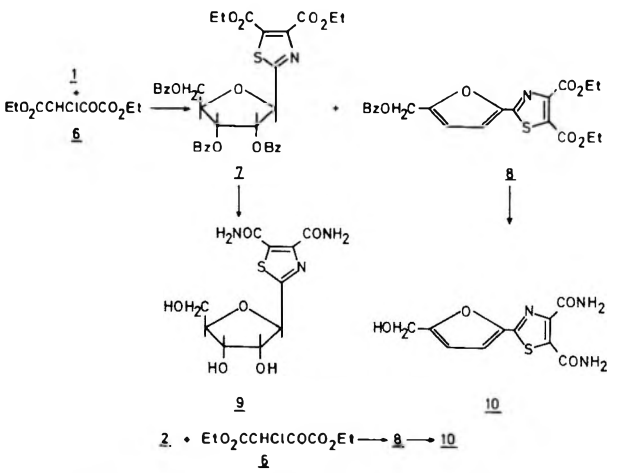
The thiocarboxamide **1** reacted smoothly with ethyl oxalochloroacetate to give a mixture of the blocked C-nucleoside **7** and the elimination product **8** which were isolated by preparative layer chromatography in yields of 31 and 27%, respectively. Compound **8** was also obtained from the reaction of furan thiocarboxamide **2** with ethyl oxalochloroacetate (Scheme II).

Treatment of compounds **7** and **8** with methanol saturated with ammonia gave the corresponding deblocked dicarboxamides in low yields. In the case of compound **7**, TLC of the crude reaction showed a complex mixture of products. Separation by preparative thick layer chromatography gave the expected deblocked β anomer **9** in 25% yield. ^{1}H NMR spectra of other minor bands showed the presence of the α anomer along with traces of compound **10**. It should be noted that no anomerization was detected in the debenzoylation reactions of the other 2-*C*-glycosyl thiazole nucleosides described in this paper.

In a similar fashion the thiocarboxamide **1**, when treated with ethyl bromopyruvate at reflux in ethanol solution, gave the protected *C*-glycosyl nucleoside **12** in 55% yield as a syrup. Although a furan derivative was expected, no compound of this type was found. Treatment of **12** with methanolic am-

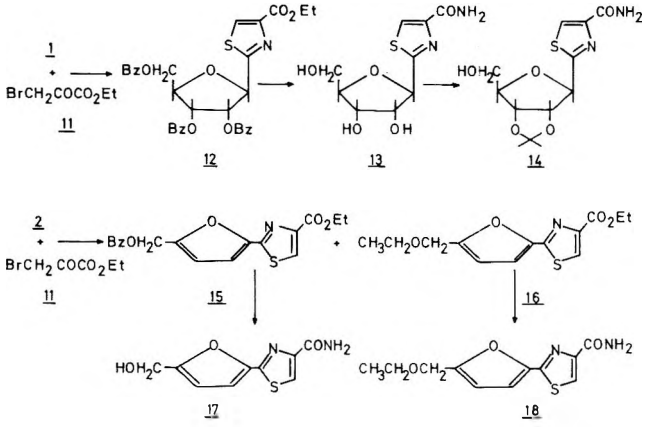
† The present paper is dedicated to the memory of Professor García-Muñoz.

Scheme II



monia afforded 2-(β-D-ribofuranosyl)thiazole-4-carboxamide (13) as a crystalline product in 81% yield. This latter compound was then converted to the 2′,3′-O-isopropylidene derivative 14. Its NMR spectrum showed the protons of the isopropylidene methyl groups as two singlets at τ 8.50 and 8.68, respectively. This difference of 0.18 ppm has been shown to be consistent only with the β configuration[9] (Scheme III).

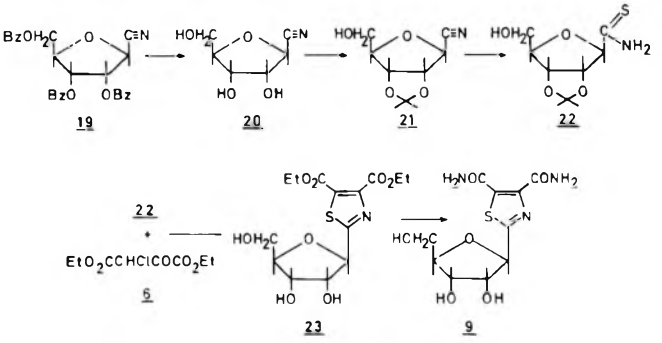
Scheme III



As before, the use of the thiocarboxamide 2 in the synthesis of nucleoside-related compounds having a furyl moiety was evaluated. Reaction of 2 with ethyl bromopyruvate in refluxing ethanol gave, besides the expected compound 15 in 30% yield, another compound in 27% yield that was identified as 2-(4-carboethoxythiazol-2-yl)-5-ethoxymethylfuran (16). The NMR spectrum of 16 indicated clearly the absence of benzoyl protons and the presence of signals corresponding to an ethoxy group, in addition to the signals of the carboethoxy thiazole substituent. Further evidence for the structure assignment for 16 stems from its conversion to the carboxamide 18, the NMR spectrum of which retains the characteristic pattern for the ethoxymethyl moiety. The formation of 16 can be explained taking account of the stability of the carbonium ion resulting from the cleavage of the C–O linkage of the benzoyloxy group due to the acidic media originated in the reaction. Attack of the carbonium ion by ethanol affords 16. Chemical evidence for this assumption was supported by the formation of 16 from 15, when this last compound was treated with ethanol–hydrogen bromide at reflux temperature. Attempts to find compounds similar to 16 in the reaction of 2 with chloroacetone or ethyl oxalochloroacetate were unsuccessful.

In order to avoid the formation of furan derivatives by loss of the benzoyl groups in the condensation of 1 with α-halo ketones, we synthesized the glycosyl thiocarboxamide 22 having an isopropylidene protecting group. The glycosyl nitrile 19 was debenzoylated at room temperature with methanolic ammonia to give the deblocked derivative 20, which was treated with ethyl orthoformate and acetone in the presence of hydrochloric acid to yield 2,3-O-isopropylidene-β-D-ribofuranosyl cyanide (21). Treatment of this product with hydrogen sulfide in ethanol containing triethylamine afforded 22 (Scheme IV).

Scheme IV

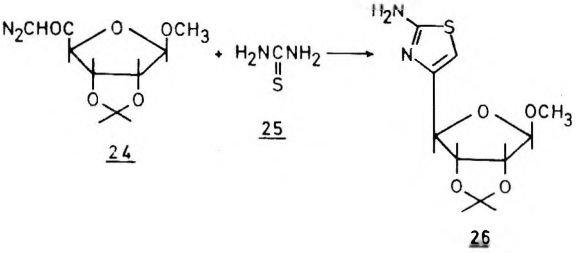


Reaction of thiocarboxamide 22 with ethyl oxalochloroacetate was then examined. As we expected, only one thiazole derivative was formed in a process involving the concomitant removal of the protecting isopropylidene group, due to the acidity of the reaction medium. Subsequent ammonolysis of the diester 23 gave the crystalline dicarboxamide derivative 9 identical with the compound obtained from 7.

It should be pointed out that compounds 7, 9, and 23 provide a series of valuable intermediates for synthesis, via cyclization, of new purinelike nucleosides.

Finally, since it has been reported that the reaction of α-diazo ketones with thioamides gives thiazole derivatives,[10] we then extended our studies to the synthesis of the 4-glycosyl thiazole derivative 26 by reaction in refluxing ethanol of the diazoketose 24[11] with thiourea (Scheme V). An analytically

Scheme V



pure sample of 26 was obtained via its picrate derivative, since all the attempts we made to obtain it from the repeatedly chromatographed reaction product were unsuccessful. The synthesis of compound 26 failed when the reaction was performed starting from the corresponding α-haloketose, probably due to the known instability of this compound.[11]

Experimental Section

Melting points were determined on a Kofler apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were recorded at 100 MHz on a Varian XL-100 spectrometer using Me_4Si as internal standard. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Uv absorption spectra were taken with a Perkin-Elmer 350 spectrophotometer. Analytical thin layer chromatography was performed on glass plates coated with a 0.25 mm layer of silica gel GF_{254} (Merck), and preparative layer chromatography on 20 × 20 cm glass plates coated with a 2-mm layer of silica gel PF_{254} (Merck). The compounds were detected with a uv light (254 nm)

or by spraying the plates with 30% sulfuric acid in ethanol and heating at ca. 110 °C.

2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosylthiocarboxamide (1) and 5-Benzoyloxymethylfuran-2-thiocarboxamide (2). A mixture of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide[7] (**19**, 1.41 g, 3 mmol), triethylamine (3.5 ml), and ethanol (60 ml) was stirred at room temperature for 2 h, while hydrogen sulfide was bubbled into the solution. The solvent was removed and the residue was chromatographed on plates using 20:1 benzene–ether as developing system. The two faster moving bands did not contain sulfur and were not further investigated. The third faster moving band yielded 0.19 g of a solid product that after crystallization from ethyl acetate–petroleum ether gave 0.11 g (14%) of compound **2** with mp 130–131 °C; NMR ($CDCl_3$) τ 3.45 (d, H-3, $J_{3,4}$ = 4 Hz), 4.71 (s, $-CH_2OBz$).

Anal. Calcd for $C_{13}H_{11}NO_3S$: C, 59.77; H, 4.21; N, 5.36; S, 12.26. Found: C, 59.85; H, 4.27; N, 5.06; S, 12.19.

The slowest moving band gave 0.46 g of product that was rechromatographed on preparative plates (1:9 ethyl acetate–chloroform) to provide 0.30 g (20%) of **1** as a yellow foam: $[\alpha]^{25}D$ + 2° (*c* 1, chloroform); NMR ($CDCl_3$) τ 4.02 (t, H-2, $J_{2,1} \simeq J_{2,3}$ = 5 Hz), 4.32 (m, H-3), 4.92 (d, H-1, $J_{1,2}$ = 5 Hz), 5.30 (m, H-4, 2 H-5).

Anal. Calcd for $C_{27}H_{23}NO_7S$: C, 64.15; H, 4.58; N, 2.77; S, 6.32. Found: C, 63.95; H, 4.75; N, 2.73; S, 6.59.

2-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-4-methylthiazole (4a) and 2-(4-Methylthiazol-2-yl)-5-benzoyloxymethylfuran (5a). A solution of 2,3,5-tri-O-benzoyl-β-D-ribofuranosylthiocarboxamide (**1**, 2.02 g, 4 mmol) and freshly distilled chloroacetone (**3**, 0.74 g, 8 mmol) in ethanol (15 ml) was heated under reflux for 7 h. The solvent was evaporated, the residue was dissolved in ethyl acetate, and the solution was washed with 5% aqueous sodium bicarbonate and with water and dried over sodium sulfate. After evaporation of the solvent the residue was purified by preparative TLC using 1:4 ethyl acetate–petroleum ether. The slowest moving band afforded 0.65 g (30%) of **4a** as a homogeneous syrup: $[\alpha]^{25}D$ −32° (*c* 1, chloroform); NMR ($CDCl_3$) τ 3.16 (H-5 thiazole ring), 4.36 (d, H-1′, $J_{1',2'}$ = 5 Hz), 7.57 (CH_3).

Anal. Calcd for $C_{30}H_{25}NO_7S$: C, 66.29; H, 4.63; N. 2.57; S, 5.88. Found: C, 66.06; H, 4.62; N, 2.48; S, 6.08.

The third band from the origin gave 0.18 g (15%) of **5a** with mp 72–73 °C (from ethyl acetate–petroleum ether); NMR ($CDCl_3$) τ 3.20 (H-5 thiazole ring), 3.09 (d, H-3 furan ring, $J_{3,4}$ = 4 Hz), 3.43 (d, H-4 furan ring, $J_{4,3}$ = 4Hz), 4.67 (s, CH_2OBz), 8.54 (CH_3).

Anal. Calcd for $C_{16}H_{13}NO_3S$: C, 64.20; H, 4.37; N, 4.68; S, 10.69. Found: C, 64.22; H, 4.44; N, 4.67; S, 10.80.

2-(4-Methylthiazol-2-yl)-5-benzoyloxymethylfuran (5a). A solution of the thiocarboxamide **2** (1.3 g, 5 mmol) and chloroacetone (**3**, 0.93 g, 10 mmol) in ethanol (25 ml) was refluxed for 7 h. The solvent was evaporated and the residue was purified by preparative TLC using 1:5 ethyl acetate–petroleum ether. The slowest moving band afforded 0.53 g (35%) of **5a** with physical properties identical with those previously reported for that compound.

2-(β-D-Ribofuranosyl)-4-methylthiazole (4b). A solution of **4a** (0.42 g, 0.73 mmol) in methanol saturated with ammonia at 0 °C (30 ml) was allowed to stand at room temperature for 48 h. The solvent was evaporated and the residue was purified by preparative TLC (9:1 chloroform–methanol) to give 0.14 g (80%) of **4b**: mp 122–124 °C (from ethyl acetate–petroleum ether); $[\alpha]^{25}D$ −24° (*c* 0.5, ethanol); uv λ_{max} (ethanol) 250 nm (ε 6700); NMR (Me_2SO-d_6–D_2O) τ 2.85 (H-5 thiazole ring), 5.12 (d, H-1′, $J_{1'2'}$ = 5 Hz), 7.68 (CH_3).

Anal. Calcd for $C_9H_{13}NO_4S$: C, 46.75; H, 5.66; N, 6.05; S, 13.84. Found: C, 46.79; H, 5.56; N, 5.90; S, 14.01.

2-(4-Methylthiazol-2-yl)-5-hydroxymethylfuran (5b). A solution of **5a** (0.30 g, 1 mmol) in saturated methanolic ammonia was kept at room temperature for 20 h. The solvent was evaporated and the residue purified by preparative TLC using 1:1 ethyl acetate–petroleum ether. Elution of the major band afforded 0.09 g (46%) of a solid which was recrystallized from ethyl acetate–petroleum ether to give pure **5b** with mp 151–153 °C; uv λ_{max} (ethanol) 219 nm (ε 8600), 318 (16 420); NMR (Me_2SO-d_6–D_2O) τ 2.79 (H-5 thiazole ring), 3.07 (d, H-3 furan ring, $J_{3,4}$ = 4 Hz), 3.55 (d, H-4 furan ring, $J_{4,3}$ = 4 Hz), 5.55 (s, CH_2OH), 7.63 (CH_3).

Anal. Calcd for $C_9H_9NO_2S$: C, 55.38; H, 4.64; N, 7.17; S, 16.40. Found: C, 55.14; H, 4.70; N, 7.32; S, 16.54.

2-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-4,5-dicarboethoxythiazole (7) and 2-(4,5-Dicarboethoxythiazol-2-yl)-5-benzoyloxymethylfuran (8). A solution of **1** (1.01 g, 2 mmol) and ethyl oxalochloroacetate[12] (**6**, 0.89 g, 4 mmol) in ethanol (15 ml) was heated under reflux for 6 h. The solvent was removed and the residue was chromatographed by preparative TLC using 1:4 ethyl acetate–petroleum ether as developing system. The slowest moving band yielded 0.65 g of a syrup which was rechromatographed (1:4 ethyl acetate–petroleum ether) to give 0.42 g (31%) of **7** as a homogeneous syrup: $[\alpha]^{25}D$ −57° (*c* 0.5, chloroform); NMR ($CDCl_3$) τ 4.01–4.24 (m, H-2′ and H-3′), 4.39 (d, H-1′, $J_{1',2'}$ = 5 Hz).

Anal. Calcd for $C_{35}H_{31}NO_{11}S$: C, 62.40; H, 4.63; N, 2.07; S, 4.74. Found: C, 62.12; H, 4.69; N, 2.12; S, 5.02.

The next moving band gave 0.23 g (27%) of **8** with mp 82–83 °C (from ethyl acetate–petroleum ether); NMR ($CDCl_3$) τ 2.87 (d, H-3 furan ring, $J_{3,4}$ = 4 Hz), 3.39 (d, H-4 furan ring, $J_{4,3}$ = 4 Hz), 4.66 (s, CH_2OBz), 5.56 and 5.66 (2 q, $2CH_2CH_3$), 8.60 and 8.65 (2t, $2CH_2CH_3$).

Anal. Calcd for $C_{21}H_{19}NO_7S$: C, 58.73; H, 4.46; N, 3.26; S, 7.45. Found: C, 58.50; H, 4.34; N, 3.14; S, 7.73.

2-(4,5-Dicarboethoxythiazol-2-yl)-5-benzoyloxymethylfuran (8). Reaction of **2** (1.05 g, 4 mmol) with ethyl oxalochloroacetate (**6**, 1.78 g, 8 mmol) in refluxing ethanol (25 ml) for 7 h afforded after three successive preparative TLC (I, 1:5 ethyl acetate–petroleum ether; II and III, 1:2 ethyl acetate–petroleum ether) 0.47 g (27%) of **8** identical with that above described.

2-(β-D-Ribofuranosyl)thiazole-4,5-dicarboxamide (9). Treatment of **7** (0.30 g, 0.44 mmol) with methanolic ammonia (25 ml) for 20 h gave a complex mixture of compounds. The residue obtained after evaporation of the solvent was purified by two consecutive preparative TLC (the first using 9:1 chloroform–methanol and the second 7:3 chloroform–methanol). Crystallization from ethanol of the solid obtained gave 0.03 g (25%) of **9**: mp 212–214 °C; $[\alpha]^{25}D$ −33° (*c* 0.5, water); uv λ_{max} (ethanol) 220 nm (ε 14 100), 269 (8420); NMR (Me_2SO-d_6–D_2O) τ 5.12 (d, H-1′, $J_{1',2'}$ = 5 Hz).

Anal. Calcd for $C_{10}H_{13}N_3O_6S$: C, 39.60; H, 4.32; N, 13.85; S, 11.54. Found: C, 39.36; H, 4.55; N, 13.58; S, 11.20.

2-(4,5-Dicarboxamidothiazol-2-yl)-5-hydroxymethylfuran (10). A solution of **8** (0.43 g, 1 mmol) in methanolic ammonia (25 ml) was allowed to stand at room temperature for 20 h. The white solid precipitated was filtered off and after treatment with active charcoal was recrystallized from methanol to give 0.06 g (21%) of **10**: mp 260–261 °C dec; uv λ_{max} (ethanol) 239 nm (ε 15 370), 337 (16 990); NMR (Me_2SO-d_6–D_2O) τ 2.80 (d, H-3 furan ring, $J_{3,4}$ = 4 Hz), 3.48 (d, H-4 furan ring, $J_{4,3}$ = 4 Hz), 5.53 (s, CH_2OH).

Anal. Calcd for $C_{10}H_9N_3O_4S$: C, 44.94; H, 3.39; N, 15.72. Found: C, 44.84; H, 3.49; N, 15.54.

2-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-4-carboethoxythiazole (12). A mixture of **1** (2.02 g, 4 mmol) and ethyl bromopyruvate (**11**, 1.56 g, 8 mmol) in ethanol (15 ml) was refluxed for 5 h. The solvent was evaporated and the residue purified by preparative TLC using 1:9 ethyl acetate–chloroform. The product obtained from the major band was rechromatographed in a mixture of 1:2 ethyl acetate–petroleum ether to give 1.33 g (55%) of **12** as a homogeneous syrup: $[\alpha]^{25}D$ −45.5° (c 1, chloroform); NMR ($CDCl_3$) τ 1.94 (s, H-5 thiazole ring), 4.31 (d, H-1′, $J_{1',2'}$ = 5 Hz), 5.66 (q, CH_2CH_3), 8.67 (t, CH_2CH_3).

Anal. Calcd for $C_{32}H_{27}NO_9S$: C, 63.88; H, 4.52; N, 2.32; S, 5.32. Found: C, 63.58; H, 4.26; N, 2.14; S, 5.61.

2-(β-D-Ribofuranosyl)thiazole-4-carboxamide (13). Treatment of **12** (1 g, 0.17 mmol) with methanolic ammonia (50 ml) at room temperature for 48 h and evaporation of the solvent afforded a product which was purified by preparative TLC using 7:3 chloroform–methanol. Elution of the major band gave 0.35 g (81%) of **13**: mp 145–146 °C (from ethanol–ethyl acetate); $[\alpha]^{25}D$ −9° (c 0.5, ethanol); uv λ_{max} (ethanol) 215 nm (ε 9450), 237 (7625); NMR (Me_2SO-d_6–D_2O) τ 1.82 (s, H-5 thiazole ring), 5.04 (d, H-1′, $J_{1',2'}$ = 5 Hz).

Anal. Calcd for $C_9H_{12}N_2O_5S$: C, 41.54; H, 4.64; N, 10.76; S, 12.30. Found: C, 41.93; H, 4.67; N, 10.86; S, 12.10.

2-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)thiazole-4-carboxamide (14). To a solution of **13** (0.20 g, 0.76 mmol), ethyl orthoformate (0.12 g, 0.80 mmol), and dry acetone (4 ml) was added a 1 M solution of hydrogen chloride in ether (0.1 ml). The mixture was stirred at room temperature until the solid was completely dissolved (24 h). The solution was neutralized with concentrated ammonium hydroxide and evaporated to dryness. The residue was dissolved in a small amount of water and the solution extracted several times with ethyl acetate. The organic phase was dried over sodium sulfate and evaporated, leaving a residue which was purified by TLC using 1:2 ethyl acetate–petroleum ether. The solid obtained from the major band was recrystallized from ethyl acetate–petroleum ether to give 0.15 g (64%) of **14**: mp 119–120 °C; $[\alpha]^{25}D$ −32° (c 0.5, water); uv λ_{max} (ethanol) 215 nm (ε 7830), 237 (7390); NMR (Me_2SO-d_6–D_2O) τ 1.82 (s, H-5 thiazole ring), 4.86 (d, H-1′, $J_{1',2'}$ = 4 Hz), 5.00 (dd, H-2′, $J_{2',3'}$ = 6, $J_{2',1'}$ = 4 Hz), 5.28 (dd, H-3′, $J_{3',2'}$ = 6, $J_{3',4'}$ = 3 Hz), 8.50 and 8.68 (2 CH_3 isopropylidene group).

Anal. Calcd for $C_{12}H_{16}N_2O_5S$: C, 47.99; H, 5.37; N, 9.33; S, 10.65.

Found: C, 47.94; H, 5.40; N, 9.46; S, 10.62.

2-(4-Carboethoxythiazol-2-yl)-5-benzoyloxymethylfuran (15) and 2-(4-Carboethoxythiazol-2-yl)-5-ethoxymethylfuran (16). A solution of **2** (1.05 g, 4 mmol) and ethyl bromopyruvate (**11**, 1.56 g, 8 mmol) in ethanol (15 ml) was refluxed for 5 h. After evaporation of the solvent the residue was purified by preparative TLC using 1:9 ethyl acetate–chloroform. The solid obtained from the slowest moving band was then rechromatographed in 1:2 ethyl acetate–petroleum ether. Elution of the major band afforded a solid material which was recrystallized from ethyl acetate–petroleum ether to give 0.30 g (27%) of **16**: mp 69–71 °C; NMR ($CDCl_3$) τ 1.94 (s, H-5 thiazole ring), 2.91 (d, H-3 furan ring, $J_{3,4}$ = 4 Hz), 3.57 (d, H-4 furan ring, $J_{4,3}$ = 4 Hz), 5.53 (s, OCH_2), 5.59 and 6.44 (2 q, 2 CH_2CH_3), 8.60 and 8.78 (2 t, 2 CH_2CH_3).

Anal. Calcd for $C_{13}H_{15}NO_4S$: C, 55.51; H, 5.33; N, 4.98; S, 11.38. Found: C, 55.68; H, 5.30; N, 5.09; S, 11.25.

The next moving band from the initial chromatography yielded a compound which was further purified by preparative TLC using 1:2 ethyl acetate–petroleum ether. The crystalline solid obtained, **15** (0.44 g, 30%), had mp 99–101 °C (from ethyl acetate–petroleum ether); NMR ($CDCl_3$) τ 1.94 (s, H-5 thiazole ring), 2.91 (d, H-3 furan ring, $J_{3,4}$ = 4 Hz), 3.42 (d, H-4 furan ring, $J_{4,3}$ = 4 Hz), 4.68 (s, OCH_2), 5.60 (q, CH_2CH_3), 8.61 (t, CH_2CH_3).

Anal. Calcd for $C_{18}H_{15}NO_5S$: C, 60.50; H, 4.23; N, 3.92; S, 8.95. Found: C, 60.72; H, 4.29; N, 4.12; S, 9.14.

2-(4-Carboxamidothiazol-2-yl)-5-hydroxymethylfuran (17). Compound **15** (0.18 g, 0.5 mmol) was treated with a saturated solution of ammonia in methanol for 24 h. Evaporation of the solvent left a residue which was crystallized from ethanol to give 0.09 g (80%) of **17**: mp 196–198 °C; uv λ_{max} (ethanol) 231 nm (ϵ 15 410), 315 (18 100); NMR (Me_2SO-d_6–D_2O) τ 1.79 (s, H-5 thiazole ring), 2.87 (d, H-3 furan ring, $J_{3,4}$ = 4 Hz), 3.45 (d, H-4 furan ring, $J_{4,3}$ = 4 Hz), 5.49 (s, OCH_2).

Anal. Calcd for $C_9H_8N_2O_3S$: C, 48.21; H, 3.59; N, 12.49; S, 14.26. Found: C, 48.41; H, 3.67; N, 12.40; S, 14.11.

2-(4-Carboxamidothiazol-2-yl)-5-ethoxymethylfuran (18). Treatment of **16** (0.14 g, 0.5 mmol) according to the procedure described for **17** afforded 0.07 g (58%) of **18** after crystallization from ethanol: mp 154–156 °C; uv λ_{max} (ethanol) 231 nm (ϵ 15 140), 313 (18 100); NMR (Me_2SO-d_6–D_2O) τ 1.78 (s, H-5 thiazole ring), 2.88 (d, H-3 furan ring, $J_{3,4}$ = 4 Hz), 3.36 (d, H-4 furan ring, $J_{4,3}$ = 4 Hz), 5.53 (s, OCH_2), 6.50 (q, CH_2CH_3), 8.86 (t, CH_2CH_3).

Anal. Calcd for $C_{11}H_{12}N_2O_3S$: C, 52.37; H, 4.79; N, 11.10; S, 12.70. Found: C, 52.42; H, 4.54; N, 10.97; S, 12.98.

2,3-*O*-Isopropylidene-β-D-ribofuranosyl Cyanide (21). Treatment of **19** (4.71 g, 10 mmol) with methanolic ammonia at room temperature for 20 h yielded **20** which was used in the next step without further purification. Isopropylidination of **20** was carried out according to the procedure described for **14**. Column chromatography of the crude reaction product (~3.7 g) on silica gel (80 g) using 1:2 ethyl acetate–petroleum ether as eluent afforded a solid material which was crystallized from ethyl acetate–petroleum ether to give 0.64 g (32% total yield) of **21**: mp 63–65 °C; $[\alpha]^{25}D$ −35° (c 0.7, chloroform); NMR (Me_2SO-d_6–D_2O) τ 4.96 (dd, H-2, $J_{2,1}$ = 2, $J_{2,3}$ = 6 Hz), 5.10 (d, H-1, $J_{1,2}$ = 2 Hz), 5.22 (dd, H-3, $J_{3,2}$ = 6, $J_{3,4}$ = 1 Hz), 5.87 (m, H-4), 6.52 (m, 2 H-5), 8.60 and 8.74 ($2CH_3$, isopropylidene group).

Anal. Calcd for $C_9H_{13}NO_4$: C, 54.27; H, 6.53; N, 7.08. Found: C, 54.41; H, 6.78; N, 6.98.

2,3-*O*-Isopropylidene-β-D-ribofuranosylthiocarboxamide (22). Hydrogen sulfide was bubbled into a solution of **21** (0.60 g, 3 mmol) in ethanol (30 ml) containing triethylamine (0.10 g, 1 mmol) for 2 h. The solvent was evaporated and the residue was purified by preparative TLC using 1:1 ethyl acetate–petroleum ether. Elution of the uv absorbing band (254 nm) afforded 0.60 g (86%) of **22** as a yellow syrup that crystallized on standing: mp 96–97 °C (from ethyl acetate–petroleum ether); $[\alpha]^{25}D$ −17° (c 1, chloroform); NMR (Me_2SO-d_6–D_2O) τ 5.21 (dd, H-2, $J_{2,1}$ = 4, $J_{2,3}$ = 6 Hz), 5.43 (dd, H-3, $J_{3,2}$ = 6, $J_{3,4}$ = 4 Hz), 5.50 (d, H-1, $J_{1,2}$ = 4 Hz), 5.93 (m, H-4), 8.54 and 8.72 (2 CH_3 isopropylidene group).

Anal. Calcd for $C_9H_{15}NO_4S$: C, 46.34; H, 6.48; N, 6.00. Found: C, 46.65; H, 6.49; N, 5.93.

2-(β-D-Ribofuranosyl)-4,5-dicarboethoxythiazole (23). A solution of the thioamide **22** (0.47 g, 2 mmol) and ethyl oxalochloroacetate (**6**, 0.39 g, 4 mmol) in ethanol (15 ml) was refluxed for 6 h. The solvent was removed and the residue purified by preparative TLC using a mixture of 9:1 chloroform–methanol. Elution of the major band afforded a material which was further chromatographed using ethyl acetate, to give 0.23 g (32%) of **23** as a homogeneous syrup: $[\alpha]^{25}D$ −29° (c 0.5, chloroform); uv λ_{max} (ethanol) 213 nm (ϵ 13 890), 263 (13 890); NMR (Me_2SO-d_6–D_2O) τ 5.06 (d, H-1′, $J_{1',2'}$ = 5 Hz), 5.67 and 5.76 (2 q, 2 CH_2CH_3), 8.70 and 8.73 (2 t, 2 CH_2CH_3).

Anal. Calcd for $C_{14}H_{19}NO_8S$: C, 46.53; H, 5.26; N, 3.87. Found: C, 46.37; H, 5.60; N, 3.57.

2-(β-D-Ribofuranosyl)thiazole-4,5-dicarboxamide (9). Treatment of **23** (0.17 g, 0.47 mmol) with methanolic ammonia for 20 h gave after recrystallization from ethanol 0.08 g (56%) of **9** identical in all respects with **9** prepared from **7**.

Methyl 2,3-*O*-Isopropylidene-4-(2-aminothiazol-4-yl)-β-D-*ribo*-tetrafuranoside (26). A mixture of methyl 6-deoxy-6-diazo-2,3-*O*-isopropylidene-β-D-*ribo*-hexofuranosid-5-ulose[11] (**24**, 0.80 g, 3.30 mmol) and thiourea (**25**, 0.76 g, 10 mmol) in ethanol (20 ml) was refluxed for 20 h, and then the solvent was evaporated. The residue was dissolved in chloroform and the unreacted thiourea removed by filtration. The filtrate was concentrated almost to dryness and the remaining residue was applied on preparative TLC plates which were developed with a mixture of 4:1 ethyl acetate–chloroform. Elution of the fastest moving band afforded 0.03 g of the starting diazo derivative **24**. The next band gave 0.28 g (32%) of **26** as a yellow syrup which was treated with a saturated ethanolic solution of picric acid. The picrate obtained was recrystallized from ethanol to yield 0.31 g of pure material with mp 167 °C.

Anal. Calcd for $C_{17}H_{19}N_5O_{11}S$: C, 40.71; H, 3.79; N, 13.97. Found: C, 40.89; H, 3.57; N, 13.62.

The free nucleoside **26** was obtained by passing the picrate through a short column of neutral alumina using ethyl acetate as eluent. This procedure afforded 0.14 g (16% total yield) of **26** as an analytically pure syrup: $[\alpha]^{25}D$ −31° (c 0.6, chloroform); NMR ($CDCl_3$) τ 3.65 (d, H-5 thiazole ring, $J_{5,4'} \simeq$ 1 Hz), 4.93 (t, H-4′, $J_{4',3'} \simeq J_{4',5}$ = 1 Hz), 4.94 (s, H-1′), 5.04 (dd, H-3′, $J_{3',2'}$ = 6, $J_{3',4'}$ = 1 Hz), 5.41 (d, H-2′, $J_{2',3'}$ = 6 Hz), 6.65 (s, OCH_3), 8.50 and 8.70 (2 CH_3 isopropylidene group).

Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.92; N, 10.29. Found: C, 48.45; H, 6.08; N, 9.95.

Registry No.—**1**, 57944-10-2; **2**, 57944-12-4; **3**, 78-95-5; **4a**, 57944-11-3; **4b**, 60084-02-8; **5a**, 60084-03-9; **5b**, 60084-04-0; **6**, 34034-87-2; **7**, 60084-05-1; **8**, 60084-06-2; **9**, 60084-07-3; **10**, 60084-08-4; **11**, 70-23-5; **12**, 60084-09-5; **13**, 60084-10-8; **14**, 60084-11-9; **15**, 60084-12-0; **16**, 60084-13-1; **17**, 60084-14-2; **18**, 60084-15-3; **19**, 23316-67-8; **20**, 26882-26-8; **21**, 60084-16-4; **22**, 60084-17-5; **23**, 60084-18-6; **24**, 54622-96-7; **25**, 62-56-6; **26**, 60084-19-7; **26** picrate, 60084-20-0.

References and Notes

(1) J. M. Sprague and A. H. Land in "Heterocyclic Compounds", Vol. V, R. C. Elderfield, Ed., Wiley, New York, N.Y., 1957, p 484.
(2) A. Cañas Rodríguez and F. J. López Aparicio, *An. R. Soc. Esp. Fis. Quim., Ser. B*, **50**, 609 (1954); H. Beyer and U. Schulz, *Ber.*, **87**, 78 (1954); J. B. Lee and B. F. Scanlon, *Tetrahedron*, **25**, 3413 (1969).
(3) A. Cañas Rodríguez, *An. R. Soc. Esp. Fis. Quim., Ser. B*, **53**, 705 (1957).
(4) J. M. J. Tronchet and H. Eder, *Helv. Chim. Acta*, **58**, 1507 (1975).
(5) M. Fuertes, T. García-López, G. García-Muñoz, and R. Madroñero, *J. Carbohydr., Nucleosides, Nucleotides*, **2**, 277 (1975).
(6) The chosen nomenclature for **1**, in our opinion, is more understandable and in better agreement with that of the rest of the compounds described in this paper than the alternative 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonthioamide.
(7) M. Bobek and J. Farkas, *Collect. Czech. Chem. Commun.*, **34**, 247 (1969).
(8) H. P. Albrecht, D. B. Repke, and J. G. Moffatt, *J. Org. Chem.*, **39**, 2176 (1974).
(9) (a) J. L. Imbach, J. L. Barascut, B. L. Kam, B. Rayner, C. Tamby, and C. Tapiero, *J. Heterocycl. Chem.*, **10**, 1069 (1973); (b) J. L. Imbach, J. L. Barascut, B. L. Kam, and C. Tapiero, *Tetrahedron Lett.*, 129 (1974); (c) J. L. Barascut, C. Tamby, and J. L. Imbach, *J. Carbohydr., Nucleosides, Nucleotides*, **1**, 77 (1974).
(10) L. C. King and F. M. Miller, *J. Am. Chem. Soc.*, **71**, 367 (1949).
(11) A. Hampton, F. Perini, and P. J. Harper, *Carbohydr. Res.*, **37**, 359 (1974).
(12) A. C. Cope, *J. Am. Chem. Soc.*, **58**, 570 (1936).

Isolation and Structure Determination of the Second Toxic Constituent from *Tetradymia glabrata*

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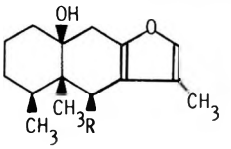
A new furanoeremophilane has been isolated and a derivative of it analyzed by x-ray crystallography. The two compounds are 10β-hydroxy-6β-isobutyrylfuranoeremophilane (II) and 6β,10β-dihydroxyfuranoeremophilane (III). Both have been shown to be hepatotoxins, LD_{50}^{IP} 400 and 113 mg/kg, respectively. Physical data are included in the publication with particular emphasis on NMR spectra correlation with x-ray structure. Compound III crystallized in a space group $P2_12_12_1$ with cell dimensions a = 21.322 (7) Å, b = 7.593 (2) Å, c = 8.387 (1) Å, with Z = 4. Counter data were refined by full-matrix least squares to a residual of 4.7%.

Recently Bohlmann[2] reported that plants belonging to the *genus Euryops, Senecio,* and *Othonna* (Senecioneae tribe) contain a variety of furanoeremophilane compounds. Further, Nagano,[3] Tada,[4] Ishii,[5] and Moriyama[6] have previously isolated a number of furanoeremophilanes from *Ligularia,* a member of the same tribe. In 1974, we reported[7] that another member of the Senecioneae tribe, *Tetradymia glabrata,* contained the furanoeremophilenic compound, I, which was subsequently shown to be one of the hepatotoxic substances responsible for the death of sheep feeding on the plant.

We now wish to report the isolation and characterization of a second hepatotoxic furanoeremophilenic compound, II, from the same plant. Compound III which is formed from the



I R=H "Tetradymol"
II R=OOC-CHMe$_2$
III R=OH "βTetradymodiol"

reductive cleavage of II is also reported. Its hepatotoxicity is greater than that of II and approximately equivalent to that of compound I. Included in this report is the x-ray structure analysis of compound III along with a discussion of the NMR spectra.

Results

Isolation. New growth and flower buds were picked in June and kept chilled until extraction with hexane. From 13.6 kg of wet plant which was ground and extracted in hexane, 6 g (0.04%) of white, crystalline material (compound II) was won via chromatography and sublimation. Since the toxin was lethal to both sheep and mice, the latter was used to monitor for toxin during the isolation steps. Similar hepatocellular damage resulted from ingestion of the toxins by both types of animals.

Furanoeremophilanes reported earlier have been generally found in the roots of the plant while the compounds reported in this paper and earlier work[7] were isolated from the new growth.

Except for the following data, a detailed discussion of toxicity will be published elsewhere.

Compd	LD_{50}^{oral}	LD_{50}^{IP}
I	275	94
II	375	400
III		113

Characterization of Compounds II and III. Compound II, which was positive to the Ehrlich test, exists as a white solid, mp 100–100.5 °C, M^+ at m/e 320, has an $[\alpha]^{26}D$ −55.85 ± 0.35 (EtOH), and analyzed correctly for $C_{19}H_{28}O_4$. Its ir, uv, NMR, and MS spectra (cf. Experimental Section) indicated a tertiary hydroxyl, an ester, a *gem*-dimethyl group, a 3-methyl substituted furan and both a secondary and a tertiary methyl group. Lithium aluminum hydride reduction of II gave diol III and isobutyl alcohol in 77% yield. This diol was analyzed by x-ray crystallography (Figure 1) and isobutyl alcohol was identified by GC/MS analysis. Esterification of diol III with isobutyric anhydride produced ester II in 33% yield which was identical with the original ester in all physical and physiological properties. Tada[4] reported the physical properties of diol III as melting at 122 °C dec and $[\alpha]D$ +50°. In our laboratory it melted at 144–145 °C and $[\alpha]D$ +26.98 ± 0.15°.[8] Several attempts at reproducing Tada's reported rotation values have failed and always resulted in a value near 26°. Despite this difference in data, the structure shown in Figure 1 is identical with the one described by Tada. In addition all our spectral data agreed with Tada's results.

Discussion

Discussion of X-Ray Analysis. Results of the single crystal x-ray analysis of 6β,10β-dihydroxyfuranoeremophilane are shown as an ORTEP drawing in Figure 1. Bond distances, bond angles, and torsion angles are given in Tables I, II, and III, respectively.

It is readily apparent from Figure 1 that diol III has the necessary cis relationships at positions C-4, C-5, and C-10 to place it in the eremophilane class.

Discussion of NMR Spectra. The nuclear magnetic resonance spectra for furanoeremophilane compounds having the three rings in an "anthranoid" arrangement[7] are characterized by a spectrum having distinctive resonances for furan methyl group near 1.9 ppm (d), a tertiary methyl group near 1.1 (s), and a secondary methyl group having virtual coupling and thus appearing as a filled-in doublet near 0.70. Also a series of peaks appear between 2.0 and 4.0 which are the protons at positions C-6 and C-9. In our first paper[7] dealing with these compounds, we identified these peaks for compound I as two overlapping AB quartets with the upfield quartet resonances due to protons at C-6 having the smaller coupling constant ≈9 Hz. The downfield quartet resonances due to protons at C-9 have a larger coupling constant ≈16–17 Hz.[9]

Factors contributing to the different environments for the α and β protons for positions 6 and 9 include (a) a fairly planar central ring, (b) rigidity of the central ring, and (c) the β hydroxyl group at C-10. These ideas are further verified by the NMR spectra reported for compounds II and III (Table IV). Since these two compounds have an oxygen functionality at

Table I. Bond Distances in Angstroms with Standard Deviations in Parentheses

C(1)–C(2)	1.528 (7)	C(8)–C(9)	1.465 (5)
C(1)–C(10)	1.524 (6)	C(8)–O(1)	1.370 (4)
C(1)–H(1α)	0.86 (3)	C(9)–C(10)	1.569 (5)
C(1)–H(1β)	1.04 (3)	C(9)–H(9α)	1.06 (3)
C(2)–C(3)	1.523 (7)	C(9)–H(9β)	0.97 (3)
C(2)–H(2α)	1.05 (4)	C(10)–O(2)	1.454 (5)
C(2)–H(2β)	0.96 (4)	C(11)–C(12)	1.350 (6)
C(3)–C(4)	1.529 (6)	C(11)–C(13)	1.468 (6)
C(3)–H(3α)	0.96 (4)	C(12)–O(1)	1.376 (5)
C(3)–H(3β)	1.04 (3)	C(12)–H(12)	1.02 (3)
C(4)–C(5)	1.567 (5)	C(13)–H(13a)	1.05 (4)
C(4)–C(14)	1.523 (6)	C(13)–H(13b)	1.33 (4)
C(4)–H(4)	1.09 (3)	C(13)–H(13c)	0.77 (4)
C(5)–C(6)	1.560 (5)	C(14)–H(14a)	1.03 (4)
C(5)–C(10)	1.556 (5)	C(14)–H(14b)	1.02 (4)
C(5)–C(15)	1.543 (5)	C(14)–H(14c)	0.94 (4)
C(6)–C(7)	1.495 (5)	C(15)–H(15a)	1.00 (3)
C(6)–O(3)	1.458 (4)	C(15)–H(15b)	0.91 (4)
C(6)–H(6)	0.98 (3)	C(15)–H(15c)	0.95 (3)
C(7)–C(8)	1.331 (5)	O(2)–H(O-2)	0.87 (3)
C(7)–C(11)	1.439 (5)	O(3)–H(O-3)	0.82 (3)

position C-6, there is only one AB quartet in the spectrum resulting from the α and β protons at C-9. In these examples the coupling constant is between 15 and 22 Hz. However, in the absence of an oxygen function at C-10, such a simplistic analysis fails.[2]

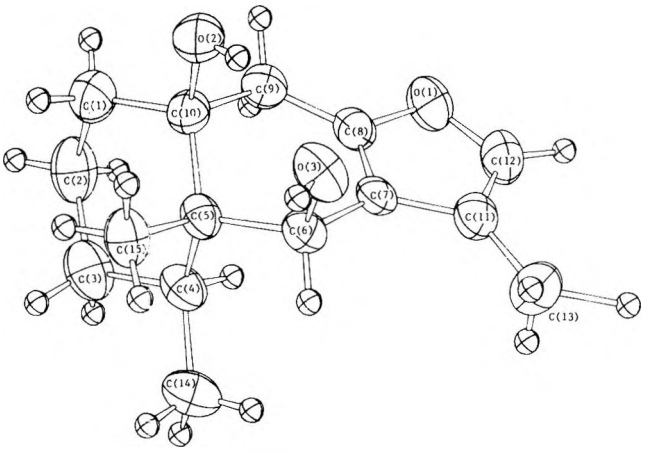


Figure 1. ORTEP drawing of tetradymodiol. Thermal ellipsoids have been scaled to include 50% probability; hydrogen atoms have been assigned an isotropic temperature factor of 1.0 for clarity.

Experimental Section

Infrared spectra were obtained using either a Beckman IR-4 or a Beckman IR-20. Nuclear magnetic resonance spectra were obtained on A-60, T-60, or HA-100 Varian spectrometers. Ultraviolet spectra were obtained on a Cary Model 14 and the mass spectra were collected from a Varian MAT CH-5 interfaced with a Varian Aerograph series 1700 gas–liquid chromatograph. Optical rotations were determined using a Bendix automatic polarimeter Model 1169.

Table II. Bond Angles in Degrees with Standard Deviations in Parentheses

C(2)–C(1)–C(10)	112.1 (4)	C(9)–C(8)–O(1)	120.4 (3)
C(2)–C(1)–H(1α)	112 (2)	C(8)–C(9)–C(10)	111.0 (3)
C(2)–C(1)–H(1β)	108 (2)	C(8)–C(9)–H(9α)	108 (2)
C(10)–C(1)–H(1α)	108 (2)	C(8)–C(9)–H(9β)	119 (2)
C(10)–C(1)–H(1β)	111 (2)	C(10)–C(9)–H(9α)	117 (2)
H(1α)–C(1)–H(1β)	104 (3)	C(10)–C(9)–H(9β)	102 (2)
C(1)–C(2)–C(3)	112.1 (4)	H(9α)–C(9)–H(9β)	100 (3)
C(1)–C(2)–H(2α)	117 (2)	C(1)–C(10)–C(5)	112.0 (3)
C(1)–C(2)–H(2β)	109 (2)	C(1)–C(10)–C(9)	109.4 (3)
C(3)–C(2)–H(2α)	98 (2)	C(1)–C(10)–O(2)	106.6 (3)
C(3)–C(2)–H(2β)	113 (2)	C(5)–C(10)–C(9)	112.9 (3)
H(2α)–C(2)–H(2β)	107 (3)	C(5)–C(10)–O(2)	110.0 (3)
C(2)–C(3)–C(4)	113.7 (4)	C(9)–C(10)–O(2)	105.7 (3)
C(2)–C(3)–H(3α)	114 (2)	C(7)–C(11)–C(12)	104.6 (3)
C(2)–C(3)–H(3β)	117 (2)	C(7)–C(11)–C(13)	128.5 (4)
C(4)–C(3)–H(3α)	101 (2)	C(12)–C(11)–C(13)	127.0 (4)
C(4)–C(3)–H(3β)	111 (2)	C(11)–C(12)–O(1)	111.9 (4)
H(3α)–C(3)–H(3β)	99 (3)	C(11)–C(12)–H(12)	129 (2)
C(3)–C(4)–C(5)	111.1 (3)	O(1)–C(12)–H(12)	119 (2)
C(3)–C(4)–C(14)	109.1 (3)	C(11)–C(13)–H(13a)	115 (2)
C(3)–C(4)–H(4)	105 (2)	C(11)–C(13)–H(13b)	126 (2)
C(5)–C(4)–C(14)	113.5 (3)	C(11)–C(13)–H(13c)	116 (3)
C(5)–C(4)–H(4)	113 (2)	H(13a)–C(13)–H(13b)	105 (3)
C(14)–C(4)–H(4)	105 (2)	H(13a)–C(13)–H(13c)	103 (3)
C(4)–C(5)–C(6)	110.5 (3)	H(13b)–C(13)–H(13c)	87 (3)
C(4)–C(5)–C(10)	108.0 (3)	C(4)–C(14)–H(14a)	120 (2)
C(4)–C(5)–C(15)	110.1 (3)	C(4)–C(14)–H(14b)	112 (2)
C(6)–C(5)–C(10)	110.3 (3)	C(4)–C(14)–H(14c)	113 (2)
C(6)–C(5)–C(15)	107.4 (3)	H(14a)–C(14)–H(14b)	100 (3)
C(10)–C(5)–C(15)	110.6 (3)	H(14a)–C(14)–H(14c)	102 (3)
C(5)–C(6)–C(7)	111.9 (3)	H(14b)–C(14)–H(14c)	109 (3)
C(5)–C(6)–O(3)	110.7 (3)	C(5)–C(15)–H(15a)	113 (2)
C(5)–C(6)–H(6)	105 (2)	C(5)–C(15)–H(15b)	113 (2)
C(7)–C(6)–O(3)	105.4 (3)	C(5)–C(15)–H(15c)	113 (2)
C(7)–C(6)–H(6)	116 (2)	H(15a)–C(15)–H(15b)	96 (3)
O(3)–C(6)–H(6)	108 (2)	H(15a)–C(15)–H(15c)	104 (3)
C(6)–C(7)–C(8)	121.0 (3)	H(15b)–C(15)–H(15c)	116 (3)
C(6)–C(7)–C(11)	131.2 (3)	C(8)–O(1)–C(12)	105.0 (3)
C(8)–C(7)–C(11)	107.5 (3)	C(10)–O(2)–H(O-2)	112 (2)
C(7)–C(8)–C(9)	128.6 (3)	C(6)–O(3)–H(O-3)	114 (2)
C(7)–C(8)–O(1)	111.0 (3)		

Table III. Torsion Angles in Degrees

C(1)–C(2)–C(3)–C(4)	−50.7	C(12)–O(1)–C(8)–C(9)	−178.4
C(2)–C(3)–C(4)–C(5)	54.2	O(1)–C(8)–C(9)–C(10)	−169.8
C(3)–C(4)–C(5)–C(10)	−56.3	C(6)–C(7)–C(8)–O(1)	174.5
C(4)–C(5)–C(10)–C(1)	58.2	C(9)–C(8)–C(7)–C(11)	177.7
C(5)–C(10)–C(1)–C(2)	−56.5	C(13)–C(11)–C(7)–C(6)	6.9
C(10)–C(1)–C(2)–C(3)	51.2	C(13)–C(11)–C(7)–C(8)	−178.8
C(5)–C(6)–C(7)–C(8)	25.4	C(13)–C(11)–C(12)–O(1)	178.8
C(6)–C(7)–C(8)–C(9)	−7.2	C(14)–C(4)–C(5)–C(6)	59.6
C(7)–C(8)–C(9)–C(10)	12.1	C(14)–C(4)–C(5)–C(10)	−179.7
C(8)–C(9)–C(10)–C(5)	−35.9	C(14)–C(4)–C(3)–C(2)	−179.9
C(9)–C(10)–C(5)–C(6)	55.0	C(15)–C(5)–C(6)–C(7)	−169.0
C(10)–C(5)–C(6)–C(7)	−48.4	C(15)–C(5)–C(10)–C(9)	173.7
C(7)–C(11)–C(12)–O(1)	−0.9	C(15)–C(5)–C(10)–C(1)	−62.3
C(11)–C(12)–O(1)–C(8)	0.5	C(15)–C(5)–C(4)–C(3)	64.5
C(12)–O(1)–C(8)–C(7)	0.0	O(2)–C(10)–C(1)–C(2)	−176.8
O(1)–C(8)–C(7)–C(11)	−0.6	O(2)–C(10)–C(5)–C(4)	176.5
C(8)–C(7)–C(11)–C(12)	0.8	O(2)–C(10)–C(5)–C(6)	−62.7
C(3)–C(4)–C(5)–C(6)	−177.1	O(2)–C(10)–C(9)–C(8)	84.4
C(4)–C(5)–C(6)–C(7)	70.9	O(3)–C(6)–C(7)–C(11)	78.9
C(8)–C(9)–C(10)–C(1)	−161.3	O(3)–C(6)–C(7)–C(8)	−94.9
C(9)–C(10)–C(1)–C(2)	69.4	O(3)–C(6)–C(5)–C(10)	68.7
C(4)–C(5)–C(10)–C(9)	−65.8	O(3)–C(6)–C(5)–C(4)	−171.9
C(1)–C(10)–C(5)–C(6)	179.0	C(14)–C(4)–C(5)–C(15)	−58.9
C(5)–C(6)–C(7)–C(11)	−160.8	C(15)–C(5)–C(10)–O(2)	56.0
C(6)–C(7)–C(11)–C(12)	−173.5	C(15)–C(5)–C(6)–O(3)	−51.9
O(2)–C(10)–C(6)–O(3)	4.4	C(14)–C(4)–C(6)–O(3)	−114.4

Isolation of II. Fourteen kilograms of frozen plant, which had been harvested approximately 20 miles south of Park Valley, Utah, was ground and extracted with 5 gal of hexane in a stainless steel cone. This procedure was carried out in a cold room at 5 °C to minimize decomposition. Solvent of the liquid extract was removed under vacuum and the semisolid material chromatographed on silica el resulting in only a crude separation of toxic constituents from other components.

The silica gel column of 4 ft × 4 in. was packed with 1500 g, charged with 75 g of crude extract and eluted with the solvent series hexane, diethyl ether, and methanol. Toxic compounds were eluted between 22% and 55% diethyl ether–hexane fractions.

Further purification was achieved using a 100-g alumina column which had been slurried and poured with a solvent containing 3% methanol in diethyl ether. Once settled, it was back eluted to hexane and charged with 1 g of crude material from the silica gel column. In the elution series hexane, diethyl ether, and methanol, compound II was eluted between 25% and 50% ether in hexane. At the end of the 50% ether fraction, another compound which as yet is unidentified is also found. Compound I and the above unknown are found in the 100% ether fraction.

Thin Layer Chromatography Results. Using prepoured Baker-flex silica gel 1B plates and solvent systems indicated, the following R_f values were obtained.

Compd	R_f
I[a]	0.28[b]
II	0.53[b]
III	0.50[c]

[a] Sulfuric dichromate. Ehrlich's reagent, and vanillin–sulfuric acid sprays were used for development. [b] Solvent system hexane–diethyl ether (1:1). [c] Solvent system hexane–diethyl ether–methanol (50:100:4).

Physical Data for 6β-Isobutyryl-10β-hydroxyfuranoeremophilane (II). The white crystals won from the wet plant by extraction, chromatography on silica gel and alumina, and sublimation melted at 100–100.5 °C, $[\alpha]^{MeOH}D$ −56.11 ± 0.35°, λ_{max} 2150 Å (log ε 3.80). Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.15; H, 8.61. Ir (CCl_4) 3590 and 1740 cm^{-1}; mass spectrum *m/e* 320, 232, 124 (base peak), and 71. LD_{50}^{mice} oral was 350–400 mg/kg.

Preparation of 6β,10β-Dihydroxyfuranoeremophilane (III). A. Saponification of II. A solution of 100 ml of hexane, 1.32 g of II, 6.3 g of KOH, and 25 ml of H_2O was refluxed (60 °C) for 8 h. Separation and cooling the hexane portion gave crystals of diol III in 42% yield. These white crystals melted at 142–143 °C; $[\alpha]^{25}D$ +26.98 ± 0.15° (EtOH); uv λ_{max} 2160 Å (log ε 3.79). Anal. Calcd for $C_{15}H_{22}O_4$: C, 71.87; H, 8.86. Found: C, 71.7; H, 8.8. Ir (KBr) 3350 (broad), 1650, and 1570 cm^{-1}; mass spectrum *m/e* 250, 231, and 124 (base peak).

The isobutyric acid garnered from the acidified water layer of the saponification by hexane extraction was proved identical with a known sample by mass spectrometry.

B. $LiAlH_4$ Reduction of II. Using 3 mmol of $LiAlH_4$ and 0.96 g of II in a standard reduction gave 0.580 g of diol III (77% yield) which was identical with III prepared by saponification. The isobutyl alcohol of the reaction was identified by GC–MS.

Preparation of II. A mixture of 250 mg of diol III, 7 ml of isobutyric anhydride, and 10 ml of anhydrous pyridine was placed in a stoppered flask at room temperature for 24 h. Extraction of the mixture with hexane which was subsequently washed with dilute HCl, dilute Na_2CO_3, and cold H_2O, dried, and evaporated gave a 33% yield of II after sublimation. Synthetic II was identical with original II according to its NMR, ir, uv, MS, mixture melting point, and elemental analysis.

Crystallographic Data Collection and Structure Analysis. Preliminary x-ray photographs of a crystal of diol III indicated the orthorhombic space group $P2_12_12_1$ with systematic absences of $h00$, $h \neq 2n$; $0k0$, $k \neq 2n$; and $00l$, $l \neq 2n$. Unit cell dimensions, refined by least squares from 16 independent 2θ values obtained with a G.E. XRD-490 diffractometer, are given in Table V. The crystal used was mounted along the *b* axis and bounded by {0·1·0}, (1·0·0), (4·0·1), ($\bar{8}$·0·$\bar{1}$), ($\bar{2}$·0·1), (2·0·$\bar{1}$), and ($\bar{2}$·0·$\bar{1}$); its approximate dimensions were 0.21 × 1.44 × 0.39 mm measured parallel to the *a*, *b*, and *c* axes, respectively. Ni filtered Cu Kα radiation and a scintillation counter detector were

Table IV. NMR Data[a]

	I ($CDCl_3$)	II ($CDCl_3$)	III (C_6D_6)
C-4 Me	0.80 d[d] (7)[b]	0.95 d[d] (7)	1.04 d (6)
C-5	0.95 s	1.05 s	1.08 s
C-11 Me	1.88 d (1)	1.85 d (1)	1.90 d (1)
C-6 H	2.2 2.4 q (9)[c]	3.2 s	4.37 d (6)
C-9 H	2.1 3.0 q (17)[c]	2.75 3.06 q (17)[c]	2.35 2.84 q (17.8)
C-12 H	7.04 s	6.98 s	6.97 s
i-Bu Me		1.07 (7) 1.3 (7)	
i-Bu H		2.45 m (7)	

[a] All data are reported in parts per million. [b] Coupling constant in hertz. [c] Major peaks of quartet. [d] Actually an A_3B splitting pattern.

Table V. Crystal Data for $C_{15}H_{22}O_3$

$a = 21.322\ (7)$	$\alpha = \beta = \gamma = 90°$
$b = 7.593\ (2)$	
$c = 8.387\ (1)$	
Space group $P2_12_12_1$	$Z = 4$
$\rho_c = 1.217$ g cm^{-3}	$\rho_{meas} = 1.203$ g cm^{-3}
μ(Cu Kα) = 6.76 cm^{-1}	

employed to collect intensity data out to a 2θ of 120° using automatic θ–2θ step scans. Of a total 1204 reflections scanned, 1053 were considered observed by the criteria $I > 3\sigma(I)$ and were included in structure refinement. Lorentz and polarization factors were applied in the normal manner,[10] and the data were corrected for absorption by the method of Tompa.[11] Weights were calculated by the method of Stout and Jensen:[12] $w(F) = [(K/4Lp\ I)(\sigma^2(I) + (0.03I)^2)]^{-1}$. Scattering factors used were as follows: for nonhydrogen atoms from Cromer and Mann;[13] and for hydrogen from Stewart, Davidson, and Simpson.[14]

The structure was solved by direct methods using the program MULTAN.[10] Positions of all nonhydrogen atoms were refined, first isotropically, then anisotropically, by full-matrix least squares minimizing $\Sigma w\Delta F^2$, and all hydrogen atoms were located from a subsequent difference Fourier map. Further refinement of positional parameters for all atoms and anisotropic temperature factors for the nonhydrogen atoms resulted in a final R factor of 4.7% ($R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$). The R factor for all data, including unobserved reflections, was 5.7%; the weighted R_w ($R_w = [\Sigma w\Delta F^2]^{1/2}/[\Sigma wF_o^2]^{1/2}$) was 5.9%: and the largest shift divided by the standard deviation was 0.27 at the end of refinement. A $\delta(R)$ normal probability plot[15] was calculated and was essentially linear with a slope of 2.11 and an intercept of 0.14. A final difference Fourier showed no peaks greater than ±0.2 eÅ^{-3}. Absolute configuration could not be determined from the data.

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Registry No.—I, 52279-13-7; II, 60410-89-1; III, 35101-40-7.

Supplementary Material Available. Dihedral angles, equations of planes, positional and thermal parameters, and standard deviations (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Abstracted in part from the Ph.D. Theses of J.C.H., 1972, Montana State University.
(2) F. Bohlmann, C. Zdero, and M. Grenz, *Chem. Ber.*, **107**, 2730–2759 (1974); F. Bohlmann and C. Zdero, *ibid.*, **107**, 2912–2922 (1974); F. Bohlmann, C. Zdero, and M. Grenz, *ibid.*, **107**, 3928–3945 (1974); F. Bohlmann and N. Rao, *Tetrahedron Lett.*, 613–616 (1973).
(3) H. Nagano, Y Tanahashi, Y. Moriyama, and T. Takahashi, *Bull. Chem. Soc. Jpn.*, **46**, 2840–2845 (1973).
(4) M. Tada, Y. Moriyama, Y. Tanahashi, and T. Takahashi, *Tetrahedron Lett.*, 4007–4010 (1971).
(5) H. Ishii, T. Tozyo, and H. Minato, *Tetrahedron*, **21**, 2605–2610 (1965); H. Ishii, T. Tozyo, and H. Minato, *J. Chem. Soc. C*, 1545 (1966); H. Ishii, T. Tozyo, M. Nakamura, and H. Minato, *Tetrahedron*, 2911–2918 (1970).
(6) Y. Moriyama. T. Sato, H. Nagano, Y. Tanahashi, and T. Takahashi, *Chem. Lett.*, 637–640 (1972).
(7) P. W. Jennings, S. K. Reeder, J. C. Hurley, C. N. Caughlan, and G. D. Smith, *J. Org. Chem.*, **39**, 3392 (1974).
(8) The melting point of III has been shown to be a function of heating rate or when you place it on the heating device. If heated slowly, it will decompose over a 5 °C range around 122 °C. However, if placed in the heating chamber which is already at 130–132 °C, III will melt at 144–145 °C.
(9) In ref 7 the assignments were inadvertently reversed.
(10) Computer programs used were by F. R. Ahmed and co-workers (NRC-2, Data Reduction; NRC-8, Fourier for Distorted and Undistorted Nets; and NRC-12, Scan of Interatomic Distances and Angles; National Research Council, Ottawa, Ontario, Canada), Busing and Levy (ORFLS), Carrol K. Johnson (ORTEP), and Germaine, Main, and Woolfson (MULTAN, 1972 version). These programs were locally modified for use with the XDS Sigma 7 computer. Other programs were written locally by G. D. Smith, C. N. Caughlan, and R. D. Larsen.
(11) J. DeMeulemaer and J. Tompa, *Acta Crystallogr.*, **19**, 1014 (1965).
(12) G. H. Stout and L. H. Jensen, "X-Ray Structure Determination", Macmillan, New York, N.Y., 1968, p 457.
(13) D. T. Cromer and J. B. Mann, *Acta Crystallogr., Sect. A*, **24**, 321 (1968).
(14) R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).
(15) S. C. Abrahams and E. T. Keve, *Acta Crystallogr., Sect. A*, **27**, 157 (1971).

Syntheses of [8][8]- and [8][10]Paracyclophanes[1]

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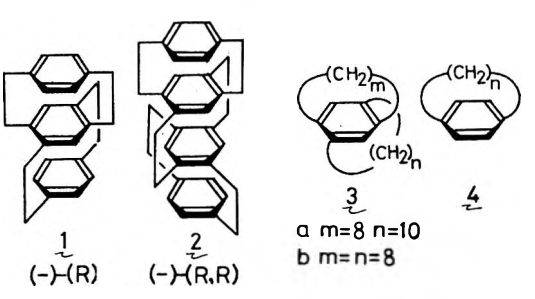
Coupling of 2,5-dimethylene-2,5-dihydrofuran with the *p*-xylylene derivative (**16b**) prepared from 10-bromomethyl-13-methyl[8]paracyclophane (**8b**) yielded the benzene–furan "hybrid" [2.2]paracyclophane (**18b**) whose furan moiety was converted to a tetramethylene chain affording [8][8]paracyclophane (**3b**). The same sequence of reactions applied to 12-bromomethyl-15-methyl[10]paracyclophane (**8a**) furnished [8][10]paracyclophane (**3a**). The uv and NMR spectra of these [*n*][*n*]- and [*m*][*n*]paracyclophanes reveal their unusually twisted benzene rings.

Preparations of the optically active triple- and quadruple-layered [2.2]paracyclophanes **1** and **2** with known absolute configurations have been reported from our laboratory;[2] these compounds have D_2 symmetry and are gyrochiral.[3] While substitution of both the outer benzene nuclei of **1** with equivalent polymethylene chains leads to **3b** with D_2 symmetry, substitution with different polymethylene chains gives **3a** with C_2 symmetry. Although the names of [*n*][*n*]- and [*m*][*n*]-paracyclophanes were proposed by Smith[4] for these types of compounds, none of them have yet been prepared. By analysis[5] of the uv spectra of [*n*]paracyclophanes **4** with short para

Chart I



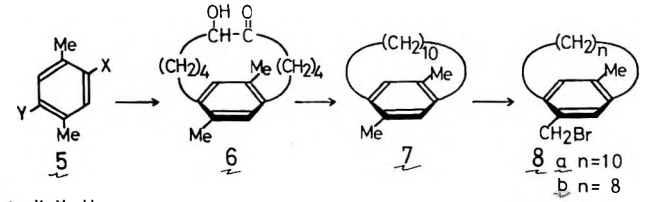
bridges, Allinger has suggested that the benzene nuclei exist in a highly strained boat form (C_{2v} symmetry). [m][n]Paracyclophanes (3) with short polymethylene bridges are accordingly expected to possess benzene nuclei with twist-boat conformations (D_2 symmetry, $m = n$; C_2 symmetry, $m \neq n$). This contribution is concerned with the syntheses of [8][8]- and [8][10]paracyclophanes (**3b, 3a**).

Results and Discussion

Our general approach (see Scheme III) to [8][8]- and [8][10]paracyclophanes, **3b** and **3a,** involved coupling of the para-bridged *p*-xylylene derivatives **16a** and **16b** with 2,5-dimethylene-2,5-dihydrofuran[6] to furnish respectively the benzene–furan "hybrid" [2.2]paracyclophanes **18a** and **18b** whose furan moieties were transformed to give octamethylene bridges.

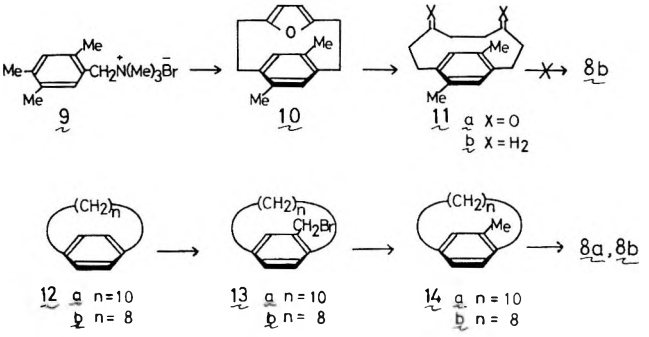
Preparations of 10-Bromomethyl-13-methyl[8]paracyclophane (8b) and 12-Bromomethyl-15-methyl[10]paracyclophane (8a). Schemes I and II summarize the

Scheme I



a X=Y=H
b X=H, Y=CO(CH2)3CO2Me
c X=H, Y=(CH2)4CO2H
d X=H, Y=(CH2)4CO2Me
e X=CO(CH2)3CO2Me, Y=(CH2)4CO2Me
f X=Y=(CH2)4CO2H
g X=Y=(CH2)4CO2Me

Scheme II



synthetic sequences to 10-bromomethyl-13-methyl[8]paracyclophane (**8b**) and 12-bromomethyl-15-methyl[10]paracyclophane (**8a**), the precursors of *p*-xylylenes **16b** and **16a.**

Friedel–Crafts acylation of *p*-xylene (**5a**) with γ-carbomethoxybutyryl chloride followed by the Wolff–Kishner reduction led to formation of the acid **5c,** which was then converted to the methyl ester **5d.** After the second γ-carbomethoxybutyl group was introduced to the methyl ester **5d,** the resulting keto ester **5e** was converted to the dimethyl ester **5g** by the Wolff–Kishner reduction followed by esterification. The dimethyl ester **5g** was submitted to acyloin condensation under high-dilution conditions to give the para-bridged acyloin **6** (64% yield) which afforded 12,15-dimethyl[10]paracyclophane (**7**) after Clemmensen reduction. Bromination of **7** in carbon tetrachloride at room temperature gave a 45% yield of the bromide **8a.**

The preparation of the bromide **8b** was first attempted by bromination of 10,13-dimethyl[8]paracyclophane (**11b**) whose synthesis was carried out by Cram's method[6] applied on duryltrimethylammonium bromide **9.**[7] "Hybrid" coupling between 2,5-dimethylene-3,5-dihydrofuran and the *p*-xylylene derivative prepared from the quaternary ammonium salt **9** gave a 21% yield of the benzene–furan "hybrid" [2.2]paracyclophane **10.** Although the desired 10,13-dimethyl[8]paracyclophane (**11b**) was accessible in a 70% yield from the "hybrid" [2.2]paracyclophane **10,** via the diketone **11a,** no clean-cut monobromination product was obtained on the direct bromination of **11b.** We divert attention from this fruitless approach to the second one which starts from [8]paracyclophane (**12b**).[6] Heating of [8]paracyclophane (**12b**) with paraformaldehyde in 47% hydrobromic acid–acetic acid solution[8] led to formation of the bromomethyl product **13b,** which was treated with lithium aluminum hydride to afford 10-methyl[8]paracyclophane (**14b**) in 55% yield based on **12b.** The second bromomethylation of the 10-methyl derivative **14b** gave the desired bromomethyl compound **8b** (74% yield). Conversion of **8b** with lithium aluminum hydride to 10,13-dimethyl[8]paracyclophane (**11b**) confirmed the para relationship of the newly introduced bromomethyl group to the original methyl group. The sequence of steps designed to lead from **12b** to **8b** was applied to [10]paracyclophane(**12a**)[9] affording 12-bromomethyl-15-methyl[10]paracyclophane (**8a**) in 55% yield based on **12a.**

[8][8]Paracyclophane (3b). An equimolecular mixture of 5-methylfurfuryltrimethylammonium iodide and the quaternary ammonium bromide **15c** obtained from the [8]para-bridged bromide **8b** was treated with silver oxide to furnish a mixture of the two Hofmann's bases which was pyrolyzed by refluxing in toluene. Chromatography of the coupling product yielded (in the order of elution) (1) the doubly [8]para-bridged [2.2]paracyclophane[10] (**19b**) (3%), (2) the benzene–furan "hybrid" [2.2]paracyclophane (**18b**) (8%), (3) [2.2]furanophane[12] (**17**) (12%). Since the furan–benzene "hybrid" [2.2]paracyclophane (**18b**) was found to be unstable, it was hydrolyzed with 10% sulfuric acid in acetic acid without further purification to afford the diketone **20c.** Treatment with ethanedithiol–boron trifluoride converted the diketone **20c** into the bisthioketal **20d** which was refluxed in ethyl acetate solution with Raney nickel to yield [8][8]paracyclophane (**3b**) (in 63% yield from the diketone **20c**).

Scheme III

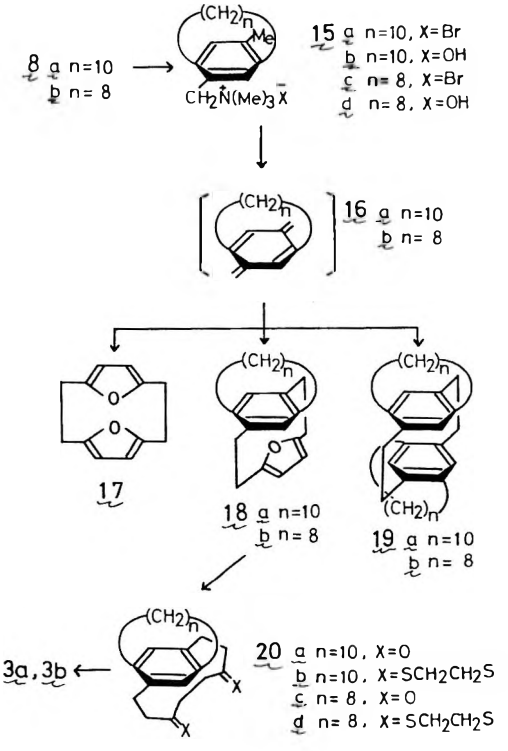


Table I. Ultraviolet Absorption Data in Isooctane

Compd	λ_{max}, nm (log ϵ)			
3a	240 (3.81)	280 (2.51)	289_{sh} (2.41)	
3b	255 (3.80)		291_{sh} (2.54)	
11b	234 (3.85)	283 (2.56)	288_{sh} (2.53)	
19a	233 (4.23)	241 (4.19)	295_{sh} (2.57)	318_{sh} (2.20)
19b	236 (4.17)	251 (4.12)	306_{sh} (2.68)	
4,7,12,15-Tetramethyl-[2.2]paracyclophane	226 (4.26)	250_{sh} (3.57)	308_{sh} (2.10)	

[8][10]Paracyclophane (3a). Coupling of the [10]para-bridged xylylene derivative **16a** with 2,5-dimethylene-2,5-dihydrofuran led to a mixture of reaction products which was submitted to chromatography to yield (in the order of elution) (1) the doubly [10]para-bridged [2.2]paracyclophane (**19a**) (12%), (2) the benzene–furan "hybrid" [2.2]paracyclophane (**18a**) (11%), (3) [2.2]furanophane (**17**) (8%). Hydrolysis followed by bisthioketalization and desulfurization with Raney nickel converted the benzene–furan "hybrid" coupling product **18a** into [8][10]paracyclophane **3a** in 49% yield from **18a**.

Uv Spectra. The uv spectra of [8][8]- and [8][10]paracyclophanes are reproduced in Figure 1 and summarized in

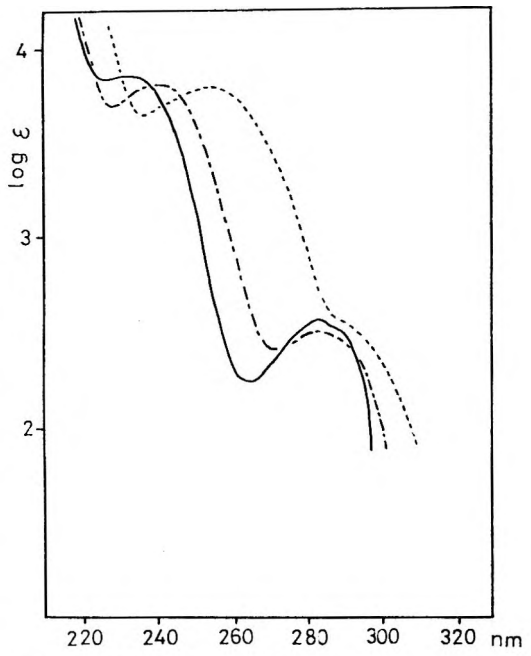


Figure 1. Uv spectra of **3a** (– – – –), **3b** (– – –), and **11b** (—) in isooctane.

Table I. Allinger analyzed[5] the uv spectra of [*n*]paracyclophanes (**4**) to indicate that the benzene ring of [8]paracyclophane (**4**, $n = 8$) is puckered, the carbon atoms of the benzene ring bearing the methylene bridge being bent out of the plane of the other four carbon atoms, the angle of distortion amounting to about 20°. Should this distortion apply to [8][8]paracyclophane (**3b**), the benzene ring must be deformed to a twist-boat conformation (D_2 symmetry) which is revealed in its rather unusual uv absorption. Compared with the uv spectrum of the open chain model compound **11b**, the maxima tend to move toward longer wavelengths and lower intensities. The similar trends with lesser degree are also evident in the uv spectrum of [8][10]paracyclophane (**3a**). Figure 2 records the uv spectra of the doubly para-bridged [2.2]paracyclophanes **19a** and **19b** as well as 4,7,12,15-tetramethyl[2.2]-paracyclophane.[7] Here also the [8]para-bridged compounds

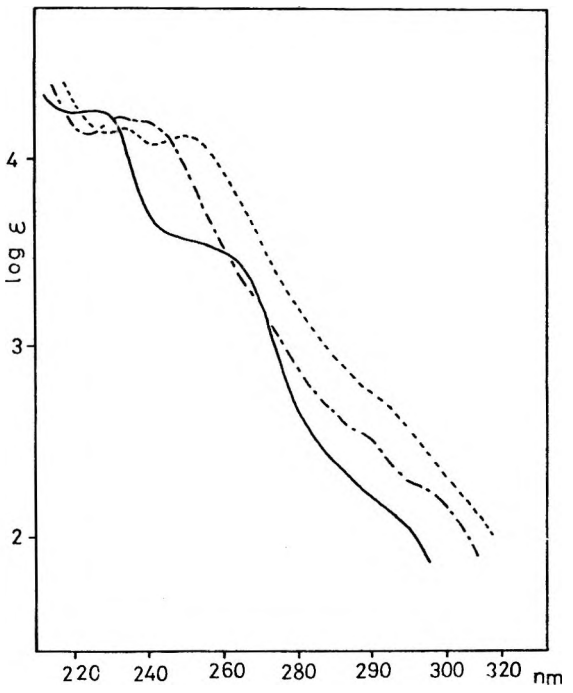


Figure 2. Uv spectra of **19a** (– – – –), **19b** (– – –), and 4,7,12,15-tetramethyl[2.2]paracyclophane (—) in isooctane.

exhibit marked bathochromic shifts with lowering intensities.

NMR Spectra. Table II summarizes the NMR data of the doubly para-bridged [2.2]paracyclophanes (**19**) and those of [8]- and [10]paracyclophanes as reference compounds. Although general feature of the spectrum of [8][8]paracyclophane are close to that of [8]paracyclophane, the high-field band due to the heavily shielded four methylene protons of [8][8]paracyclophane appears to move toward slightly higher field.

Chemical Topology. It is pertinent to note here some considerations important to chemical topology inherent to these [*n*][*n*]- and [*m*][*n*]paracyclophanes. Inspection of the molecular models of [8][8]- and [8][10]paracyclophanes reveals that their polymethylene bridges should be on the opposite sides of the central benzene ring, and this is supported by the observation that they were unable to form a molecular complex with tetracyanoethylene. However, when the polymethylene chains become long enough, we can expect to have anti (D_2 symmetry) **21** and syn (C_2 symmetry) **22** geometrical isomers for [*n*][*n*]paracyclophane, and one anti (C_2 symmetry) **23** and two syn forms (C_1 symmetry) **24, 25** for [*m*][*n*]paracyclophane depending upon which chain comes nearer to the benzene ring (Chart II).

Experimental Section

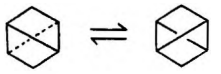
Melting points and boiling points are uncorrected. Infrared spectral data were obtained from a Hitachi EPI-S2 spectrophotometer. Nuclear magnetic resonance spectra were obtained from a JNM-MH-100 spectrometer. Ultraviolet spectra were recorded on a Hitachi EPS-3T

Table II. 100-MHz ^{1}H NMR Data in CCl_4 (τ)

Compd	Aromatic protons	Benzylic protons	Methyl protons	Methylene protons
3a	3.26 (2 H)	6.77–7.23 (4 H)		8.09–8.74 (8 H)
		7.87–7.91 (4 H)		8.74–9.14 (8 H)
				9.14–9.84 (10 H)
				9.84–10.42 (2 H)
3b	3.22 (2 H)	6.70–7.11 (4 H)		8.18–9.04 (14 H)
		7.37–7.85 (4 H)		9.15–9.75 (6 H)
				9.83–10.52 (4 H)
7	3.23 (2 H)	7.02–7.29 (2 H)	7.76 (6 H)	8.40–8.64 (4 H)
		7.46–7.87 (2 H)		8.79–9.12 (4 H)
				9.18–9.72 (8 H)
11b	3.27 (2 H)	6.86–7.15 (2 H)	7.75 (6 H)	8.20–9.00 (6 H)
		7.48–8.04 (2 H)		9.10–9.65 (4 H)
				10.02–10.44 (2 H)
19a	3.95 (4 H)	6.61–6.83 (4 H)		8.48–8.84 (8 H)
		6.93–7.48 (8 H)		8.95–9.27 (8 H)
		7.62–7.94 (4 H)		9.35–9.92 (16 H)
19b	3.85 (4 H)	6.55–6.90 (4 H)		8.35–9.29 (12 H)
		6.90–7.29 (8 H)		9.35–10.10 (8 H)
		7.76–8.10 (4 H)		10.22–10.94 (4 H)

Chart II

[n][n]Paracyclopane



21 22

[m][n]Paracyclopane

23 24 25

spectrometer. Mass spectral data were measured on a Hitachi RMS-4 spectrometer. Elemental analyses were determined by Yanagimoto CHN-Corder type II.

Methyl γ-(2,5-Dimethylbenzoyl)butyrate (5b). A mixture of *p*-xylene (**5a**, 54 g, 0.51 mol), γ-carbomethoxybutyryl chloride (83 g, 0.51 mol), and *s*-tetrachloroethane (300 ml) was cooled to −10 °C. Anhydrous aluminum chloride (200 g, 1.5 mol) was added to the stirred mixture in six portions during 2 h, and the reaction mixture was stirred for 3 h at 0 °C. The resulting dark solution was poured over ice, and the separted organic phase was washed with 2 N hydrochloric acid, water, 3% sodium bicarbonate solution, and again water, and then dried. After evaporation of the solvent, the residual oil was distilled to give **5b** (87 g, 73%), bp 177–179 °C (4 mm), n^{18}D 1.5201.

Methyl δ-(2,5-Dimethylphenyl)valerate (5d). A mixture of **5b** (76 g, 0.327 mol), 80% hydrazine hydrate (100 g, 1.6 mol), potassium hydroxide (106 g, 1.9 mol), and triethylene glycol (300 ml) was heated at 140 °C, and then water and excess hydrazine hydrate was allowed to distill until the temperature reached 200 °C. The reaction mixture was heated for 10 h at 200–210 °C, and cooled, and then diluted with water (500 ml). The aqueous solution was neutralized with concentrated hydrochloric acid and the resulting precipitate was extracted with chloroform. The chloroform solution was washed with water, dried, and then evaporated. The crude acid (**5c**) was esterified by heating for 3 h in methanol (300 ml) containing concentrated sulfuric acid (15 g), and the reaction mixture was poured into cold water and then extracted with ether. The ether solution was washed with water, 5% sodium bicarbonate solution, and again with water, and then dried. After removal of the solvent, distillation of the residue gave **5d** (63 g, 87.6%), bp 148–149 °C (6 mm), n^{17}D 1.5043.

Methyl γ-4-(ω-Carbomethoxybutyl)-2,5-dimethylbenzoylbutyrate (5e). Friedel–Crafts acylation of **5d** was carried out by the same method described for the preparation of **5b**, utilizing **5d** (63 g, 0.286 mol), γ-carbomethoxybutyryl chloride (49 g, 0.3 mol), *s*-tetrachloroethane (220 ml), and anhydrous aluminum chloride (122 g, 0.9 mol). The reaction mixture was worked up to give **5e** (77 g, 77.3%), bp 191–193 °C (0.01 mm). Recrystallization of this material from methanol–water gave mp 53–54 °C.

Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 69.01; H, 8.06.

1,4-Bis(ω-carbomethoxybutyl)-2,5-dimethylbenzene (5g). Wolff–Kishner reduction of **5e** was carried out by the same method described for the preparation of **5d**, utilizing **5e** (77 g, 0.221 mol), 80% hydrazine hydrate (69 g, 1.11 mol), potassium hydroxide (83 g, 1.5 mol), and triethylene glycol (350 ml). The crude acid **5f** was esterified in the usual manner to give **5g** (6.5 g, 88%), bp 183–185 °C (0.01 mm). Recrystallization of this ester from methanol–water gave mp 29–30 °C.

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.77; H, 9.10.

Saponification of **5g** with methanolic potassium hydroxide afforded the acid **5f**, and recrystallization of this from methanol gave mp 148–149 °C.

Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.51; H, 8.56.

12,15-Dimethyl[10]paracyclophane (7). Preparation of the hydrocarbon **7** was carried out ccording to the usual sequence involving acyloin condensation and Clemmensen reduction.[13]

A. Acyloin Condensation of the Diester 5g. To a suspension of sodium (3.2 g, 0.144 mol) in dry xylene (400 ml) was added during 36 h a solution of **5g** (12 g, 0.036 mol) in dry xylene (300 ml). After an additional 1 h of heating and stirring, the reaction mixture was cooled to 0 °C, and acetic acid (10 ml) was slowly added. The polymer and sodium acetate were removed, and the resulting filtrate was concentrated under vacuum. Distillation of the residual oil gave the acyloin **6** (6.3 g, 64%), bp 152–153 °C (0.1 mm), n^{27}D 1.5412.

B. Clemmensen Reduction of the Acyloin 6. Amalgamated zinc was prepared by swirling zinc (66 g) with a solution of mercuric chloride (1.9 g) in water (200 ml) which contained concentrated hydrochloric acid (1.4 ml). A solution of **6** (6.3 g, 0.023 mol) in toluene (50 ml) was added to the amalgamated zinc with 200 ml each of concentrated hdyrochloric acid and acetic acid. The mixture was heated to reflux for 48 h, during which four 30-ml portions of concentrated hydrochloric acid were added. The reaction mixture was cooled and diluted with water, and then extracted with ether. The ether solution was washed with water, 5% sodium bicarbonate solution, and again with water, and then dried. After evaporation of the solvent, the residual solid was recrystallized from methanol to give **7** (3.7 g, 67%): mp 42–43 °C; ir (KBr) 2970, 2880, 2830, 1495, 1452, 1443, 1338, 1285, 1088, 1027, 910, 894, 835, 781, 711, 703 cm^{-1}; uv (isooctane) λ_{max} 262.5, 272.5, 281.7 nm (log ϵ 2.48, 2.75, 2.78); NMR (CCl_4) τ 3.23 (s, 2 H), 7.02–7.29 (m, 2 H), 7.46–7.87 (m, 2 H), 7.76 (s, 6 H), 8.40–8.64 (m, 4 H), 8.79–9.12 (m, 4 H), 9.18–9.72 (m, 8 H); MS *m/e* 244 (M^+).

Anal. Calcd for $C_{18}H_{28}$: C, 88.45; H, 11.55. Found: C, 88.51; H, 11.49.

Benzene–Furan Hybrid [2.2]Paracyclophane (10). A solution of duryltrimethylammonium bromide (**9**,[7] 60 g, 0.19 mol) in distilled

water (1.5 l.) was passed through a column containing Amberlite IRA-400 (30–100 mesh, 200 g) which had been converted to the OH form by passing 2 N sodium hydroxide solution (3 l.). The elute was combined with the quaternary ammonium hydroxide prepared from 5-methylfurfurylammonium iodide[6] (53 g, 0.19 mol) following the procedure described above, and the solution was concentrated to 500 ml under vacuum. The concentrate was heated with toluene (1 l.) containing phenothiazine (1 g), and water was removed by azeotropic distillation. After refluxing with stirring for 5 h, the solution was allowed to cool, and insoluble polymers were removed. Concentration to 200 ml under vacuum again gave some polymers which were filtered off. The filtrate was chromatographed on neutral alumina and eluted with hexane. The elution afforded the following sequence of compounds: the hybrid [2.2]paracyclophane **10** (9 g, 21%), 4,7,12,15-tetramethyl[2.2]paracyclophane[7] (4.5 g, 11%), and [2.2]furanophane[12] (4.3 g, 10%). After recrystallization from hexane, the hybrid [2.2]paracyclophane **10** melted at 65–66 °C; ir (KBr) 2970, 2920, 2860, 1600, 1536, 1490, 1446, 1425, 1393, 1365, 1318, 1210, 1162, 1131, 1008, 943, 892, 773, 721, 707 cm^{-1}; NMR (CCl_4) τ 3.63 (s, 2 H), 4.50 (s, 2 H), 6.77–7.12 (m, 2 H), 7.25–7.65 (m, 6 H), 7.90 (s, 6 H).

Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 85.07; H, 7.96.

3,6-Diketo-10,13-dimethyl[8]paracyclophane (11a). A mixture of **10** (8.8 g, 0.0388 mol), acetic acid (11 ml), water (6 ml), and 10% sulfuric acid (3 ml) was refluxed for 10 h. The solution was poured into water (300 ml) and extracted with chloroform. The organic solution was washed with water, 5% sodium bicarbonate solution, and again with water, and then dried. Removal of the solvent yielded 9.4 g of yellow solid which on recrystallization from benzene–hexane gave **11a** (8.1 g, 85%): mp 189–190 °C; ir (KBr) 2997, 2925, 2880, 1697, 1500, 1458, 1404, 1352, 1288, 1151, 1104, 1083, 895 cm^{-1}; NMR ($CDCl_3$) τ 3.24 (s, 2 H), 6.70–7.85 (m, 8 H), 7.70 (s, 6 H), 8.16–8.78 (m, 4 H).

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.68; H, 8.15.

10,13-Dimethyl[8]paracyclophane (11b). A mixture of **11a** (8 g, 0.0328 mol), 100% hydrazine hydrate (5 g, 0.1 mol), potassium hydroxide (7 g, 0.125 mol), and diethylene glycol (40 ml) was refluxed for 10 h. The reaction mixture was cooled and poured into water, and the product was extracted with ether. After evaporation of the solvent, the residual oil was distilled to give **11b** (5.8 g, 82%): bp 132–134 °c (4 mm); $n^{15}D$ 1.5406; ir (film) 2980, 2930, 2860, 1498, 1458, 1446, 1372, 882, 803, 721, 687 cm^{-1}; NMR (CCl_4) τ 3.27 (s, 2 H), 6.86–7.15 (m, 2 H), 7.48–8.04 (m, 2 H), 7.75 (s, 6 H), 8.20–9.00 (m, 6 H), 9.10–9.65 (m, 4 H), 10.02–10.44 (m, 2 H); MS *m/e* 216 (M^+).

Anal. Calcd for $C_{16}H_{24}$: C, 88.82, H, 11.18. Found: C, 88.86; H, 10.92.

12-Bromomethyl[10]paracyclophane (13a). A mixture of **12a** (28 g, 0.13 mol), paraformaldehyde (7.8 g, 0.26 mol of formaldehyde), acetic acid (60 ml), 85% phosphoric acid (20 ml), and 47% hydrobromic acid (20 ml) was refluxed with stirring for 40 min. The cooled mixture was poured into cold water and extracted with ether. The ethereal solution was washed with water, 5% sodium bicarbonate solution, again with water, and then dried. The solvent was evaporated and distillation of the residue gave **13a** (22.8 g, 81.4%): bp 154–156 °C (1.0 mm); $n^{24}D$ 1.5747; NMR (CCl_4) τ 2.82–3.11 (m, 3 H), 5.52 (q, J = 10.5, 24 Hz, 2 H), 6.68–7.80 (m, 4 H), 7.95–9.98 (m, 16 H).

10-Bromomethyl[8]paracyclophane (13b). The bromomethylation of **12b** was carried out by the same method described for the preparation of **13a,** utilizing **12b** (9 g, 0.048 mol), paraformaldehyde (4.3 g, 0.144 mol of formaldehyde), acetic acid (32 ml), 85% phosphoric acid (10 ml), and 47% hydrobromic acid. The reaction mixture was worked up to give **13b** (8.8 g, 65%): bp 148–150 °C (0.6 mm); $n^{24}D$ 1.5781; NMR (CCl_4) τ 2.84–3.12 (m, 3 H), 6.12 (q, J = 14, 22 Hz, 2 H), 6.82–8.02 (m, 4 H), 8.14–10.35 (m, 12 H).

12-Methyl[10]paracyclophane (14a). A solution of **13a** (20 g, 0.064 mol) in dry tetrahydrofuran (80 ml) was added dropwise to a suspension of lithium aluminum hydride (5 g, 0.18 mol) in dry tetrahydrofuran (180 ml). The mixture was refluxed with stirring for 6 h, and excess reducing reagent was decomposed by addition of ethyl acetate. After acidifying the mixture with dilute hydrochloric acid, the organic phase was extracted with ether. The ether solution was washed with water, 5% sodium bicarbonate solution, and again with water. After evaporation of the solvent, the residual oil was distilled to give **14a** (12 g, 81%): bp 152–154 °C (4 mm); $n^{18}D$ 1.5336; MS *m/e* 230 (M^+); NMR (CCl_4) τ 3.16–3.22 (m, 3 H), 6.82–7.88 (m, 4 H), 7.76 (s, 3 H), 8.24–9.72 (m, 16 H).

Anal. Calcd for $C_{17}H_{26}$: C, 88.62; H, 11.38. Found: C, 88.66; H, 11.40.

10-Methyl[8]paracyclophane (14b). The reduction of **13b** was carried out by the same method described for the preparation of **14a,** utilizing **13b** (8 g, 0.028 mol) and lithium aluminum hydride (2 g, 0.053 mol). Distillation of the product gave **14b** (4.8 g, 85%): bp 124–126 °C (4 mm); $n^{27}D$ 1.5352; MS *m/e* 202 (M^+); NMR (CCl_4) τ 3.12–3.18 (m, 3 H), 6.77–7.93 (m, 4 H), 7.68 (s, 3 H), 8.27–10.45 (m, 12 H).

Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 89.02; H, 10.93.

12-Bromomethyl-15-methyl[10]paracyclophane (8a). A. A mixture of **14a** (10 g, 0.043 ml), paraformaldehyde (2.1 g, 0.07 mol of formaldehyde), acetic acid (15 ml), 85% phosphoric acid (6 ml), and 47% hydrobromic acid (15 ml) was refluxed with stirring for 1 h. After the same treatment described for the preparation of **13a,** distillation of the product gave **8a** (11.7 g, 84%): bp 142–144 °C (1.0 mm); $n^{19}D$ 1.5776; NMR (CCl_4) τ 3.14 (s, 1 H), 3.45 (s, 1 H), 5.62 (q, J = 10, 24 Hz, 2 H), 7.8 (s, 3 H), 6.9–8.0 (m, 4 H), 8.1–9.7 (m, 16 H); MS *m/e* 323 (M^+).

Anal. Calcd for $C_{18}H_{27}Br$: C, 66.86; H, 8.42; Br, 24.72. Found: C, 66.77; H, 8.36; Br, 24.82.

B. A solution of bromine (3 g, 0.018 mol) in carbon tetrachloride (20 ml) was added during 4 h to a stirring solution of **7** (3.7 g, 0.015 mol) in carbon tetrachloride (20 ml) at room temperature. After an additional 5 h of stirring, the reaction mixture was poured into cold water and extracted with ether. The ether solution was washed with water, 5% sodium bicarbonate solution, again with water, and then dried. After evaporation of the solvent, the product was distilled to give **8a** (2.1 g, 45%).

10-Bromomethyl-13-methyl[8]paracyclophane (8b). The bromomethylation of **14b** was carried out by the same method described for the preparation of **8a,** utilizing **14b** (8.5 g, 0.042 mol), paraformaldehyde (1.64 g, 0.054 mol of formaldehyde), acetic acid (14 ml), 85% phosphoric acid (5.5 ml), and 47% hydrobromic acid (14 ml). Distillation of the product gave **8b** (9.2 g, 74%): bp 146–148 °C (2 mm); $n^{24}D$ 1.5778; NMR (CCl_4) τ 3.25 (s, 1 H), 3.44 (s, 1 H), 6.13 (q, J = 14, 23 Hz, 2 H), 6.8–7.2 (m, 2 H), 7.4–7.9 (m, 2 H), 7.71 (s, 3 H), 8.2–9.7 (m, 10 H), 10.0–10.3 (m, 2 H); MS *m/e* 295 (M^+).

Anal. Calcd for $C_{16}H_{23}Br$: C, 65.08; H, 7.85; Br, 27.07. Found: C, 64.96; H, 7.76; Br, 27.18.

12-Dimethylaminomethyl-15-methyl[10]paracyclophane Methanobromide (15a). A solution of **8a** (11.5 g, 0.035 mol) in ether (100 ml) was treated with excess anhydrous trimethylamine. The resulting salt was collected by filtration, washed with ether, and dried to afford **15a** (12.3 g, 92%). An analytical sample was recrystallized from ethanol, mp 224–226 °C.

Anal. Calcd for $C_{21}H_{36}NBr$: C, 65.95; H, 9.49; N, 3.66; Br, 20.90. Found: C, 65.95; H, 9.48; Br, 20.97.

10-Dimethylaminomethyl-13-methyl[8]paracyclophane Methanobromide (15c). A solution of **8b** (9 g, 0.031 mol) in ether (100 ml) was treated with excess anhydrous trimethylamine. The resulting salt was removed by filtration, washed with ether, and dried to afford **15c** (10.1 g, 95%). An analytical sample was recrystallized from ethanol, mp 198–200 °C dec.

Anal. Calcd for $C_{19}H_{32}NBr$: C, 64.39; H, 9.10; N, 3.95; Br, 22.55. Found: C, 64.48; H, 9.15; N, 3.91; Br, 22.42.

Benzene–Furan Hybrid [2.2]Paracyclophane (18a) and Doubly Bridged [2.2]Paracyclophane (19a). A mixture of **15a** (8.0 g, 0.021 mol) and 5-methylfurfuryltrimethylammonium iodide (6.0 g, 0.021 mol) was dissolved in water (300 ml) and converted to the hydroxide **15b** with freshly prepared silver oxide. The resulting aqueous solution was mixed with toluene (300 ml) and phenothiazine (0.1 g), and heated with stirring. After removal of water by azeotropic distillation, the reaction mixture was refluxed for 5 h and allowed to cool. The insoluble polymer was removed and the filtrate was concentrated under vacuum. The concentrate was extracted with hot hexane, and the hexane-soluble portion was chromatographed on neutral alumina in a cold room. Elution of the column with hexane afforded **19a** (0.9 g, 12%), which, when recrystallized from ethanol, gave mp 240–241 °C; ir (KBr) 2960, 2880, 2830, 1597, 1482, 1452, 1440, 1427, 886, 722, 708 cm^{-1}; MS *m/e* (rel intensity) 484 (18), 241 (53), 227 (56), 159 (57), 145 (100), 132 (87), 119 (56), 105 (27).

Anal. Calcd for $C_{36}H_{52}$: C, 89.19; H, 10.81. Found: C, 89.10; H, 10.80.

Further elution with hexane–benzene (9:1) furnished **18a** (1.23 g, 11%), which when recrystallized from ethanol gave mp 74–75°; ir (KBr) 2960, 2880, 2835, 1596, 1536, 1482, 1455, 1437, 1422, 1211, 1174, 1162, 1130, 1008, 946, 892, 773, 723, 707, 670 cm^{-1}; NMR (CCl_4) τ 3.6 (s, 2 H), 4.52 (s, 2 H), 6.6–7.9 (m, 12 H), 8.4–9.9 (m, 16 H); MS *m/e* 336 (M^+).

Anal. Calcd for $C_{24}H_{32}O$: C, 85.66; H, 9.59. Found: C, 85.27; H, 9.69.

Elution with hexane–benzene (5:1) gave [2.2]furanophane (**17**,[12] 0.32 g, 8%), mp 180–181 °C.

Benzene–Furan Hybrid [2.2]Paracyclophane (18b) and Doubly Bridged [2.2]Paracyclophane (19b). A solution (300 ml) of the mixed quaternary ammonium hydroxides derived from a mixture of **15c** (12 g, 0.0034 mol) and 5-methylfurfuryltrimethylammonium iodide (9.5 g, 0.0034 mol) in the usual manner was mixed with toluene (400 ml) and phenothiazine (0.5 g), and then pyrolyzed. Insoluble polymers were removed from the reaction mixture and the filtrate was chromatographed on neutral alumina. Elution with hexane provided **19b** (0.32 g, 3%), which, when recrystallized from ethanol, gave mp 229–231 °C; ir (KBr) 2960, 2875, 2820, 1587, 1478, 1440, 1428, 1045, 1003, 882, 805, 710, 687 cm^{-1}; MS *m/e* (rel intensity) 428 (70), 214 (100), 199 (80), 171 (37), 159 (37), 145 (50), 132 (83), 119 (43).

Anal. Calcd for $C_{32}H_{44}$: C, 89.65; H, 10.35. Found: C, 89.49; H, 10.39.

Further elution with hexane–benzene (9:1) produced **18b** (0.91 g, 8%). Because of instability of **18b,** the oily product could not be purified further: MS *m/e* 308 (M^+).

Elution with hexane–benzene (5:1) gave **17** (0.75 g, 12%).

3,6-Diketo[8][10]paracyclophane (20a). A mixture of **18a** (0.5 g, 1.5 mmol), water (0.5 ml), acetic acid (10 ml), and 10% sulfuric acid (0.3 ml) was heated at 65 °C with stirring for 1 h. The reaction mixture was poured into water (50 ml) and extracted with dichloromethane. The organic layer was washed with water, 5% sodium bicarbonate solution, and again with water, and then dried. After removal of the solvent, the residue was chromatographed on neutral alumina. Elution with dichloromethane afforded **20a** (0.47 g, 89%), which when recrystallized from hexane gave mp 161–162 °C; ir (KBr) 2970, 2890, 2830, 1700, 1593, 1488, 1452, 1435, 1408, 1318, 1287, 1170, 1145, 1000, 1077, 999, 770, 744, 732, 705 cm^{-1}; NMR (CCl_4) τ 3.33 (s, 2 H), 6.65–7.95 (m, 12 H), 8.15–8.60 (m, 8 H), 8.80–9.10 (m, 4 H), 9.15–9.70 (m, 8 H); MS *m/e* 354 (M^+).

Anal. Calcd for $C_{24}H_{34}O_2$: C, 81.31; H, 9.65. Found: C, 81.27; H, 9.70.

3,6-Diketo[8][8]paracyclophane (20c). Hydrolysis of **18b** was carried out by the method described for the preparation of **20a,** utilizing **18b** (0.4 g, 1.3 mmol), water (0.4 ml), acetic acid (10 ml), and 10% sulfuric acid (0.3 ml). The resulting product was chromatographed on neutral alumina. Elution with dichloromethane produced **20c** (0.24 g, 57%), which, when recrystallized from hexane, gave mp 156–157 °C; ir (KBr) 2970, 2890, 2840, 1700, 1595, 1484, 1454, 1431, 1408, 1317, 1287, 1168, 1143, 1098, 1075, 898, 734, 720, 687 cm^{-1}; NMR (CCl_4) τ 3.21 (s, 2 H), 6.82–7.93 (m, 12 H), 8.16–9.13 (m, 10 H), 9.17–9.65 (m, 4 H), 9.90–10.32 (m, 2 H); MS *m/e* 326 (M^+).

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 80.62; H, 9.18.

Bisethanedithioketal 20b. A solution of **20a** (0.35 g, 1.0 mmol) in glacial acetic acid (20 ml) was mixed with a solution of ethanedithiol (0.2 g, 20 mmol) in glacial acetic acid (6 ml) which contained 47% boron trifluoride etherate (2 ml). After standing for 2 days at room temperature, the reaction mixture was poured into water (100 ml). The product was extracted with chloroform and washed with water and then dried. Removal of the solvent yielded the white solid product which on crystallization from ethanol gave **20b** (0.34 g, 87%), mp 153–154 °C.

Anal. Calcd for $C_{28}H_{42}S_4$: C, 82.97; H, 10.40. Found: C, 83.01; H, 10.36.

[8][10]Paracyclophane (3a). To a solution of **20b** (0.25 g, 0.6 mmol) in ethyl acetate (10 ml) was added W-5 Raney nickel (2 g), and the mixture was refluxed for 1.5 h. After being cooled and filtered, the resulting solution was concentrated under vacuum. The residual oil was chromatographed on neutral alumina. Elution with hexane afforded a colorless oil, which was distilled to give **3a** (0.13 g, 65%): bp 179–181 °C (2.0 mm); $n^{24}D$ 1.5472; ir (film) 2960, 2880, 2860, 2675, 1602, 1485, 1451, 1436, 1336, 1207, 1056, 1005, 883, 833, 730, 705, 687 cm^{-1}; MS *m/e* (rel intensity) 326 (100), 241 (28), 227 (38), 145 (30), 131 (30), 119 (26), 105 (24).

Anal. Calcd for $C_{24}H_{38}$: C, 88.27; H, 11.73. Found: C, 88.29; H, 11.74.

[8][8]Paracyclophane (3b). A solution of **20c** (0.15 g, 0.5 mmol) in glacial acetic acid (10 ml) was mixed with a solution of ethanedithiol (0.2 g, 20 mmol) in glacial acetic acid (5 ml). After 47% boron trifluoride etherate (2 ml) was added, the mixture was kept in a tightly sealed bottle and allowed to stand for 2 days at room temperature. Then the mixture was poured into water (100 ml). The product was extracted with chloroform, washed with 3% sodium bicarbonate solution and water, and then dried. After evaporation of the solvent, the crude thioketal **20d** was directly desulfurized as follows. To a solution of the crude thioketal **20d** (0.16 g) in ethyl acetate (10 ml) was added W-5 Raney nickel (1 g). The mixture was refluxed for 1 h, cooled, and filtered. After concentration of the filtrate, the oily product was subjected to alumina column chromatgraphy. Elution with hexane gave **3b** (0.09 g, 63%), which, when recrystallized from ethanol, gave mp 60–61 °C; ir (KBr) 2970, 2900, 2840, 2670, 1598, 1483, 1452, 1437, 1337, 1203, 1050, 1007, 876, 836, 726, 715, 707, 686 cm^{-1}; MS *m/e* (rel intensity) 298 (100), 199 (35), 185 (48), 145 (36), 131 (35), 119 (34), 105 (27).

Anal. Calcd for $C_{22}H_{34}$: C, 88.52; H, 11.48. Found: C, 88.46; H, 11.48.

Registry No.—**3a,** 34106-24-6; **3b,** 32543-09-2; **5a,** 106-42-3; **5b,** 60438-86-0; **5c,** 30098-17-0; **5d,** 60438-87-1; **5e,** 60438-88-2; **5f,** 60438-89-3; **5g,** 60438-90-6; **6,** 60438-91-7; **7,** 32543-11-6; **8a,** 32543-10-5; **8b,** 32543-03-6; **9,** 27742-95-6; **10,** 33357-05-0; **11a,** 60438-92-8; **11b,** 60438-93-9; **12a,** 5649-96-7; **12b,** 4685-74-9; **13a,** 26878-19-3; **13b,** 60438-94-0; **14a,** 60438-95-1; **14b,** 60438-96-2; **15a,** 32543-12-7; **15b,** 60438-97-3; **15c,** 32691-02-4; **17,** 5088-46-0; **18a,** 32540-67-3; **18b,** 32543-04-7; **19a,** 32585-31-2; **19b,** 32543-05-8; **20a,** 60438-98-4; **20b,** 60438-99-5; **20c,** 32543-07-0; **20d,** 32543-08-1; γ-carbomethoxybutyryl chloride, 1501-26-4; hydrobromic acid, 24959-67-9; 5-methylfurfuryltrimethylammonium iodide, 1197-60-0.

References and Notes

(1) Presented at the 24th Annual Meeting of the Chemical Society of Japan, Osaka, April 1971, Preprint, Vol. III, p 1293. M. Nakazaki, K. Yamamoto, and S. Tanaka, *Tetrahedron Lett.*, 341 (1971).
(2) M. Nakazaki, K. Yamamoto, and S. Tanaka, *J. Chem. Soc., Chem. Commun.*, 433 (1972).
(3) M. Nakazaki, "Syntheses and Stereochemistry of Twisted Organic Compounds", Invited Lecture at 30th National Meeting of the Chemical Society of Japan, Osaka, April 1974.
(4) D. H. Smith, "Bridged Aromatic Compounds", Academic Press, New York, N.Y. 1964, p 13.
(5) N. L. Allinger, L. A. Freiberg, R. B. Hermann, and M. A. Miller, *J. Am. Chem. Soc.*, **85,** 1171 (1963).
(6) D. J. Cram, C. S. Montgomery, and G. R. Knox, *J. Am. Chem. Soc.*, **88,** 515 (1966).
(7) D. T. Longone and C. L. Warren, *J. Am. Chem. Soc.*, **84,** 1507 (1962); D. T. Longone and F. P. Boettcher, *ibid.*, **85,** 3436 (1963).
(8) A. T. Blomquist and B. H. Smith, *J. Am. Chem. Soc.*, **82,** 2073 (1960); A. T. Blomquist, R. E. Stahl, Y. C. Meinwald, and B. H. Smith, *J. Org. Chem.*, **26,** 1687 (1961).
(9) D. J. Cram and H. U. Daeniker, *J. Am. Chem. Soc.*, **76,** 2743 (1954).
(10) Stereochemical consideration suggests the chiral trans configuration (D_2 symmetry) to this doubly [8]para-bridged [2.2]paracyclophane (**19b**), which was supported by comparison of racemic **19b** with the optically active **19b**[11] recently prepared from the optically active **15c.**
(11) K. Yamamoto and M. Nakazaki, *Chem. Lett.*, 1051 (1974).
(12) H. E. Weiberg, F. S. Fawcett, W. E. Mochel, and C. W. Theobald, *J. Am. Chem. Soc.*, **82,** 1428 (1960).
(13) D. J. Cram, N. L. Allinger, and H. Steinberg, *J. Am. Chem. Soc.*, **76,** 6132 (1954).

Synthetic Organic Electrochemistry. Application to Perhydrophenanthrene Syntheses

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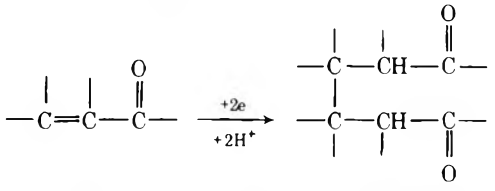
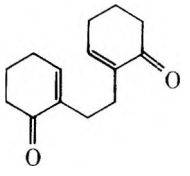
Compound **2** was synthesized and subjected to controlled potential reduction. The product was shown to be **3a** indicating the process to be both regio- and stereospecific.

The electrochemical reduction of α,β-unsaturated ketones has been well studied.[2] It has been shown that the process can be carried out in a way to produce β-β coupling products as the primary product though the precise mechanism of the dimerization is still in question. It is apparent that

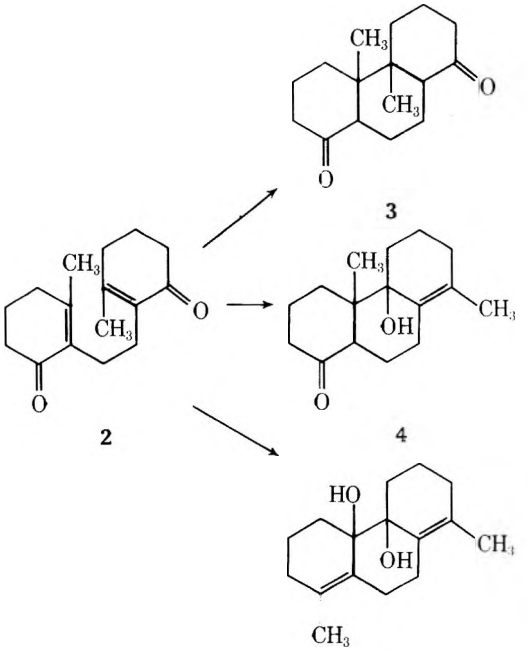


this process could have interesting applications to synthetic organic chemistry as it represents the formation of a carbon to carbon bond between two electron-deficient centers. We wished to establish the potential utility of this reaction for perhydrophenanthrene syntheses by applying it to compounds of type **1**.



1

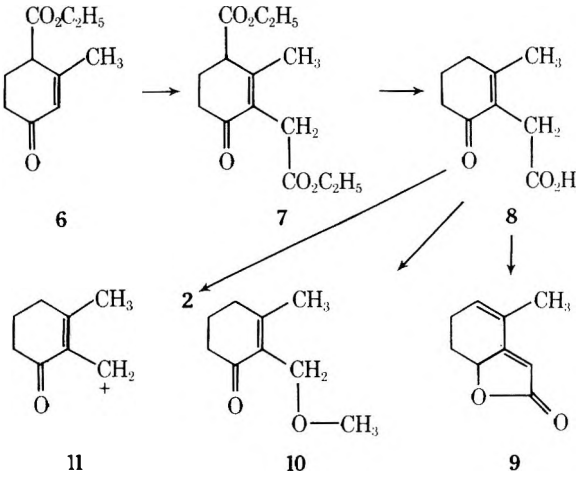
Two questions arise in considering the applicability of electrochemical predictions of this type; namely, the regiospecificity and stereospecificity of the process. Consider, for example, the reduction of compound **2**. Three cyclization products are possible, **3**, **4**, and **5**, depending on whether the normal β-β mode of coupling (leading to **3**), or "head to tail" coupling (leading to **4**), or "head to head" coupling (leading to **5**) would be realized.[6] Further, the stereochemistry of the coupling products at the nonepimerizable centers (those asymmetric centers not adjacent to carbonyl groups) must also be established. The dienedione **2** is an ideal substrate to answer these questions for the structures of the products should be easily established by nuclear magnetic resonance spectroscopy using the methyls as "tagging" substituents.



2 **3** **4** **5**

The synthesis of compound **2** is given in Scheme I. Hagemann's ester, **6**, was alkylated with ethyl chloroacetate to yield **7**, which could be smoothly hydrolyzed and decarboxylated with barium hydroxide to **8**. Electrolysis of **8** as its carboxylate anion in methanol (the usual Kolbe oxidative dimerization[7] conditions) afforded **10**, apparently by oxidation of the intermediate radical to carbonium ion **11** and thence solvation by methanol to the ether **10**. In one oxidation attempt, where only 20% of the acid was present as its sodium salt, lactone **9** was isolated rather than the usual Kolbe product. This transformation required the presence of an electrode, apparently to function as a Lewis acid. The conversion of **8** to **9** also occurred by treatment of **8** with sulfuric acid in acetic acid. Structural assignment to **9** was made on the basis of ^{1}H NMR, ^{13}C NMR, ir, uv, and mass spectral analysis. The desired dimerization of **8** to **2** could be realized, albeit in poor yield (11%), by doing the reaction in dimethylformamide solution.

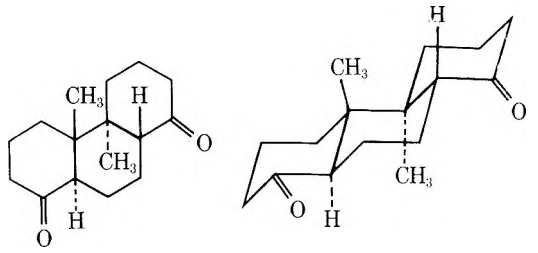
Scheme I



6 **7** **8** **2** **11** **10** **9**

The conditions for the controlled potential reduction of **2** were determined from the polarography of **2** in acetonitrile–water (20% water). A 90% material recovery was obtained from the electrolysis. The reduced material was separated by chromatography into two fractions which proved to be the coupled product **3** (80%) and starting material (20%). The structure of **3** was clearly indicated by its NMR spectrum which exhibited uncoupled angular methyl protons at 0.93 ppm and no methyls on olefinic carbons.

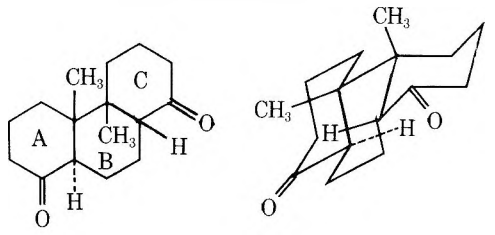
It is possible to assign stereochemistry to **3** by considering the two possible dispositions of the angular methyls, namely, either trans or cis. If they are trans, then the product would have the stereochemistry shown in **3a** since during the cou-



3a

pling process the more stable configuration may obtain at the epimerizable centers adjacent to the carbonyl groups. In this configuration, the ring system is in the most stable trans-anti-trans arrangement.

If the two angular methyls are cis, the configuration of the product would be as shown in **3b.** The cis (rather than trans)



3b

B/C ring fusion would be expected since this allows ring B to exist in a chair conformation.[3] In **3a** the angular methyls are in chemically shift equivalent positions and in axial conformations. In **3b,** the angular methyl at the trans ring fusion is axial while the angular methyl at the cis ring fusion is equatorially disposed to the B ring. One would therefore expect two NMR resonances for the angular methyl groups of **3b** whereas **3a** should show only one angular methyl resonance. The NMR spectra of the coupling product in $CHCl_3$, pyridine, and at −40 °C in chloroform shows only one angular methyl resonance and hence the product may be assigned structure **3a.**

This assignment was further confirmed by the ^{13}C NMR spectrum, which had only eight peaks. The symmetry of **3a** is in accord with eight chemical shift nonequivalent carbons, whereas one would have expected **3b** to have more than eight resonances.

These results indicate that this route to the perhydrophenanthrene ring system is attended by both regio- and stereospecificity.

Experimental Section

All solvents are distilled. Where specified as dry, they were distilled from calcium hydride and stored over molecular sieves. Reagents were used without further purification, except for Hagemann's ester, which was distilled. Analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga.

Infrared spectra were recorded on either a Perkin-Elmer Model 257 or Model 467 spectrometer. Ultraviolet spectra were determined on a Cary Model 14. Nuclear magnetic resonance spectra (60 MHz) were obtained on a Varian Model T-60 or EM-360, while 100-MHz spectra were obtained on a JEOL MH-100 spectrometer. Carbon-13 magnetic resonance spectra were run on a Varian CFT-20 spectrometer. Mass spectra were obtained on a Varian M-66 spectrometer. The reductive coupling reaction was done using a Princeton Applied Research Model 170 electrochemistry system.

Synthesis of Diester 7. Sodium metal (3.5 g, 0.15 mol) was added to 150 ml of anhydrous ethanol. The resulting solution was cooled to 0 °C. Then 27 g (0.15 mol) of Hagemann's ester, **6,** was added dropwise to the solution. After stirring for 30 min under a N_2 atmosphere, the reaction mixture was warmed to 40 °C and 18.2 g (0.16 mol) of α-chloroethyl acetate was added dropwise. The temperature was raised to 60 °C and the reaction mixture was stirred further for 2.5 h. The ethanol was evaporated under reduced pressure and the residue was taken up in water. This was extracted with 3 × 150 ml of ether. After workup the residue was distilled at 132–133 °C (0.27 mm). This gave 24.8 g (62%) of diester **7.**

Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.59; H, 7.54.

Hydrolysis of the Diester 7. To a solution of 5 g of NaOH in 25 ml of water was added 5 g of diester **7.** Enough ethanol was added (about 15 ml) to bring the ester into solution. This solution was stirred at 50–60 °C for 1.5 h and then poured into about 50 ml of water. The reaction mixture was acidified with 40% H_2SO_4 and extracte with 3 × 50 ml of methyl ethyl ketone (MEK), and the extract washed with saturated NaCl. Evaporation of the solvent afforded a solid which was crystallized from MEK. This gave 1.95 g (49%) of diacid, mp 148–148.5 °C with gas evolution.

Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.83; H, 5.78.

3-Methyl-2-cyclohexen-1-one-2-acetic Acid (8). Procedure A. Into the distilling flask of a Kugelrohr apparatus was placed 9.42 g (0.045 mol) of the above solid diacid. This was heated under a vacuum with the temperature slowly increased to 175 °C when a semisolid material began to distill. This distillation began with much foaming. The temperature was maintained at 175 °C until distillation stopped; 7.4 g of distillate was obtained. Recrystallization from a 3:1 mixture of benzene and petroleum ether (bp 30–60 °C) yielded 4.5 g (61%) of crystalline **8,** mp 113–114 °C.

Procedure B. To a mixture of 263 g (0.72 mol) of $Ba(OH)_2$ decahydrate, 750 ml of water, and 250 ml of ethanol was added 89 g (0.30 mol) of diester **7.** The reaction mixture was refluxed for 24 h, cooled, and cautiously acidified with 10% HCl. Enough acid was added to dissolve all the precipitate from the reaction. The resultant solution was extracted with 3 × 150 ml of MEK. The combined extracts were washed with saturated NaCl solution. Evaporation of the solvent left a solid residue which was recrystallized from a benzene and petroleum ether mixture to afford 35.5 g (64%) of acid **8,** mp 113–114 °C.

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.16; H, 7.22.

Kolbe Electrolysis[7] of 8. To 75 ml of dry methanol was added 2.1 g (0.012 mol) of keto acid **8** and 25 ml of 0.1 M sodium methoxide in methanol. This solution was placed into a 200-ml three-neck round-bottom flask equipped with a magnetic stirring bar, condenser in the center neck, and a pair of 1-cm^2 platinum sheet electrodes about 2 in. apart. Fifty-five volts at 0.5 A was applied to the solution. The solution was stirred until the pH reached about 8 to pH paper or about 2 h. The methanol was distilled and the residue extracted with benzene. The benzene was removed under vacuum and the resultant oil distilled at 100–102 °C (0.35 mm). The solid distillate was recrystallized from petroleum ether to give 1.35 g (72%) of white needles: mp 63–63.5 °C; infrared 1739 cm^{-1}; ^1H NMR 6.03 ppm broad, 1 H; 5.72 ppm, s, 1 H; 4.93 ppm, 8-line multiplet, 1 H, $J_{vic} = 12$, $J_{vic} = 7$ Hz, $J_{allylic} = 2$ Hz; 2.47 ppm, m, 4 H; 1.96 ppm, s, 3 H. The decoupled ^{13}C NMR: 173.5, 166.8, 135.3, 127.8, 108.9, 79.8, 29.3, 24.9, 17.9 ppm. The ^{13}C NMR in which carbon–hydrogen coupling was allowed showed the resonances at 173.5, 166.8, and 127.8 ppm as singlets, the resonances at 135.3, 108.9, and 79.8 ppm as doublets, the resonances at 29.3 and 24.9 ppm as triplets, and the resonance at 17.9 ppm as quartet. Mass spectrum: parent ion and base peak m/e 150. Ultraviolet λ_{max} 261 nm (ϵ 2.64 × 10^4). These spectra are consistent with the unsaturated lactone **9.**

Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.88, 71.85; H, 6.70, 6.69.

Synthesis of Lactone 9. To 15 ml of a 1 M solution of H_2SO_4 in acetic acid was added 250 mg of the keto acid **8.** This solution was stirred at room temperature for 6 h. The solution was then poured into 100 ml of 5% NaCl solution and extracted with MEK. The solvent was removed and the residue distilled to give 190 mg (85%) of lactone **9.**

Kolbe Electrolysis[7] of the Salt of 8. To 75 ml of dry methanol were added 2.0 g (0.0118 mol) of the acid **8** and 5.9 ml of 2 M sodium methoxide in methanol. This solution was placed in the cell described above. Fifty-five volts at 1.5 A was applied to the reaction mixture for 2 h. The workup was as described above. Distillation of the resultant product at 85.8 °C (0.28 mm) gave 1.55 g of a colorless oil: infrared 1652, 1637 cm^{-1}; ^1H NMR 4.18 ppm, s, 2 H; 3.32 ppm, s, 3 H; 2.40 ppm, m, 6 H; 2.08 ppm, s, 3 H. Mass spectrum: parent ion m/e 154, base peak m/e 139. These spectra are consistent with the methyl ether **10.**

Electrolysis of 8 in Dimethylformamide.[5] To 70 ml of dry DMF were added 2.52 g (0.015 mol) of keto acid **8** and 0.25 g (0.0022 mol)

of triethylamine. The solution was placed in the cell described above and electrolyzed at 0 °C and 105–170 V with the current maintained at 0.25 A for 9 h. The reaction mixture was poured into 350 ml of saturated NaCl solution and extracted with 4 × 100 ml of ether. The solvent was removed and the resultant oil distilled at 120–130 °C (0.15 mm) to produce a solid distillate. Chromatography on neutral alumina with a 1:1 mixture of ether to petroleum ether gave 210 mg of a white, crystalline solid: mp 121–121.5 °C; infrared 1655 cm^{-1}; mass spectrum parent ion *m/e* 246; ultraviolet λ_{max} 241 nm (ϵ 2.14 × 10^4). These data are consistent with the structure of compound 2. The yield was 11.4%.

Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.92; H, 9.04.

Reductive Coupling of 2. To 50 ml of acetonitrile were added 200 mg (0.81 mmol) of **2**, a solution of 5 g of tetraethylammonium chloride in 50 ml of acetonitrile, and 13 ml of distilled water. The solution was placed in the electrolysis cell and degassed by bubbling nitrogen through the stirred solution for 45 min. The half-wave reduction potential was determined by polarography to be at −1.7 V (vs. SCE). The preparative reaction was run at −1.80 V (vs. SCE) for 7 h. The acetonitrile was distilled and the residue taken up in 200 ml of 5% NaCl solution and extracted with 3 × 50 ml of ether. The ether was dried and removed under vacuum and the oily residue was placed on a neutral alumina column and eluted with 15% ether in petroleum ether. This yielded 130 mg of a slightly yellowish, crystalline solid: mp 180–181 °C; infrared 1707 cm^{-1}; ^1H NMR 0.93 ppm, s, in $CHCl_3$; 0.97 ppm, s, in C_5H_5N. The NMR spectrum in $CHCl_3$ at −40 °C was essentially unchanged. The ^{13}C NMR in $CDCl_3$ exhibited eight resonances at 213.0, 52.3, 44.7, 41.0, 31.2, 22.1, 19.6, and 15.5 ppm. Mass spectrum: parent ion *m/e* 248. These data identified the product as **3a**. The yield was 81% taking into account recovered starting material (see below).

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.95; H, 9.03.

Elution of the alumina with 50% ether–petroleum ether afforded 40 mg of the starting diketone **2**.

Registry No.—**2**, 60410-71-1; **3a**, 60410-72-2; **6**, 487-51-4; **7**, 20653-49-0; **7** diacid, 60410-73-3; **8**, 60410-74-4; **9**, 60410-75-5; **10**, 60410-76-6; ethyl chloroacetate, 105-39-5.

References and Notes

(1) Abstracted from the Ph.D. Dissertation of Richard F. Daley, Emory University, 1976.
(2) J. P. Zimmer, J. A. Richards, J. C. Turner, and D. H. Evans, *Anal. Chem.*, **43**, 1000 (1971), and references cited therein; N. L. Weinberg "Technique of Electro-organic Synthesis", in two parts, "Techniques of Chemistry", Vol. V, A. Weissberger, Ed., Wiley, New York, N.Y., 1975.
(3) W. S. Johnson, *J. Am. Chem. Soc.*, **75**, 1498 (1953).
(4) S. Swann, Jr., and W. E. Garrison, Jr., "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 463.
(5) M. Finkelstein and R. C. Peterson, *J. Org. Chem.*, **25**, 136 (1960).
(6) For example Δ^4-3 keto steroids seem to couple to afford pinacols similar to **5** [P. Kabasakalian and J. McGlotten, *J. Am. Chem. Soc.*, **78**, 5032 (1956)] and even cyclohexenone gives a mixture of β-β coupling and "head to tail" coupling (similar to 4) [E. Touboul, F. Weisbuck, and J. Wiemann, *C. R. Acad. Sci.*, **268**, 1170 (1969)].
(7) J. H. P. Utley in the text cited in ref 2, p 793.

Cis Reduction of Acetylenes by Organocopper Reagents[1a]

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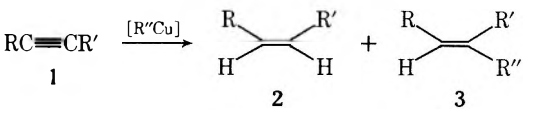
The stereoselective reduction of several disubstituted acetylenes to the corresponding cis olefins has been effected by an organocopper reagent prepared from CuI and 2 equiv of a primary Grignard reagent. A mechanistic pathway is proposed which involves the generation of a copper hydride species and subsequent cis addition of this intermediate to the acetylene function. Evidence for a vinylcopper intermediate of type 13 was obtained by trapping experiments with D_2O and allyl bromide. Phenyl-substituted acetylenes also undergo competitive addition of the alkylcopper reagent when THF is employed as the solvent (but not in ether solution). On the other hand, 3-phenyl-2-propyn-1-ol (11) shows only a regioselective trans addition of alkylcopper reagents leading to allylic alcohols of type **10**.

Organocopper reagents are known to add to terminal[2] and certain functionalized acetylenes[3] in synthetically useful reactions usually with high regio- and stereoselectivity. In connection with a study of related intramolecular analogues,[4] we have found that organocopper reagents also react with simple disubstituted acetylenes under some conditions. The predominant reaction in this case is reduction of the acetylene to the corresponding cis olefin, a highly stereoselective transformation of some synthetic potential. In several instances, addition of the organometallic species also takes place in the same fashion as with terminal acetylenes.[2]

Results

The organocopper reagent obtained by mixing *n*-BuMgBr and CuI in a 2:1 ratio at −35 °C in THF solution undergoes obvious decomposition upon warming to room temperature. The inclusion of 1-phenylpropyne (**1a**) in a fivefold excess of this reagent during the warming process resulted in 98% conversion of **1a** to a 68:30 mixture of (*Z*)-phenylpropene (**2a**) and (*E*)-2-methyl-1-phenyl-1-hexene (**3a**) after hydrolysis at the end of a 1-h reaction period. Under these conditions the cis reduction product **2a** was formed with a minimum of 99% stereoselectivity, although allowing the reaction mixture to stand for 24 h before hydrolysis resulted in contamination of the **2a** with 6% of **4a**, its *E* isomer. Quenching a similar reaction with D_2O gave **2a** with the incorporation of 41% deuterium, exclusively at C-1 as determined by NMR analysis. The addition product **3a** incorporated 86% deuterium in this experiment.



1 2 3

The structure of **3a** was established by comparison with an authentic sample obtained from the Wittig reaction[5] of the ylide derived from benzyltriphenylphosphonium chloride with 2-hexanone. The isomeric olefins produced in this fashion were separated by GLC and examined by ^{13}C NMR in order to secure stereochemical assignments. Thus, *E* isomer **3a** displays its allylic methyl at higher field (17.5 ppm) than that of the *Z* isomer **5** (23.8 ppm), whereas the allylic methylene carbon appears at higher field for **5** (32.0 ppm) than it does for **3a** (40.2 ppm). These assignments are based on the expecta-

Table I. Reactions of Acetylenes with Organocopper Reagents

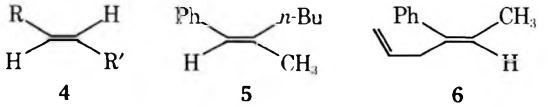
Acetylene				Time,	Conversion,	Products, %	
1	R	R′	R″MgX	h	%	2	3
a	Ph	CH_3	*n*-Bu[a]	1	98	68	30
			n-Bu	0.75	100	100	
			i-Pr	48	35	35	
			t-Bu	15	0		
			Et	1	99	99	
b	Ph	Ph	*n*-Bu[a]	5	100	30	70
			Et	4	65	65	
c	*n*-C_5H_{11}	CH_3	*n*-Bu	6	80	80	
d	*t*-Bu	*t*-Bu	*n*-Bu		0		

[a] THF solvent.

tion that the group cis to the phenyl substituent will have its carbon shifted to higher field owing to steric interactions.[6]

The addition reaction leading to **3a** has not heretofore been observed for disubstituted acetylenes of a nonfunctionalized type except for the intramolecular examples recently reported by us.[4] Interestingly, this product predominates during the initial phases of the reaction as observed by GLC monitoring of the course of the reaction. However, attempts to find experimental conditions under which the addition process predominates at high conversions of acetylene have thus far proven unsuccessful, since decomposition of the reagent (and the resulting reduction of **1a** to **2a**) occurs at the minimum temperatures needed for the formation of **3a**.

In an effort to develop a more efficient reducing system, several other Grignard reagents were utilized; in these experiments diethyl ether was used as the solvent. The organocopper reagent derived from *t*-BuMgBr decomposed more readily as anticipated, but no reduction of **1a** was observed. The reagent prepared from *i*-PrMgBr gave reduction of **1a** to **2a** without competing addition, but conversions were low. However, utilization of EtMgBr in the general procedure resulted in essentially complete conversion to **2a**. These experiments and related ones described below suggested that THF might be promoting the addition reaction, and, indeed, an experiment using *n*-BuMgBr *in diethyl ether* also gave clean reduction of **1a** to **2a** without the formation of appreciable amounts of **3a**. The reaction product from a similar experiment was treated with allyl bromide in the presence of HMPA prior to hydrolysis, whereupon 40% of the alkylated product **6** was obtained in addition to **2a** (57%). Compound

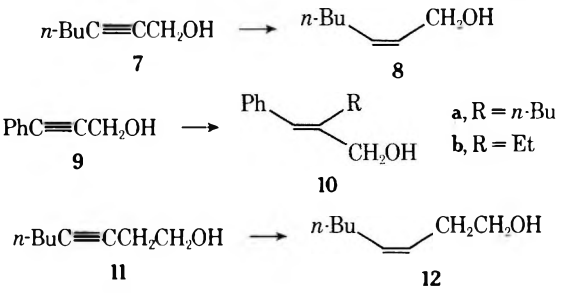


4 **5** **6**

6 is assigned the *Z* configuration on the basis of the proton chemical shift of the allylic methyl which is found at high field (1.56 ppm) relative to the corresponding methyl (1.70 ppm) in the known *E* isomer.[7] The shielding effect of the *cis*-phenyl substituent in **6** accounts for this upfield shift.[8] An attempt to alkylate the intermediate organometallic species with CH_3I was not successful. Interestingly, the lithium cuprate derived from *n*-BuLi did not react with **1a** in THF–pentane even on prolonged treatment.

Other acetylenes behave in an analogous fashion. Thus, diphenylacetylene (**1b**) was converted stereoselectively to *cis*-stilbene (**2b**) by the *n*-BuMgBr-derived reagent in THF, although the addition compound **3b**[9] was the major product under these conditions. Only reduction to **2b** was observed in an experiment using EtMgBr in ether, albeit with a lower conversion of **1b**. 2-Octyne (**1c**) gave an 80% conversion exclusively to (*Z*)-2-octene (**2c**) with *n*-BuMgBr in ether. Highly hindered di-*tert*-butylacetylene (**1d**) was not reactive under similar conditions.

Propargyl alcohols also react with organocopper reagents. Thus, the reagent prepared from EtMgBr promoted an efficient conversion of 2-heptyn-1-ol (**7**) to (*Z*)-2-hepten-1-ol (**8**) (58%) and a mixture of several volatile hydrocarbons (which was not further characterized except to note an allene band at 1960 cm^{-1} in the ir). On the other hand, 3-phenyl-2-propyn-1-ol (**9**) gave the trans addition product **10a** in high yield



7 **8** **9** **10** **11** **12**

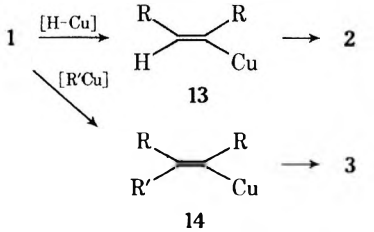
upon treatment with the *n*-butyl reagent in THF solution. The same product has recently been reported from the reaction of *n*-BuLi to **9**.[10] The identity of the two products was demonstrated by direct comparison. A similar addition leading to **10b** was obtained upon reacting **9** with the EtMgBr-derived reagent in ether solution. The stereochemical assignment for **10b** follows from the great similarity in the relevant NMR signals of both the proton and ^{13}C spectra of **10a** and **10b**. The high regioselectivity in these clean addition reactions is noteworthy, as is the trans nature of the addition process.

Finally, homopropargyl alcohol **11** was partially converted to the cis olefinic alcohol **12** by an excess of the *n*-butyl reagent in ether. The stereochemistry was assigned on the basis of the magnitude of the coupling constant (J = 10 Hz) between the olefinic protons in the NMR spectrum of **12**.[11]

Discussion

The reductions of the type **1** → **2** appear to offer some promise for the highly stereoselective reduction of simple disubstituted acetylenes to cis olefins. The reaction seems to be generally applicable, although the large excess of reagent required for high conversions may be undesirable in some synthetic applications. The competing addition reaction (**1** → **3**) can generally be suppressed by choosing appropriate experimental conditions, notably the use of ether as a solvent.

The reduction process probably involves the in situ generation of a copper hydride species of undefined structure which adds to the acetylene function in a cis manner. The resulting vinylcopper intermediate **13** is then transformed into the



13 **14**

observed product **2**. The decomposition of alkylcopper species to olefin and copper hydride is a well-precedented process[12] and attention has recently been focused on the importance of copper hydride reactions in side processes attending organocuprate conversions.[13] The cis mode of the copper hydride addition is analogous to the usual stereochemistry for alkylcopper additions to acetylenes.[2,3] A number of copper hydride reagents have been reported during the course of this study,[14,15] and in a couple of instances, these reagents were

shown to reduce acetylene functions.[15] Such reductions are predominantly cis, but the reported stereoselectivities are significantly lower than those observed in the present work, where trans isomers were not usually detected. Concrete evidence for an intermediate vinylcopper species is provided by the trapping experiments on **1a** with D_2O and allyl bromide. These experiments also reveal a regioselectivity for **1a** which adds copper hydride in such a manner as to preferentially place the copper at the phenyl-substituted carbon. However, the inefficiencies of the trapping experiments with **1a** indicate that substantial conversion of **13** to olefinic product occurs prior to hydrolysis. This is attributed to the reaction of **13** with additional copper hydride resulting in substitution of the vinylic copper by hydrogen. Such substitutions are documented for a range of organocopper compounds, and have been shown to proceed with retention of configuration at an olefinic center.[16] Unfortunately this process limits the potential of intermediate **13** insofar as further synthetic transformations are concerned.

The addition reaction leading to products of type **3** is favored by conjugating phenyl substituents and by the use of THF as a solvent. The D_2O quenching experiment with **1a** supports the notion that this product is formed by the regio- and stereoselective addition of the organocopper reagent to yield an intermediate of type **14**. This more hindered vinylcopper derivative is less susceptible than **13** to further reaction with copper hydride as indicated by the higher incorporation of deuterium in **3a** relative to **2a**.

The results with the acetylenic alcohols present an interesting contrast. The alkyl-substituted compounds **7** and **11** undergo reduction in a clean cis fashion much like the unfunctionalized alkynes, although the propargyl compound is more reactive and suffers competing side reactions. On the other hand, the phenyl-substituted propargyl alcohol **9** not only shows a high propensity for regioselective addition of the alkylcopper reagent, but involvement of the hydroxyl function results in overall trans addition. While this stereochemistry contrasts with that of the addition reactions of simple alkynes, it is nonetheless characteristic of the additions of *n*-butyllithium[10] and certain Grignard reagents[17] to propargyl alcohols. Finally, a recent publication reports similar additions of a range of Grignard reagents to variously substituted propargyl alcohols in the presence of catalytic amounts of CuI.[18] Moreover, these catalyzed additions result in organomagnesium intermediates which can be trapped in high yield, a feature of obvious advantage in synthetic work.

Experimental Section

General. Nuclear magnetic resonance (NMR) spectra were recorded on CCl_4 solutions relative to internal Me_4Si using Varian EM-360 and HR-220 spectrometers for proton measurements and a Varian XL-100 for ^{13}C determinations. Infrared (ir) spectra were obtained on liquid films with Perkin-Elmer Model 137 Infracord and Unicam SP 1000 instruments. Mass spectra were recorded at 70 eV on a Varian-MAT CH-7 spectrometer. Gas chromatography (GLC) was performed on Aerograph 600C, 600D, 1200, and A700 instruments using an analytical column of 20% Carbowax 20M on Chromosorb W and a preparative column of 20% PDEAS on Chromosorb W.

Reaction of 1-Phenylpropyne (1a) with Organocopper Reagents. A. To a suspension of 2.3 g (12 mmol) of anhydrous CuI in 12 ml of dry THF under a N_2 atmosphere at −35 °C was added dropwise 27.5 ml (24 mmol) of a 0.87 M solution of *n*-BuMgBr in THF. To the light yellow suspension thus obtained was added 464 mg (4 mmol) of **1a** and the reaction mixture was allowed to warm to room temperature. Above 15 °C the suspension turned brown and then black. The course of the reaction was monitored by removing aliquots periodically, hydrolyzing with aqueous NH_4Cl, washing with water, and analyzing by GLC. After 15 min of warming (temperature >15 °C) a 54:21:26 mixture of **1a**:**2a**:**3a** was observed; after 30 min the mixture was 9:64:27 and after 45 min it was 2:68:30. However, no reaction had occurred at 0 °C, prior to visible decomposition of the reagent. Less than 1% of **4a** was present in the above mixtures as demonstrated by GLC comparison with an authentic sample. Upon standing for 24 h the amount of **3a** had decreased substantially relative to the 1-phenylpropene which contained 6% of **4a** at this point. The reaction was worked up as described for the aliquots and the products were isolated by GLC and characterized spectroscopically. Compound **4a** was identified on the basis of its GLC retention time only. (*E*)-2-Methyl-1-phenyl-1-hexene (**3a**) showed ir 1650 and 908 cm^{-1}; NMR (220 MHz) δ 7.2–6.9 (m, 5), 6.13 (s, 1), 2.11 (t, 2, J = 7 Hz), 1.79 (s, 3), 1.5–1.2 (m, 4), and 0.92 (t, 3, J = 7 Hz); ^{13}C NMR δ 137.8, 128.3, 127.4, 125.3, 124.9, 40.1, 30.0, 22.2, 17.5, and 13.9; mass spectrum *m/e* (rel intensity) 175 (7), 174 (55), 145 (10), 132 (22), 131 (100), 129 (13), 118 (14), 117 (24), 116 (13), 115 (21), 91 (42), and 77 (5); exact mass 174.140 (calcd for $C_{13}H_{18}$, 174.1409). This material was identical in all respects with the synthetic sample described below. Isomer **5** was not observed by GLC.

B. An identical reaction was hydrolyzed with D_2O after 1 h. The products were isolated by GLC and analyzed for deuterium incorporation by NMR integration. In this fashion 41% deuterium label exclusively at C-1 was found for **2a** and 86% was present in the **3a**.

C. A similar reaction was performed by adding 0.23 g (2 mmol) of **1a** to the reagent prepared from 1.9 g (10 mmol) of CuI in 15 ml of ether and 23.8 ml (20 mmol) of a 0.84 M solution of *n*-BuMgBr in ether at −40 °C. Proceeding as described above resulted in the disappearance of **1a** with concomitant formation of **2a** which was complete after 45 min as determined by GLC. No appreciable amounts of products with longer retention times were observed.

D. A similar reaction was performed on 0.46 g (4 mmol) of **1a** using the reagent prepared from 2.3 g (12 mmol) of CuI and 26 ml (24 mmol) of 0.92 M *n*-BuMgBr in ether. After the starting material had disappeared a solution of 6 g of allyl bromide in 5 ml of hexamethylphosphorous triamide was added. After 4 h at room temperature the reaction was worked up in the usual fashion. GLC analysis of the product showed **2a**, **3a**, and **6** in the proportions 57:3:40. (*Z*)-4-Phenyl-1,4-hexadiene (**6**) showed ir 1648, 995, 960, and 910 cm^{-1}; NMR δ 7.2 (s, 5), 6.2–5.3 (m, 2), 5.2–4.7 (m, 2), 3.05 (d, 2, J = 6 Hz), and 1.56 (d, 3, J = 7 Hz); mass spectrum *m/e* (rel intensity) 158 (56), 143 (50), 129 (100), 128 (48), 117 (42), 115 (75), 91 (43), and 77 (20); exact mass 158.109 (calcd for $C_{12}H_{14}$, 158.1096).

E. To a suspension of 2.3 g (12 mmol) of CuI in 12 ml of ether at −30 °C was added 28 ml (24 mmol) of 0.86 M EtMgBr in ether. The resulting yellow-green suspension turned black upon warming to room temperature. At a temperature of about 10 °C, 0.46 g (4 mmol) of **1a** was added to this warming mixture. After 1 h essentially complete conversion to **2a** had occurred. Neither **4a** nor longer retention time products were visible by GLC in significant amounts.

F. To the reagent prepared from 3.8 g (20 mmol) of CuI and 50 ml (40 mmol) of a 0.8 M solution of *i*-PrMgBr in ether was added 0.46 g (4 mmol) of **1a**. After reaction for 48 h GLC analysis showed a 65:35 mixture of **1a** and **2a**. No products with longer GLC retention times were detected.

G. To a solution of 53 ml (24 mmol) of 0.45 M *t*-BuMgBr in ether was added in portions 2.3 g (12 mmol) of CuI at −20 °C under a nitrogen atmosphere. After stirring for 10 min 0.46 g (4 mmol) of **1a** was added and the mixture was allowed to warm to room temperature. Analysis by GLC after 15 h showed only unreacted **1a**.

H. To a suspension of 4 g (21 mmol) of CuI in 40 ml of THF at −30 °C was added 30 ml (40 mmol) of a 1.3 M solution of *n*-BuLi in pentane. After 30 min 0.47 g (4 mmol) of **1a** was added, and the reaction mixture was allowed to warm to room temperature and then heated to reflux. Analysis of an aliquot showed only starting material after 17 h.

(*E*)-and (*Z*)-2-Methyl-2-phenyl-1-hexene (3a and 5). A suspension of 56% NaH in mineral oil (3.3 g, 77 mmol) was washed several times with dry pentane to remove the mineral oil, 115 ml of Me_2SO was added, and the mixture was heated to 80 °C for 45 min under a N_2 atmosphere. The resulting solution was cooled and 30 g (77 mmol) of benzyltriphenylphosphonium chloride was added, followed after 10 min by 7.7 g (77 mmol) of 2-hexanone. After 12 h at 60 °C the mixture was cooled and poured into ice–water, pentane was added, and the solid precipitate was removed by filtration and washed with pentane. The filtrate was separated, washed with water, dried ($MgSO_4$), and concentrated. Unreacted 2-hexanone was removed from the resulting product by distillation and the residual oil containing a 6:4 mixture of (*E*)- and (*Z*)-2-methyl-1-phenyl-1-hexene was separated by GLC. The *Z* isomer **5** showed ir 1650 cm^{-1}; NMR (220 MHz) δ 7.2–6.9 (m, 5), 6.13 (s, 1), 2.15 (t, 2, J = 7 Hz), 1.82 (s, 3), 1.5–1.2 (m, 4), and 0.87 (t, 3, J = 7 Hz); ^{13}C NMR δ 138.2, 137.9, 128.1, 127.4, 125.5, 125.3, 31.9, 30.0, 23.8, 22.5, and 13.8; mass spectrum *m/e* (rel intensity) 175 (7), 174 (59), 145 (11), 132 (21), 131 (100), 129 (13), 118 (14), 117 (29), 116 (13), 115 (20), 91 (37), and 77 (5); exact mass 174.140 (calcd for $C_{13}H_{18}$, 174.1409).

Reaction of Diphenylacetylene (1b). A. To the reagent prepared as described above from 2.85 g (15 mmol) of CuI and 35 ml of 0.87 M *n*-BuMgBr in THF was added 0.53 g (3 mmol) of **1b**. Warming and workup as usual gave after 5 h at room temperature a 30:70 mixture of *cis*-stilbene and (*Z*)-1,2-diphenyl-1-hexene (**3b**):[9] NMR δ 7.3–6.9 (m, 5), 6.4 (s, 1), 2.5 (t, 2, *J* = 7 Hz), 1.7–1.1 (m, 4), and 0.94 (t, 3, *J* = 7 Hz). No evidence for *trans*-stilbene or the *E* isomer of **3b** was found by GLC or spectral examination.

B. Performing a similar reaction on 0.53 g (3 mmol) of **1b** with the reagent prepared from 1.72 g (9 mmol) of CuI and 21 ml (18 mmol) of a 0.86 M solution of EtMgBr in ether gave upon the usual workup after 4 h a 35:65 mixture of **1b** and **2b**. No significant products of longer retention times were observed by GLC.

Reaction of 2-Octyne (1c). A reaction of 0.44 g (4 mmol) of **1c** with the reagent prepared from 3.8 g (20 mmol) of CuI and 43.5 ml (40 mmol) of 0.92 M *n*-BuMgBr in ether gave a 20:80 mixture of **1c** and **2c**. No trans isomer **4c** was observable by GLC. (*Z*)-2-Octene (**2d**) showed ir 3030, 1665, and 690 cm^{-1}; NMR δ 5.8–5.1 (m, 2), 2.2–1.8 (m, 2), 1.6 (d, 3, *J* = 6 Hz), 1.4–1.1 (m, 6), and 0.89 (t, 3, *J* = 6 Hz).

Reaction of Di-*tert*-butylacetylene (1d). Treating 1 equiv of **1d** with the reagent prepared from 7.5 equiv of CuI and 15 equiv of *n*-BuMgBr in ether in the usual manner for 2 days gave only unchanged starting material.

Reaction of 2-Heptyn-1-ol (7). Reaction of 0.448 g (4 mmol) of **7** with the reagent prepared from 2.3 g (12 mmol) of CuI and 27.5 ml (24 mmol) of 0.86 M EtMgBr in ether in the usual manner for 4 h resulted in a mixture of **8** (58% yield by GLC) and several volatile products which distilled with the ether. These were not further characterized except to note a band at 1960 cm^{-1} in the ir indicating the presence of an allene. (*Z*)-2-Hepten-1-ol (**8**) showed ir 3400, 3030, 1650, and 1010 cm^{-1}; NMR δ 5.8–5.3 (m, 2), 4.1 (d, 2, *J* = 6 Hz), 2.3–1.9 (m, 2), 1.6–1.1 (m, 4), and 0.9 (t, 3, *J* = 6 Hz).[19] The *E* isomer was not present to the limit of detection by NMR.

Reaction of 3-Phenyl-2-propyn-1-ol (9). The usual reaction of 0.53 g of **9** with the reagent prepared from 5 equiv of CuI and 10 equiv of *n*-BuMgBr in THF for 5 h resulted in essentially complete conversion to (*E*)-2-(*n*-butyl)-3-phenyl-2-propen-1-ol (**10a**):[10] ir 3400, 3030, 1650, 1030, 910, 745, and 700 cm^{-1}; NMR (C_6D_6, 220 MHz) δ 7.23 (d, 2), 7.13 (t, 2) 7.07 (t, 1), 3.55 (s, 1), 4.03 (s, 2), 2.52 (s, 1), 2.25 (t, 2, *J* = 7 Hz), 1.36 (quint, 2, *J* = 7 Hz), 1.16 (sext, 2, *J* = 7 Hz), and 0.77 (t, 3, *J* = 7 Hz); ^{13}C NMR δ 142.2, 137.6, 128.4, 127.8, 126.1, 125.2, 66.4, 30.4, 28.3, 22.8, and 13.9; mass spectrum *m/e* (rel intensity) 190 (20), 148 (25), 133 (98), 130 (20), 129 (49), 128 (20), 117 (52), 116 (14), 115 (60), 105 (39), 92 (31), 91 (100), and 77 (22). There was no spectroscopic evidence for the presence of the *Z* isomer.

A similar reaction of 0.53 g of **9** with the reagent prepared from 3 equiv of CuI and 6 equiv of EtMgBr in ether for 4 h gave complete conversion to a product which was 96% (*E*)-2-ethyl-3-phenyl-2-propen-1-ol (**10b**): ir 3400, 3030, 1660, 1020, 910, 745, and 700 cm^{-1}; NMR δ 7.2 (s, 5), 6.46 (s, 1), 4.15 (s, 2), 3.2 (s, 1), 2.25 (q, 2, *J* = 7 Hz), and 1.10 (t, 3, *J* = 7 Hz); ^{13}C NMR 143.2, 137.3, 128.3, 127.9, 126.2, 124.5, 66.0, 21.6, and 12.9.[18] There was no spectroscopic evidence for the presence of the *Z* isomer.

Reaction of 3-Octyn-1-ol (11). A reaction of 0.50 g of **11** with the reagent from 5 equiv of CuI and 10 equiv of *n*-BuMgBr in ether was processed after 24 h to give a 65:35 mixture of **11** and (*Z*)-3-octen-1-ol (**12**): ir 3400, 3030, 1655, and 1045 cm^{-1}; NMR (220 MHz) δ 5.43 (d of t, 1, *J* = 10, 6.5 Hz), 5.26 (d of t, 1, *J* = 10, 6.5 Hz), 3.49 (t, 2, *J* = 6.5 Hz), 2.23 (q, 2, *J* = 6.5 Hz), 2.03 (m, 2), 1.4 (s, 1), 1.32 (m, 4), and 0.89 (t, 3, *J* = 6 Hz).[20] There was no evidence for the presence of the *E* isomer in the ir or NMR.

Registry No.—**1a,** 673-32-5; **1b,** 501-65-5; **1c,** 15232-76-5; **2d,** 7433-78-5; **3a,** 60428-21-9; **3b,** 5041-40-7; **5,** 60428-22-0; **6,** 60428-23-1; **7,** 20739-58-6; **8,** 55454-22-3; **9,** 1504-58-1; **10a,** 60428-24-2; **10b,** 56407-97-7; **11,** 14916-80-4; **12,** 20125-84-2; benzyltriphenylphosphonium chloride, 1100-88-5; pentane, 109-66-0; R″Cu (R″ = Bu), 34948-25-9; R″Cu (R″ = *i*-Pr), 55883-86-8; R″Cu (R″ = *t*-Bu), 56583-96-1; R″Cu (R″ = Et), 18365-11-2.

References and Notes

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(2) J. F. Normant, G. Cahiez, C. Chuit, and J. Villieras, *J. Organomet. Chem.*, **77**, 269, 281 (1974); J. F. Normant, G. Cahiez, M. Bourgain, C. Chuit, and J. Villieras, *Bull. Soc. Chim. Fr.*, 1656 (1974), and references cited therein; P. L. Coe and N. E. Milner, *J. Organomet. Chem.*, **70**, 147 (1974).
(3) J. F. Normant, *Synthesis*, 63 (1972); G. H. Posner, *Org. React.*, **19**, 1 (1972). See also W. F. Truce and M. J. Lusch, *J. Org. Chem.*, **39**, 3174 (1974); J. Meijer and P. Vermeer, *Recl. Trav. Chim. Pays-Bas*, **94**, 14 (1975), and references cited therein.
(4) J. K. Crandall, P. Battioni, J. T. Wehlacz, and R. Bindra, *J. Am. Chem. Soc.*, **97**, 7171 (1975).
(5) A. Maercker, *Org. React.*, **14**, 270 (1965).
(6) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, p 80.
(7) G. Hata and D. Aoki, *J. Org. Chem.*, **32**, 3754 (1967).
(8) H. Rottendorf, S. Sternhell, and J. R. Wilmshurst, *Aust. J. Chem.*, **18**, 1759 (1965).
(9) J. E. Mulvaney, Z. G. Gardlund, and S. L. Gardlund, *J. Am. Chem. Soc.*, **85**, 3897 (1963).
(10) L. I. Olsson and A. Claesson, *Tetrahedron Lett.*, 2161 (1974).
(11) R. M. Silverstein, G. C. Bassler, and T. C. Morrill, "Spectrometric Identification of Organic Compounds", 3d ed, Wiley, New York, N.Y., 1974, p 226.
(12) G. M. Whitesides, E. R. Stredronsky, C. P. Casey, and J. San Filippo, Jr., *J. Am. Chem. Soc.*, **92**, 1426 (1970).
(13) H. O. House and J. C. DuBose, *J. Org. Chem.*, **40**, 788 (1975).
(14) R. K. Boeckmann, Jr., and R. Michalak, *J. Am. Chem. Soc.*, **96**, 1623 (1974); E. C. Ashby, T. F. Korenowski, and R. D. Schwartz, *J. Chem. Soc., Chem. Commun.*, 157 (1974); S. Masamune, P. A. Rossy, and G. S. Bates, *J. Am. Chem. Soc.*, **95**, 6452 (1973); S. Masamune, G. S. Bates, and P. E. Georghiou, *ibid.*, **96**, 3686 (1974).
(15) T. Yoshida and E. Negishi, *J. Chem. Soc., Chem. Commun.*, 762 (1974); M. F. Semmelhack and R. D. Stauffer, *J. Org. Chem.*, **40**, 3619 (1975); P. Vermeer, J. Meijer, C. Eylander, and L. Brandsma, *Recl. Trav. Chim. Pays-Bas*, **95**, 25, (1975).
(16) G. M. Whitesides, J. San Filippo, Jr., E. R. Stredronsky, and C. P. Casey, *J. Am. Chem. Soc.*, **91**, 6542 (1969).
(17) F. W. von Reim and H. G. Richey, *Tetrahedron Lett.*, 3777, 3781 (1971).
(18) B. Jousseaume and J. G. Duboudin, *J. Organomet. Chem.*, **91**, C1 (1975).
(19) L. F. Hatch, H. D. Weiss, and T. P. Li, *J. Org. Chem.*, **26**, 61 (1961).
(20) H. R. Sonawane, M. S. Wadig, and B. C. Subba Rao, *Indian J. Chem.*, **6**, 297 (1968).

Mechanism and Catalysis for Phenylhydrazone Formation from Aromatic Heterocyclic Aldehydes[1]

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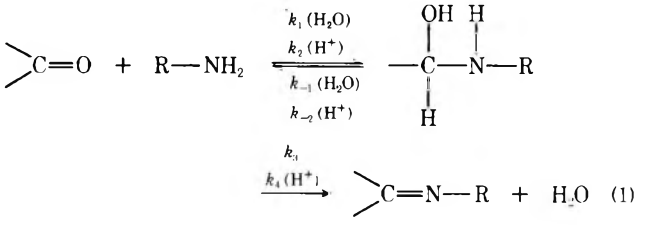
As is typical for the addition of amines to carbonyl compounds, the reaction of 2-thiophenecarboxaldehyde, pyrrole-2-carboxaldehyde, and *N*-methylpyrrole-2-carboxaldehyde with phenylhydrazine exhibits rate-determining formation of carbinolamine under acidic conditions and rate-determining dehydration of the carbinolamine intermediate under neutral and basic conditions. The addition of phenylhydrazine to form carbinolamines from these substrates is subject to general acid catalysis by carboxylic acids; the Bronsted exponent is 0.35 for addition to 2-thiophenecarboxaldehyde and *N*-methylpyrrole-2-carboxaldehyde, and 0.90 for addition to pyrrole-2-carboxaldehyde. Logarithms of rate constants for catalysis of the attack of phenylhydrazine on furfural, 2-thiophenecarboxaldehyde, pyrrole-2-carboxaldehyde, and *N*-methylpyrrole-2-carboxaldehyde by the hydrated proton, carboxylic acids, and water are linearly related to values of pK_a for the corresponding acids: $\log k = \gamma \log K_a + C$. Values of γ increase with increasing pK_a of catalyst. The dehydration of the carbinolamines derived from the addition of phenylhydrazine to the aromatic heterocyclic aldehydes exhibits both acid-catalyzed and pH-independent reactions.

The addition of amines to carbonyl compounds usually proceeds with one or more changes in rate-determining step which are reflected in breaks in pH–rate profiles.[2,3] Under slightly acidic conditions, formation of the carbinolamine intermediate is slow, reflecting either rate-determining attack of the nucleophile or rate-determining protonation of the zwitterionic addition product.[4,5] Under neutral or basic conditions, dehydration of the carbinolamine becomes the slow step:



(1)

There exist a number of quantitative relationships between structure and reactivity. Most of these correlations are concerned with the effect of substituents on the reactivity of a functional group linked to an aromatic ring. One of the oldest is the Hammett equation,[6] which correlates the nature of polar substituents in meta/para-substituted benzene derivatives with both equilibrium and rate constants for their reactions. Subsequent to the formulation of the Hammett equation, a very large amount of experimental information concerning the effects of polar substituents on reaction rates and equilibria has been correlated with the appropriate substituent constants in the benzene series.[7-10] Corresponding treatment of substituent effects in heterocyclic aromatic systems is limited, although some progress has been made.[8,10-13]

In work reported herein a previous study of furfural phenylhydrazone formation[13] has been elaborated to include a series of aromatic five-membered heterocyclic aldehydes, viz., 2-thiophenecarboxaldehyde, pyrrole-2-carboxaldehyde, and *N*-methylpyrrole-2-carboxaldehyde, to attempt to understand the relationship between structure and reactivity in this series.

Experimental Section

Materials. All reagents employed were obtained commercially and, with the exception of reagent grade inorganic salts, were either redistilled or recrystallized before used. Solutions of phenylhydrazine were prepared just prior to use. Solutions of carboxylic acids in 20% aqueous ethanol were prepared just prior to use to avoid esterification.

Kinetic measurements were carried out spectrophotometrically at 25 °C with the aid of a Zeiss PMQ II spectrophotometer equipped with a thermostated cell holder. The reaction of 2-thiophenecarboxaldehyde and phenylhydrazine was followed by observing the appearance of the product at 354 nm (pyrrole-2-carboxaldehyde and *N*-methylpyrrole-2-carboxaldehyde at 340 nm) with an initial concentration of aldehydes of 5.0×10^{-5} M. In all cases a sufficient excess of nucleophilic reagent was employed so that pseudo-first-order rate behavior was observed. First-order rate constants were evaluated from plots of log $(OD_\infty - OD_t)$ against time in the usual manner.

It was difficult to determine spectrophotometrically the equilibrium constants for the formation of the carbinolamines from the aldehydes and phenylhydrazine owing to the strong interference absorption of the latter substance. Similar difficulties have been noted in attempts to determine equilibrium constants for the formation of other phenylhydrazones.[14,15] Sander and Jencks[16] have determined the values of the equilibrium constants for the addition of hydroxylamine (pK_a = 5.97) and semicarbazide (pK_a = 3.65) to furfural; these are respectively 5.2 and 1.1 M^{-1}. On the basis of these values, it is estimated that the equilibrium constants for the addition of phenylhydrazine (pK_a = 5.2) to furfural is close to 3 M^{-1}. Since 2-thiophenecarboxaldehyde, pyrrole-2-carboxaldehyde, and *N*-methylpyrrole-2-carboxaldehyde are less reactive than furfural toward phenylhydrazine it is possible to use relatively high concentrations of phenylhydrazine under neutral and basic conditions without accumulation of appreciable carbinolamine. In addition, with each of the aromatic heterocyclic aldehydes studied, the reaction is first order in phenylhydrazine over the concentration 5.0×10^{-3} to 5.0×10^{-2} M at pH 7. Consequently, all kinetic studies above pH 7 (in which dehydration is rate determining) have been made employing phenylhydrazine concentrations lower than 5.0×10^{-2} M. Second-order rate constants could therefore be determined directly by dividing first-order rate constants by the concentration of phenylhydrazine free base.

In the pH region in which phenylhydrazine attack is principally rate determining, rate constants have been corrected for the influence of the rate of carbinolamine dehydration as described by Sayer and Jencks.[17] Catalytic (third-order) rate constants were evaluated from the slopes of plots of second-order rate constants against the concentration of catalyst. All kinetic experiments were carried out at 25.0 ± 0.1 °C in 20% aqueous ethanol at an ionic strength of 0.50, maintained with KCl, with 2.0×10^{-4} M EDTA. Values of apparent pH were recorded with a Radiometer Model PHM 4d meter equipped with a glass electrode. Calculation of the concentration of phenylhydrazine free base and undissociated carboxylic acids were made employing the Henderson–Hasselbalch equation and values of pK_a determined in this work.

pK_a Determinations. The pK_a of *N*-methylpyrrole-2-carboxylic acid (pK_a = 4.64 ± 0.01) was measured at 25.0 ± 0.1 °C in water at an ionic strength of 0.01 by careful partial neutralization of nine samples of the acid with known amounts of standard potassium hydroxide solution, to obtain different buffer solutions. The pH values of these solutions were measured with a Methron Herisau Compensator E 388 equipped with a combined glass electrode. The pK_a was obtained from the Henderson–Hasselbalch equation (Table I, supplementary material), and the thermodynamic value was calculated.

The values of pK_a of acetic acid (4.741 ± 0.017), β-bromopropionic acid (4.103 ± 0.008), formic acid (3.625 ± 0.014), chloroacetic acid (2.881 ± 0.020), and cyanoacetic acid (2.462 ± 0.004) (Table II, sup-

Table IV. Catalytic Constants for Several Acids for Attack of Phenylhydrazine on Aromatic Heterocyclic Aldehydes in 20% Ethanol at 25 °C and Ionic Strength 0.50 [a]

Catalyst	pK_a	Furfural[b]	2-Thiophene-carboxal-dehyde	Pyrrole-2-carboxal-dehyde	*N*-Methyl-pyrrole-2-carboxaldehyde
H_3O^+	−1.74	3.3×10^5	2.5×10^5	1.4×10^5	1.3×10^5
$CNCH_2CO_2H$	2.46	2.6×10^4	1.2×10^4	1.8×10^3	6.5×10^2
$ClCH_2CO_2H$	2.88	1.6×10^4	7.1×10^3	9.0×10^2	3.7×10^2
HCO_2H	3.63	8.3×10^3	3.2×10^3	1.7×10^2	2.1×10^2
$BrCH_2CH_2CO_2H$	4.10	9.2×10^3	3.3×10^3	7.3×10^1	2.2×10^2
CH_3CO_2H	4.74	4.8×10^3	1.7×10^3	1.3×10^1	1.0×10^2
H_2O	15.74	3.3	1.1	1.0×10^{-1}	6.0×10^{-2}

[a] Catalytic constants have the units M^{-2} min^{-1}. [b] Reference 13.

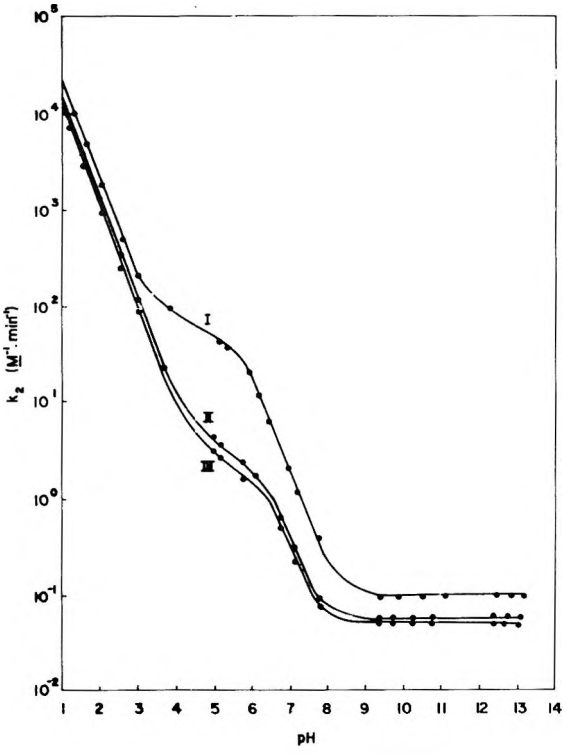


Figure 1. Logarithms of second-order rate constants for phenylhydrazone formation from 2-thiophenecarboxaldehyde (I), pyrrole-2-carboxaldehyde (II), and *N*-methylpyrrole-2-carboxaldehyde (III) in 20% aqueous ethanol at 25 °C and ionic strength 0.50 plotted as a function of pH. All points refer to zero buffer concentration. The lines are theoretical (see text).

plementary material), and phenylhydrazinium ion (5.302 ± 0.028) (Table III, supplementary material) were measured at 25.0 ± 0.1 °C in 20% aqueous ethanol and ionic strength 0.50, maintained with KCl, by careful partial neutralization of four samples of the acids with known amounts of standard potassium hydroxyde solution, to obtain different solutions. The pH values of these solutions were measured with a Methron Herisau Compensator E 148, equipped with a combined glass electrode. The glass electrode was initially calibrated with a blank solution of the same ionic strength containing 0.0100 M hydrochloric acid, whose pH was taken as 2.00. Under such conditions the measured values of pH refer to hydronium ion concentration, rather than hydronium ion activities. The pK_a's were obtained from the Henderson-Hasselbalch equation. The results were excellent, except for those for cyanoacetic acid, with acid concentration higher than 0.100 M.

Results

In Figure 1 second-order rate constants for the reaction of phenylhydrazine with 2-thiophenecarboxaldehyde (I), pyrrole-2-carboxaldehyde (II), and *N*-methylpyrrole-2-carboxaldehyde (III) in 20% aqueous ethanol at 25 °C and ionic strength 0.50 are plotted as a function of pH. Where necessary,

Table V. Rate Constants for the Acid-Catalyzed and pH-Independent Reactions for Aromatic Heterocyclic Aldehyde Phenylhydrazone Formation under Conditions of Rate-Determining Dehydration at 25 °C

Aldehyde	k_H, M^{-2} min^{-1}	k_0, M^{-1} min^{-1}
Furfural[a]	5.0×10^7	2.0×10^{-1}
2-Thiophenecarboxaldehyde	1.8×10^7	1.0×10^{-1}
Pyrrole-2-carboxaldehyde	3.5×10^6	6.0×10^{-2}
N-Methylpyrrole-2-carboxaldehyde	3.0×10^6	5.5×10^{-2}

[a] Reference 13.

the second-order rate constants were extrapolated to zero buffer concentration. The lines in this figure are theoretical ones based on the following rate law derived from eq 1.

$$\text{Rate} = \frac{k_3[k_1(H_2O) + k_2a_{H^+}] + k_4a_H[k_1(H_2O) + k_2a_{H^+}]}{k_{-1}(H_2O) + k_{-2}a_{H^+} + k_3 + k_4a_{H^+}} \times (>C{=}O)(RNH_2) \quad (2)$$

The values of the rate constants were taken from Tables IV and V and it was assumed that the equilibrium constant for the addition of phenylhydrazine to the aromatic heterocyclic aldehydes, K_{ad}, is 1.0 M^{-1}.

The general shape of the curves is familiar and reflects (going from basic to acid conditions) uncatalyzed and acid-catalyzed dehydration of the carbinolamine intermediate as rate-determining step, and water-catalyzed and acid-catalyzed attack of the nucleophile (or trapping of the zwitterionic intermediate[4,5]), as rate determining.[2,3,13,14]

In the region of rate-determining formation of carbinolamine, second-order rate constants are sensitive functions of the nature and concentration of the carboxylic acid–carboxylate buffers employed to maintain constant pH. Studies of the buffer catalysis demonstrated that, as usual, it is of the general acid type[2,3] (Table VI, supplementary material). Catalytic constants for various carboxylic acids were evaluated in the usual way. These constants are collected in Table IV.

Catalytic constants for the carboxylic acids are well correlated by the Bronsted catalysis law. Least-squares treatment of the data yield the following values for α: 2-thiophenecarboxaldehyde, 0.35; pyrrole-2-carboxaldehyde, 0.90; and *N*-methylpyrrole-2-carboxaldehyde, 0.35 (Figure 2).

In Figure 3, values of the logarithms of the catalytic constants for the hydrated proton and water for the attack of phenylhydrazine on furfural, 2-thiophenecarboxaldehyde, pyrrole-2-carboxaldehyde, and *N*-methylpyrrole-2-carboxaldehyde, and values of the logarithms of the catalytic constants for cyanoacetic acid catalysis and acetic acid catalysis for the attack of phenylhydrazine on furfural, 2-thiophene-

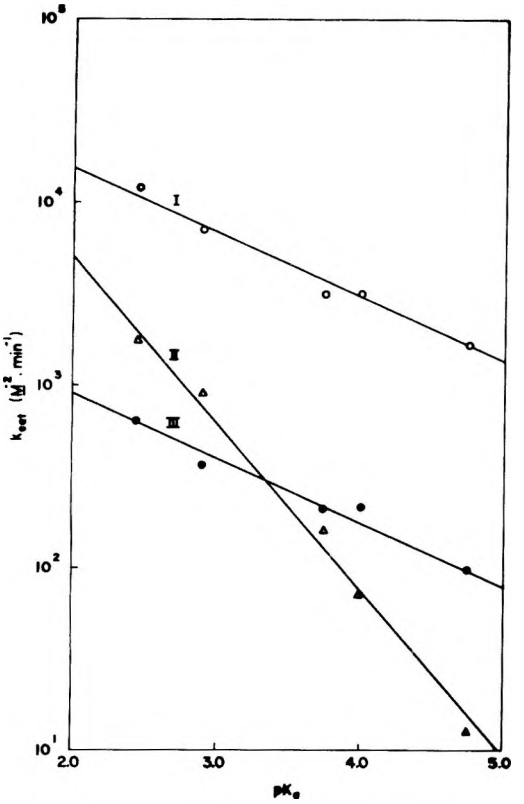


Figure 2. Logarithms of the catalytic constants for several acids for the attack of phenylhydrazine on 2-thiophenecarboxaldehyde (I), pyrrole-2-carboxaldehyde (II), and *N*-methylpyrrole-2-carboxaldehyde (III) in 20% aqueous ethanol at 25 °C and ionic strength 0.50 plotted against the pK_a values of the catalytic constants listed in Table IV.

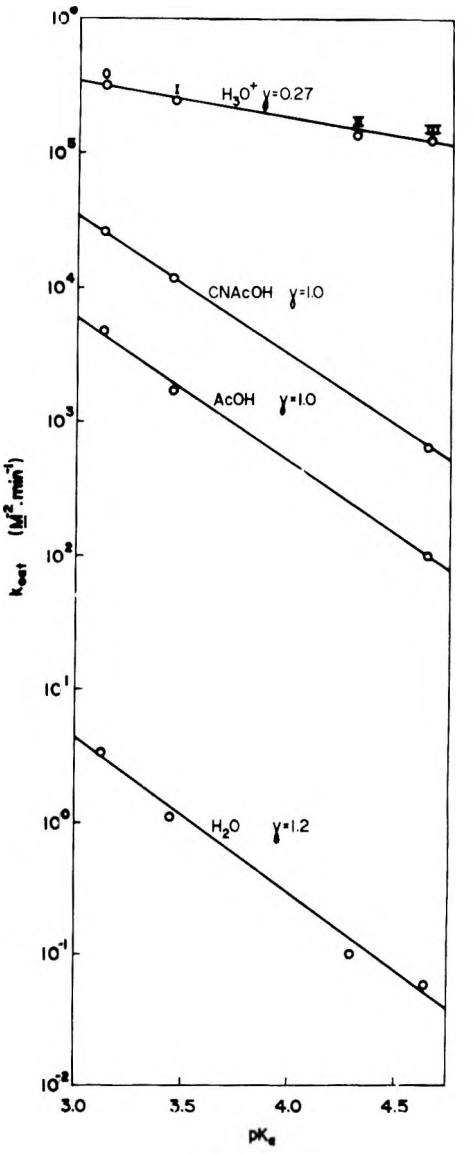


Figure 3. Logarithms of catalytic constants for the hydrated proton and water for the attack of phenylhydrazine on furfural (0), 2-thiophenecarboxaldehyde (I), pyrrole-2-carboxaldehyde (II), and *N*-methylpyrrole-2-carboxaldehyde, and logarithms of catalytic constants for cyanoacetic acid and acetic acid for the attack of phenylhydrazine on furfural (0), thiophene-carboxaldehyde (I), and *N*-methylpyrrole-2-carboxaldehyde (III) plotted against the pK_a values of 2-furoic acid, 2-thiophenecarboxylic acid, pyrrole-2-carboxylic acid, and *N*-methylpyrrole-2-carboxylic acid. Data have been taken from Table IV.

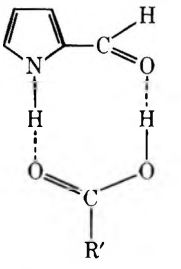
carboxaldehyde, and *N*-methylpyrrole-2-carboxaldehyde are plotted against the pK_a values of the corresponding acids (2-furoic acid, 3.12;[18] 2-thiophenecarboxylic acid, 3.47;[19] pyrrole-2-carboxylic acid, 4.41;[20] and *N*-methylpyrrole-2-carboxylic acid, 4.64, this work). Data for all the compounds fall on good straight lines. The straight lines of Figure 3 can conveniently be expressed by the equation $\log k = \gamma \log K_a + C$, in which the two variables are lcg k and log K_a, the slope of the line is γ, and the intercept is C. The significance of γ is that it measures the sensitivity of the reaction to the nature of the aromatic heterocyclic ring system.

Dehydration of the intermediate carbinolamine is the rate-determining step above pH 7. The dehydration reaction for all the aromatic heterocyclic aldehydes studied is susceptible to specific acid catalysis and to a pH-independent reaction (Figure 1). The appropriate rate constants are collected in Table V.

Discussion

A. The Bronsted Catalysis Law. Correlation of catalytic constants with pK_a values of carboxylic acids for meta/para-substituted benzaldehyde phenylhydrazone formation and for 5-substituted 2-furfural phenylhydrazone formation[13] in Bronsted plots by least-squares analysis yields values for α of 0.35 ± 0.01; significantly smaller values characterize a number of related reactions.[17] In this work, correlations of the catalytic constants of carboxylic acids for 2-thiophenecarboxaldehyde and *N*-methylpyrrole-2-carboxaldehyde phenylhydrazone formation in Bronsted plots by least-squares analysis yields values for α of 0.35. In contrast, general acid catalysis for pyrrole-2-carboxaldehyde phenylhydrazone formation yields a value for α of 0.90. As the *N*-methylpyrrole-2-carboxaldehyde exhibits the usual behavior, but the pyrrole-2-carboxaldehyde does not, it is reasonable to assume that the hydrogen linked to heterocyclic nitrogen plays a role in this unique behavior.

One possible explanation is that the carboxylic acid catalysts for this reaction function as bifunctional catalysts for the attack reaction in the way shown below:



In this formulation, the carbonyl oxygen acts as a general base catalyst by withdrawing a proton from the substrate in the transition state. At the same time, the hydroxyl component

acts as a general acid catalyst by partially protonating the carbonyl oxygen atom of the substrate. Since polar substituents in the carboxylic acid will affect the proton-donating powers of the hydroxyl function and the proton-withdrawing powers of the carbonyl oxygen atom in opposite fashions, it would be anticipated that the catalytic constants would be independent of the nature of such substituents. In other words, α should be smaller than 0.35. This is in contrast with the observed value of α (0.90) and rules out this explanation.

The possibility of rate-determining proton transfer from the carboxylic acid to the zwitterionic addition compound[4,5] is also inconsistent with the data since such reactions are expected to be diffusion controlled or nearly so and, hence, have rate constants independent of the acidity of the catalyst. In addition, unusual mechanisms for phenylhydrazone formation from pyrrole-2-carboxaldehyde seem unlikely since the reactivity of this compound is consistent with that expected on the basis of its relatives (see below).

We are left without a satisfactory explanation for the unusually large value of α for this reaction. It evidently depends on having the proton on the heterocyclic nitrogen atom and may or may not depend on the bifunctional character of the carboxylic acid. Further studies will be required to settle this point.

B. Free Energy Relationships. In this work we have found a linear free energy relationship between the reactivity of derivatives of aromatic heterocyclic rings, viz., furan, thiophene, and pyrrole, and the acidity of the corresponding acids.

The sensitivity of the attack reaction of phenylhydrazine on the aromatic heterocyclic aldehydes is highest when the reaction is water catalyzed (γ = 1.2), intermediate when the reaction is catalyzed by carboxylic acids (γ = 1.0), and smallest when the reaction is catalyzed by the hydronium ion (γ = 0.27). The variation of the γ values with the acidity of the general acid catalyst together with the considerations concerning variation in transition state structures as function of reactivity is in accord with the considerations of Hammond,[21] Leffler,[22] and Swain and Thornton.[23]

Acknowledgment. The author is indebted to Dr. Eugene H. Cordes for helpful comments concerning this work.

Registry No.—Phenylhydrazine, 100-63-0; furfural, 98-01-1; 2-thiophenecarboxaldehyde, 98-03-3; pyrrole-2-carboxaldehyde, 1003-29-8; *N*-methylpyrrole-2-carboxaldehyde, 1192-58-1; *N*-methylpyrrole-2-carboxylic acid, 6973-60-0; acetic acid, 64-19-7; β-bromopropionic acid, 590-92-1; formic acid, 64-18-6; chloroacetic acid, 79-11-8; cyanoacetic acid, 372-09-8; phenylhydrazinium ion, 55668-06-9.

Supplementary Material Available. Tables I, II, III, and VI that report full determination of the acidity constants data for *N*-methylpyrrole-2-carboxylic acid, acetic acid, bromopropionic acid, formic acid, chloroacetic acid, cyanoacetic acid, and phenylhydrazinium ion (4 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Supported in part by the Fundação de Amparo à Pesquisa do Estado de São Paulo.
(2) W. P. Jencks, *Prog. Phys. Org. Chem.*, **2**, 63 (1964).
(3) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N.Y., 1969.
(4) J. M. Sayer, G. Pinsky, A. Schonbrunn, and W. Washsturi, *J. Am. Chem. Soc.*,. **96**, 7998 (1974).
(5) S. Rosenberg, S. M. Silver, J. M. Sayer, and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 7986 (1974).
(6) L. P. Hammett, *J. Am. Chem. Soc.*, **59**, 96 (1937).
(7) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).
(8) P. R. Wells, *Chem. Rev.*, **63**, 171 (1963).
(9) S. Ehrenson, *Prog. Phys. Org. Chem.*, **2**, 196 (1964).
(10) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", Wiley, New York, N.Y., 1963.
(11) M. J. S. Dewar and P. J. Grisdale, *J. Am. Chem. Soc.*, **84**, 3584 (1962).
(12) H. H. Jaffé and H. Lloyde Jones, *Adv. Heterocycl. Chem.*, **3**, 209 (1964).
(13) L. do Amaral, *J. Org. Chem.*, **37**, 1433 (1972).
(14) L. do Amaral and M. P. Bastos, *J. Org. Chem.*, **36**, 3412 (1971).
(15) W. P. Jencks, *J. Am. Chem. Soc.*, **81**, 475 (1959).
(16) E. G. Sander and W. P. Jencks, *J. Am. Chem. Soc.*, **90**, 6154 (1968)
(17) J. M. Sayer and W. P. Jencks, *J. Am. Chem. Soc.*, **91**, 6353 (1971).
(18) Y. Otsuji, M. Kubo, and E. Imoto, *Nippon Kagaku Zasshi*, **80**, 1300 (1959).
(19) E. Imoto and R. Motoyama, *Bull. Naviwa Univ.*, **A2**, 127 (1954).
(20) G. Magnani, *Gazz. Chim. Ital.*, **26**, 92 (1896).
(21) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).
(22) J. E. Leffler, *Science*, **117**, 340 (1953).
(23) C. G. Swain and E. R. Thornton, *J. Am. Chem. Soc.*, **84**, 817 (1962).

Stereochemistry of Photochemical Cycloadditions: Addition of Ethylene to a Δ^9-1-Octalone[1]

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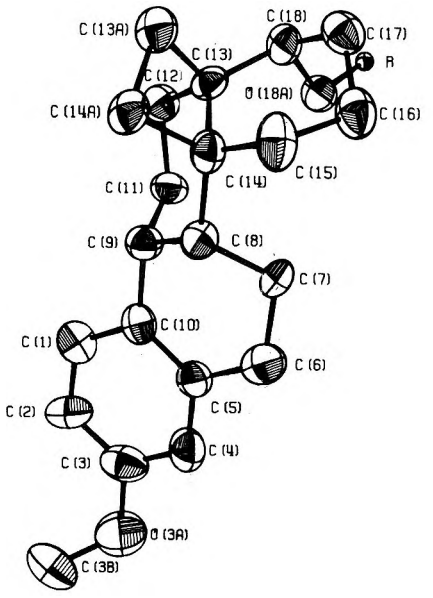
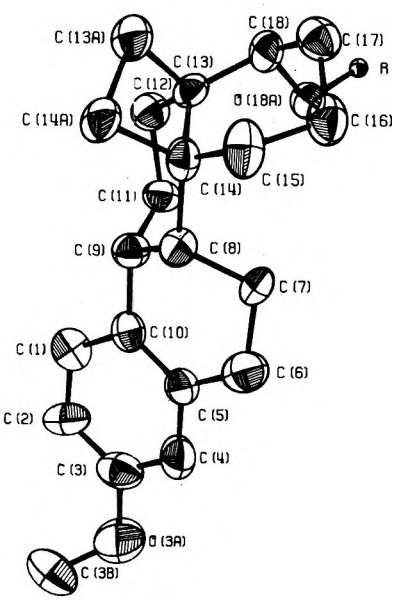
Photochemical cycloaddition of ethylene and **1** gave only **2**, a result consistent with the Wiesner model for photoaddition of olefins to cyclohexenones.

The photochemical cycloaddition of olefins to enones is a synthetically useful reaction. Wiesner[2] has rationalized the stereochemistry of such additions to cyclohexenones in terms of an excited enone in which the β carbon becomes nearly tetrahedral with an electron-rich orbital in a pseudoaxial orientation. This model is consistent with a large number of cycloadditions to cyclohexenones of the cholestenone type. We report here the first test of the Wiesner model in a Δ^9-1-octalone.

The enone **1**[3] underwent photochemical cycloaddition with ethylene in methylene chloride solution at −60 °C to give exclusively **2** in 82% yield. The structure of **2** was established by single-crystal x-ray diffraction analysis of the *p*-bromobenzoate **3b**.





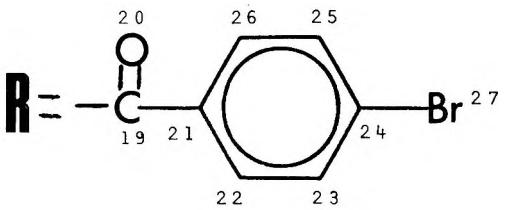
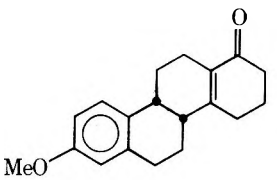
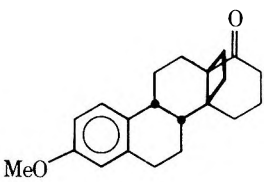


Figure 1. Stereoview of **3b.**



1



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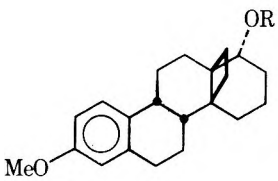
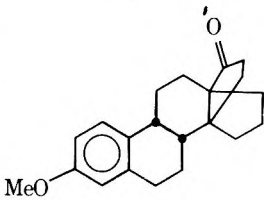


3a, R = H
b, R = *p*-BrC_6H_4CO



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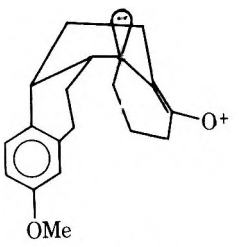

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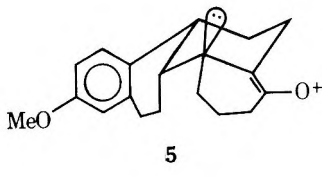

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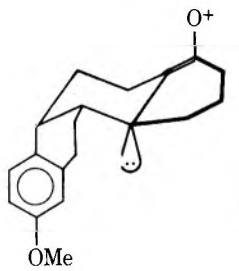

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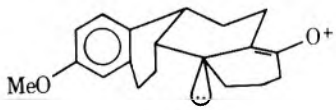

7

According to the Wiesner model, four excited forms of **1** may be considered: **4, 5, 6,** and **7.** In two of these, **4** and **7,** ring C is held in the boat conformation and these are presumed to be considerably less important than **5** or **6.** Cycloaddition with **6** must occur from the α face, which is severely hindered by rings A and B. No obstacles impede cycloaddition with the remaining species, **5.** Thus, the formation of **2** as the sole product of cycloaddition of ethylene and **1** is adequately rationalized in terms of the Wiesner model and intermediate **5.**

Reduction of **2** with lithium tri-*tert*-butoxyaluminum hydride gave only **3a.** Conversion of this alcohol into its *p*-bromobenzoate **3b** gave a crystalline derivative suitable for x-ray analysis.

When **2** was heated with *p*-toluenesulfonic acid in boiling benzene for 2 h, a new cyclopentanone **8** was isolated in 64% yield. The structure of **8** follows from spectral data and ample precedent.[4]

Experimental Section[5]

Cycloaddition of Ethylene and 1. An irradiation apparatus equipped with a Hanovia 450-Watt Type L mercury vapor lamp and a Pyrex probe cooled by circulating ethanol maintained at ca. −60 °C by a dry ice–isopropyl alcohol bath was charged with a solution of 7.25 g of **1** in 130 ml of methylene chloride. The apparatus was cooled in a dry ice–isopropyl alcohol bath and ethylene was bubbled through the solution during irradiation. After 1 h of irradiation all the starting material had reacted. The solvent was removed and the resulting solid was recrystallized from methanol to yield 5.03 g of **2,** mp 131.5–133 °C. The mother liquors yielded another 1.49 g of **2** (total 82.1% yield), ir (CH_2Cl_2) 1690 cm^{-1}.

Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 80.94; H, 8.08.

Reduction of 2. To a solution of 1.20 g (5.83 mmol) of lithium tri-*tert*-butoxyaluminum hydride in 6 ml of dry tetrahydrofuran was

Table I

A. Crystal Parameters

Formula	$C_{28}H_{31}O_3Br$ (495.5)
Crystal size, mm	0.2 × 0.2 × 0.3
Cell dimensions	a = 11.874 (2) Å
	b = 7.520 (1) Å
	c = 27.095 (5) Å
	β = 101.08 (1)°
	V = 2374.3 (7) Å^3
Space group	$P2_1/c$
Molecules/unit cell	4
Density observed, g/cm^3	1.35
Density calculated, g/cm^3	1.386
Linear absorption coefficient (μ), cm^{-1}	28.1

B. Refinement Parameters

Number of reflections	2443
Nonzero reflections	2038
R index ($R = \Sigma\|\|F_o\| - \|F_c\|\|/\Sigma\|F_o\|$)	0.061
Weighted R ($R' = \omega(F_o^2 - F_c^2)^2/\Sigma\omega F_o^4$)	0.010
Final shifts	$<0.3\sigma$

added a solution of 600 mg (1.94 mmol) of **2** in 6 ml of dry tetrahydrofuran. The resulting mixture was stirred at 0 °C for 75 min. After the usual workup alcohol **3a** was isolated as a white solid (570 mg, 94.5%, mp 153–159 °C). Recrystallization from methanol gave material of mp 158.5–160 °C; ir (CH_2Cl_2) 3630, 3500 cm^{-1}. Alcohol **3a** was converted into the *p*-bromobenzoate **3b** by treatment with *p*-bromobenzoyl chloride in dioxane–pyridine. The crystalline product obtained after usual workup was recrystallized twice from benzene–hexane: mp 175.5–177 °C; ir (CH_2Cl_2) 1710, 1615 cm^{-1}. This material was used for x-ray diffraction analysis.

Anal. Calcd for $C_{28}H_{31}O_3Br$: C, 67.87; H, 6.31; Br, 16.14. Found: C, 67.63; H, 6.21; Br, 16.32.

Acid-Catalyzed Isomerization of 2. A solution of 500 mg (1.64 mmol) of **2** and 1.5 g of *p*-toluenesulfonic acid monohydrate in 125 ml of benzene was refluxed for 2 h. The resulting mixture was washed with aqueous $NaHCO_3$ and water, and dried ($MgSO_4$). Removal of solvent gave 540 mg of a dark oil. A solution of this oil in methanol was stirred with activated charcoal, filtered and concentrated to yield 320 mg (64%) of crystalline **8**, mp 119–120 °C. Two additional recrystallizations from methanol gave an analytical sample: mp 120–121 °C; ir (CH_2Cl_2) 1735, 1615 cm^{-1}.

Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.07; H, 8.26.

X-Ray Analysis of 3b. The crystal structure of this compound was concluded in a routine manner. Suitable crystals were grown from a mixture of benzene and hexane. The crystals were surveyed and a 1-Å intensity data set (maximum sin θ/λ = 0.5) was obtained on a Syntex $P\bar{1}$ diffractometer using copper radiation (λ = 1.5418 Å) at room temperature. The crystal density was measured by the flotation technique in aqueous KI. Final unit cell dimensions were obtained using 15 high angle reflections ($2\theta > 40°$). The diffractometer was equipped with a graphite incident beam monochromator mounted in the perpendicular mode. During data collection a θ–2θ scan technique was employed, the scan rate was 2°/min in 2θ, the scan range was 1.0° above $K\alpha_2$ and 1.0° below $K\alpha_1$, and the background was counted for half the scan time on each side of the peak. A single check reflection was monitored every 30 reflections and indicated no crystal damage since it was reproducible within counting statistics.

The diffractometer output was processed using subprograms of the CRYM crystallographic computer system.[6] The processing included corrections for background, Lorentz, and polarization effects. The polarization effect due to the graphite monochromator was included in these corrections.[7] No corrections were made for absorption. The data processing also included calculation of the F^2 value and its standard deviation for each reflection. The standard deviations were assigned on the basis of the equation

$$\sigma^2(I) = S + \alpha^2(B_1 + B_2) + (dS)^2$$

where S is the scan count, B_1 and B_2 are the background counts, d is an empirical constant equal to 0.02, and α is the scan time to total background time ratio. All intensities with values less than three times the standard deviation were set equal to zero with zero weight. The data set was placed on an approximately absolute scale by means of Wilson statistics. Crystal parameters are summarized in Table I.

Determination of Structure and Refinement. A trial structure for **3b** was obtained by conventional Patterson and Fourier techniques. This trial structure refined routinely to an acceptable R index (see Table I). The latter stages of the refinement procedure included a full matrix least-squares treatment of all nonhydrogen coordinates in one matrix, and anisotropic temperature factors and scale factor in a second matrix. Methylene and methine hydrogen positions were calculated; all other hydrogen positions were located by difference Fourier techniques. While hydrogen parameters were added to the structure factor calculation in the latter stage of refinement, they were not refined. The quantity minimized by the least-squares procedure was $\Sigma\omega(F_o^2 - F_c^2)^2$, where $\omega = 1/\sigma^2(F_o^2)$. A final difference Fourier revealed no missing or misplaced electron density. A stereoplot of **3b** is given in Figure 1. Atomic parameters and bond distances and angles appear in Tables II and III.[8]

Acknowledgment. This work was supported by HEW (Grant AM18802).

Registry No.—**1**, 60428-06-0; **2**, 60428-07-1; **3a**, 60428-08-2; **3b**, 60428-09-3; **8**, 60428-10-6; ethylene, 74-85-1; *p*-bromobenzoyl chloride, 586-75-4.

Supplementary Material Available. Tables II and III, atomic parameters and bond distances and angles (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) This research was supported at USC by Contract N01-HD-3-2734 from the National Institute of Child Health and Human Development, NIH.
(2) K. Wiesner, *Tetrahedron*, **31**, 1655 (1975).
(3) W. S. Johnson, I. A. David, H. C. Dehm, R. J. Highet, E. W. Warnhoff, W. D. Wood, and E. T. Jones, *J. Am. Chem. Soc.*, **80**, 661 (1958), have previously described this enone.
(4) R. L. Cargill, T. E. Jackson, N. P. Peet, and D. M. Pond, *Acc. Chem. Res.*, **7**, 106 (1974).
(5) All melting points are uncorrected. Microanalyses were performed by Bernhardt Microanalytisches Laboratorium, Elbach über Engelskirchen, West Germany. Infrared spectra were recorded using a Perkin-Elmer 337 or 700 spectrophotometer. ^1H and ^{13}C NMR spectra of all new compounds were determined and are consistent with assigned structures. Since they offer no new insight, however, they are not recorded here.
(6) D. J. Duchamp, American Crystallographic Association Meeting, Bozeman, Mont., 1964, Paper B-14, p 29.
(7) L. V. Azaroff, *Acta Crystallogr.*, **8**, 701 (1955).
(8) See paragraph at end of paper regarding supplementary material.

On Attempts at Solvolytic Generation of Aryl Cations

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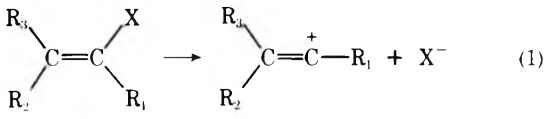
The solvolysis of phenyl triflate (3), phenyl nonaflate (4), *o*-methylphenyl nonaflate (5), *o*-cyclopropylphenyl nonaflate (6), *o*-methoxypheny. triflate (7), 2,6-dimethoxyphenyl triflate (8), 2,6-diisopropylphenyl triflate (9), 3,5-dimethoxyphenyl triflate (10), 3,5-dicyclopropylphenyl triflate (11), 3,5-di(2-methylcyclopropyl)phenyl triflate (12), 2,4,6-tricyclopropylphenyl triflate (13), and 2,4,6-triisopropylphenyl triflate (14) were examined in great detail under a wide variety of conditions. In highly polar nonnucleophilic solvents no reaction was observed and the unreacted triflates were recovered quantitatively. In the presence of nucleophiles or nucleophilic solvents the sole products observed were the corresponding phenols. Careful labeling and product studies showed that these phenols arose by nucleophilic attack on sulfur and S–O bond cleavage. We have not been able to find any evidence for aryl cation intermediates.

Contrary to earlier assumptions, the solvolyses of a number of vinyl substrates have been shown to proceed by rate-limiting heterolyses of their vinyl C–X bonds (eq 1), especially



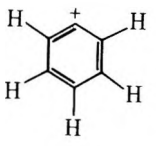
(1)

1

X = Cl, Br, OSO_2F, OSO_2CF_3, $OSO_2C_4F_9$

when cation stabilizing substituents are present or a fluorosulfonate leaving group is employed.[2] Rather than being elusive, vinyl cations **1** are now commonplace in organic chemistry.

Of the numerous species related[2] to vinyl cations one of the most interesting is the phenyl (aryl) cation, **2**. Despite con-



2

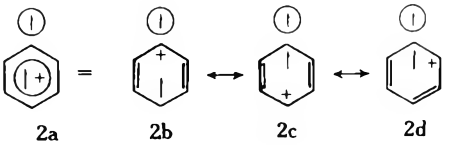
siderable research, the existence of aryl cations as reactive intermediates long eluded firm proof.[3] In the gas phase the phenyl cation is a high-energy species with $\Delta H_f°$ (298 °C) = 270 ± 4 kcal/mol,[4a] which means that it is 11 kcal/mol less stable than the ethyl cation[4b] (Table I). Nevertheless, aryl cations have been postulated as intermediates in the thermal and photochemical decomposition of aryl diazonium salts.[5] However, dediazonization reactions can follow several pathways[5a,6] involving possible biradical species,[7] aryne intermediates,[8] or one-step bimolecular mechanisms;[9] the elucidation of precise reaction mechanisms and the exact nature of reactive intermediate(s) is complicated.

Recently, Swain and co-workers[6] have shown that, in the absence of strong bases, reducing agents, or light, displacements on $C_6H_5N_2^+$ in solution proceed by rate-determining formation of a singlet phenyl cation. Independent observations by Zollinger and co-workers[10] on the reaction of molecular nitrogen under pressure with a phenyl cation adds support to the existence of such species as reaction intermediates.

In order to study the possible solvolytic generation of aryl cations we investigated the preparation and reactions of a large number of aryl triflates and nonaflates.

Results and Discussion

The singlet phenyl cation, **2**, has a nominally vacant sp^2 orbital orthogonal to the π electrons of the benzene ring. Vacant orbitals of cations generally prefer to possess maximum p character. This would require aryl cations, in analogy to vinyl cations,[11] to have a linear geometry about the electron-deficient carbon. This electron-deficient carbon in a phenyl cation, however, due to symmetry, must be constrained to an unfavorable nonlinear geometry.[12b] Taft[13] suggested that a triplet ion radical might be the structure of the aryl cation on the basis of aryldiazonium ion decomposition studies. In such a triplet ion radical, a π electron from the benzene ring has entered the vacant sp^2 orbital formerly occupied by the C–N bonding electrons. Hence, one unpaired electron is in the π system, delocalized as shown in **2a–d** (for the $^3B_1$ state). An alternative triplet state ($^3A_2$) is also possible, for which the resonance forms **2a–d** do not provide a description of the π



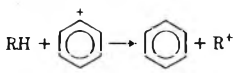
2a 2b 2c 2d

charge distribution; ab initio calculations[12] indicate this state to lie slightly higher in energy that the $^3B_1$ one. Either of the triplet states can be strongly stabilized by resonance with π-donating substituents.[12c]

Theoretical calculations using the extended Hückel,[14] INDO,[6,15] CNDO/S,[12d] and most recently ab initio[12b,c] levels predict the singlet phenyl cation to be the ground state with substantial delocalization of the positive charge throughout the molecule. The energy differences between the $^1A_1$ singlet and the $^3B_1$ and $^3A_2$ triplet states have been variously calculated to be 20–150 kcal/mol in favor of the singlet state for the phenyl cation,[6,12] but the energy separation strongly depends on substituents.[12,15] Gleiter, Hoffmann, and Stohrer found[14]

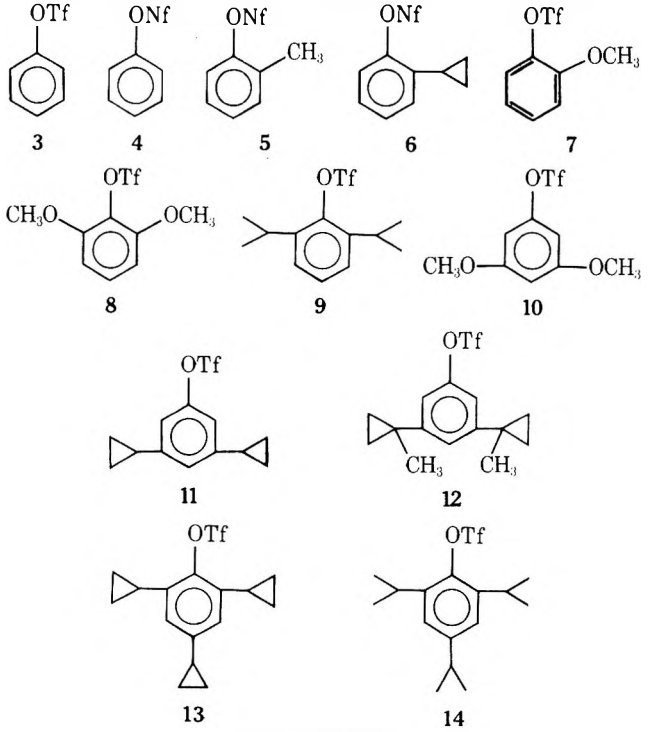
Table I Relative Phenyl Cation Stabilization Energies

Species	$\Delta H_f°$, 25 °C, gas phase	Phenyl cation stabilization energies
	270	
$C_2H_3^+$	266	+3
$C_2H_5^+$	219	−11
$CH_3C^+{=}CH_2$	237	−18
$CH_3{}^+CHCH_3$	192	−33



that electron-donating substituents in the meta position (relative to the carbon bearing the empty sp^2 orbital) should stabilize the singlet electronic state by "through-bond" stabilization,[14] although more recent calculations predict para substitution to be even more favorable.[12] Possible credence is lent to the "through-bond" hypothesis by further theoretical calculations which show that the C–N bond order is decreased in substituted phenyldiazonium ions by π-donor groups in the meta position and increased (or unchanged) by meta electron acceptors, in accord with thermal decomposition rates and quantum yields of substituted phenyldiazonium salts.[15] Possible experimental evidence for the "through-bond" stabilization of aryl cations by meta π-donor substituents has been provided by Derocque et al.[16] by mass spectral studies. Among a large number of aryl triflates investigated, 3,5-di(α-methylcyclopropyl)phenyl triflate (**12**) showed the largest percentage of direct formation of the corresponding aryl cation under electron impact,[16] although the exact structural assignments of such species are never secure in the gas phase.

Guided by these theoretical considerations,[17] we prepared the following aryl triflates and nonaflates, **3–14**, and investi-



OTf = OSO_2CF_3
ONf = $OSO_2C_4F_9$

gated their solvolytic behavior under a wide variety of conditions.

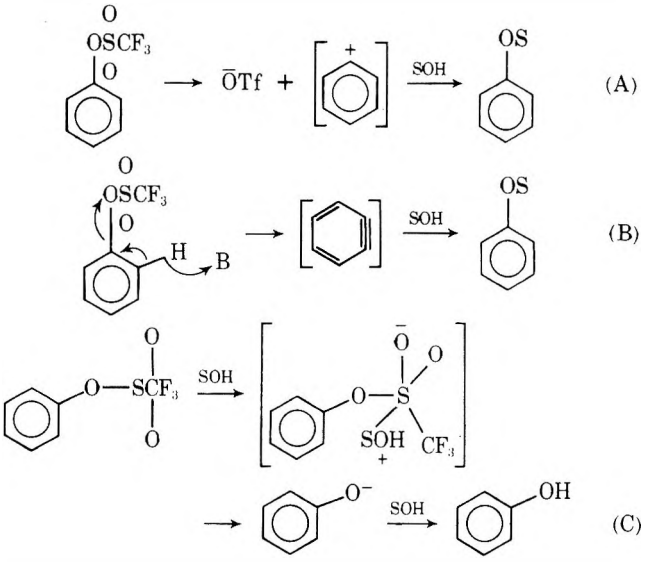
Compounds **3** and **4** were chosen as possible progenitors of the unsubstituted parent phenyl cation, compounds **5–9** were selected for possible classical inductive stabilization of aryl cations via electron-donating ortho substituents, and meta isomers **10–12** were selected to test the "through-bond" stabilization hypothesis of Gleiter and Hoffman.[14,17] Cyclopropane substituents were selected for their efficacious stabilization of cations by "through-space" nonclassical overlap of orbitals[18] and their demonstrated ability to stabilize vinyl cations.[19] In addition aryl sulfonates **9** and **14** were chosen for possible relief of ground state steric crowding upon solvolysis and hence possible enhanced solvolytic reactivity.

Table II. Solvolysis of Phenyl Sulfonates 3 and 4

Substrate	Rxn conditions	Product(s)
3	H_2O, 150 °C, 14 days	No reaction 3 recovered
3	CF_3COOH, CF_3CO_2Na 150 °C, 21 days	No reaction 3 recovered
3	CH_3COOH, CH_3CO_2Na, 150 °C, 21 days	No reaction 3 recovered
3	CH_3OH, Et_3N, 150 °C, 21 days	100% phenol
3	50% EtOH, Et_3N, 150 °C, 21 days	100% phenol
3	CF_3CH_2OH, Et_3N, 150 °C, 21 days	100% phenol
3	98% CF_3CH_2OH, Et_3N, 150 °C, 21 days	100% phenol
3	50% CF_3CH_2OH, Et_3N, 150 °C, 21 days	100% phenol
3	H_2O, NaOH, 150 °C, 12 hours	100% phenol
4	CF_3COOH, CF_3CO_2Na, 150 °C, 21 days	No reaction 4 recovered
4	50% EtOH, Et_3N, 150 °C, 21 days	100% phenol

The results of the solvolytic investigations are reported in Tables II–V. In buffered media at relatively high temperatures, arylsulfonate esters may undergo reaction via three possible mechanisms, illustrated in Scheme I for the parent

Scheme I. Mechanisms of Reaction of Arylsulfonate Esters



phenyl system. Reaction A involves aryl–oxygen cleavage, formation of the aryl cation, and subsequent capture by solvent. Path B involves abstraction of a proton by a base (solvent or buffer), loss of triflate anion, and benzyne formation. This pathway would require the formation of a mixture of meta- and ortho-substituted products from an ortho-substituted arylsulfonate as well as the incorporation of deuterium into the ring in the presence of deuterated solvent. Mechanism C involves sulfur–oxygen cleavage via nucleophilic attack on sulfur resulting in the formation of phenol, rather than a

Table III. Solvolysis of Ortho-Substituted Arylsulfonates

Substrate	Rxn conditions	Product(s)
5	CH_3COOH, CH_3CO_2Na, 150 °C, 21 days	No reaction, 5 recovered
5	50% EtOH, Et_3N, 150 °C, 21 days	o-$CH_3C_6H_4OH$ (100%)
6	CH_3OH, Et_3N, 150 °C, 21 days	o-$C_3H_5C_6H_4OH$ (50%), 6 (50%)
6	50% EtOH, Et_3N, 150 °C, 21 days	o-$C_3H_5C_6H_4OH$ (100%)
7	CH_3OH, 2,6-lutidine, 125 °C, 5 days	o-$CH_3OC_6H_4OH$ (2%), 7 (98%)
7	97% CF_3CH_2OH, 2,6-lutidine, 125 °C, 20 days	o-$CH_3OC_6H_4OH$ (7%), 7 (93%)
7	60% EtOH, NaOAc, 180 °C, 39 h	o-$CH_3OC_6H_4OH$ (83%), 7 (17%)
8	60% EtOH, NaOAc, 180 °C, 27 h	2,6-$(CH_3O)_2C_6H_3OH$ (72%), 8 (10%)
9	CH_3OH, $NaOCH_3$, 150 °C, 5 h	2,6-(i-Pr)$_2C_6H_3OH$ (100%)
9	80% EtOH, 150 °C, 10 days	No reaction, 9 recovered
9	50% EtOH, 150 °C, 10 days	No reaction, 9 recovered
9	H_2O, 150 °C, 10 days	No reaction, 9 recovered
9	CH_3COOH, 150 °C, 10 days	No reaction, 9 recovered
9	50% EtOH, NaOH, 150 °C, 5 h	2,6-(i-Pr)$_2C_6H_3OH$ (100%)

Table IV. Solvolysis of Meta-Substituted Arylsulfonates

Substrate	Rxn conditions	Product(s)
10	CH_3OH, 1,8-bis(N,N-dimethyl)naphthalene, 180 °C, 20 days	3,5-$(CH_3O)_2C_6H_3OH$ (100%)
10	CF_3CH_2OH, 1,8-bis(N,N-dimethyl)naphthalene, 125 °C, 5 days	3,5-Di-CH_3O-C_6H_3OH (38%) + 3,5-Di-CH_3O-$C_6H_3OCH_2CF_3$ (62%)
11	EtOH–$H_2{}^{18}O$, Et_3N, 150 °C, 21 days	3,5-Dicyclopropyl C_6H_3OH (100%)
12	EtOH–$H_2{}^{18}O$, Et_3N, 150 °C, 21 days	60% phenol, 40% 12

Table V. Solvolysis of 2,4,6-Trisubstituted Arylsulfonates

Substrate	Rxn conditions	Product(s)
13	EtOH–$H_2{}^{18}O$, Et_3N, 150 °C, 21 days	2,4,6-(c-C_3H_5)$_3C_6H_2OH$ (15%), 13 (85%)
14	50% EtOH, Et_3N, 150 °C, 21 days	2,4,6-(i-Pr)$_3C_6H_2OH$ (<10%), 14 (>90%)

phenyl ether, when alcoholic solvents are employed. Such nucleophilic attack upon sulfur, and the attendant S–O bond cleavage in the presence of bases, is a well-known phenomenon.[20]

Examination of the data in Table II reveals that the phenyl fluorosulfonate esters **3** and **4** do not lead to phenyl cation. Indeed they are totally inert even under extreme solvolytic conditions (2–3 weeks at 150–180 °C in polar, nonnucleophilic solvents). On the other hand, in nucleophilic solvents[21] in the presence of amine buffers, quantitative phenol formation occurs. Solvolysis of **3** in EtOD–D_2O under similar conditions also yielded phenol as the sole product. Mass spectral analysis of this phenol gave no indication (<1%) of deuterium incorporation into the ring. This rules out the possibility of benzyne formation (path B) in this reaction. These results strongly implicate nucleophilic attack on sulfur and sulfur–oxygen bond cleavage[20] as depicted in mechanism C in Scheme I.

Results in Table III reveal either no reaction or, under forcing conditions, sole formation of substituted phenols as products. In the case of ortho-substituted arylsulfonates only ortho-substituted phenols were observed with no detectable amount of meta isomers. In particular **5** gave only *o*-cresol in 50% EtOH as determined by GC analysis. Similarly, solvolysis of **6** in 50% EtOH gave only *o*-cyclopropylphenol. This solvolysis product was methylated with diazomethane, and the methyl ether so obtained was found to be identical in all respects with an authentic sample prepared from pure o-cyclopropylphenol. Again, both a mechanism involving a benzyne or an aryl cation as possible intermediates are ruled out.

Solvolyses of **11**, **12**, and **13** were conducted in EtOH–$H_2{}^{18}O$ in order to check for ^{18}O incorporation in the phenolic products; however, careful mass spectral analysis revealed none, hence providing direct evidence for path C and S–O cleavage rather than aryl–oxygen cleavage. The formation of the trifluoroethyl ether in the reaction of **10** in CF_3CH_2OH might, at first glance, indicate the intermediacy of an aryl cation. However, control experiments demonstrated that the ether was formed subsequently from phenol and CF_3CH_2OH. This is further substantiated by the reaction of ^{18}O (aryl–oxygen) labeled **10** in CF_3CH_2OH. The 3,5-dimethoxyphenyl trifluoroethyl ether thus formed had retained all of the ^{18}O originally in the starting triflate. This rules out an aryl cation intermediate.

Finally, as the data in Table V as well as the results of substrate **9** indicate, even bulky substituents do not assist the solvolytic formation of aryl cations. The small yields of phenol formed in the reaction of **14** indicate that nucleophilic attack on sulfur and the subsequent S–O cleavage is sterically hindered.

Summary. It is evident from the foregoing results and discussion that although aryl cations may be intermediates in the reactions of certain aryldiazonium ions or may be observed in the gas phase[4,16] they certainly do not form in the solvolyses of arylsulfonate esters even when "super" sulfonate leaving groups are employed.[3] Instead of reaction via aryl cations, aryl triflates prefer to react via nucleophilic attack on sulfur and S–O cleavage. These experimental results further confirm the high energy and unstable nature of aryl cations.[4,12] Moreover, because of the orthogonal arrangement of the vacant orbital at C, and the filled π orbitals of the ring, substituents are not very effective in providing significant stabilization of singlet aryl cations.[12]

Experimental Section

General. All boiling points and melting points are uncorrected. NMR, ir, and mass spectra were recorded on standard instruments as were GC determinations using the following columns: A, 3 ft × 0.25 in. 20% Carbowax 20M on Chromosorb W; B, 5 ft × 0.25 in. 3% SE-30 on Chromosorb W; C, 3 ft × 0.125 in. 5% FFAP on Chromosorb W; D, 3 ft × 0.125 in. 10% Carbowax 20M on Chromosorb W; E, 5 ft × 0.125 in. 5% FFAP on Chromosorb W; F, 5 ft × 0.125 in. 5% SE-30 on Chromosorb W; G, 9 ft × 0.25 in. 15% silicon oil DC 200 on Chromosorb P.

Reagents. Trifluoromethanesulfonic acid (triflic acid) was pur-

Table VI. Physical and Spectral Properties of Arylsulfonate Esters[a]

Compd	Bp, °C (mm)	Ir[a]	NMR[b,c]
3	67–68 (15)	1430, 1255, 1220, 1140	7.0–7.3 (m, 5 H)
6	140–145 (15)	1440, 1250, 1210, 1155	0.5–1.3 (m, 4 H) 1.9–2.4 (m, 1 H) 7.0–7.45 (m, 4 H)
7		1435, 1245, 1210, 1145	3.9 (3 H), 6.9–7.5 (m, 4 H)
8		1430, 1250, 1215, 1145	3.8 (s, 6 H), 6.4–7.3 (m, 3 H)
9	110–115 (12–15)	1385, 1205, 1130	1.12 (d, 12 H, J = 5.9 Hz) 3.25 (septet, 2 H), 7.08 (s, 3 H)
10		1430, 1250, 1215, 1150	3.8 (s, 6 H), 6.4 (m, 3 H)
13	127 (0.05)		0.45–1.15 (m, 12 H), 1.79 (m, 1 H) 2.08 (m, 2 H), 6.47 (s, 2 H)
14	62 (0.001)		1.24 (d, 12 H), 1.26 (d, 6 H) 2.90 (septet, 1 H), 3.33 (septet, 2 H) 7.02 (s, 2 H)

[a] Satisfactory elemental C and H analyses were obtained for all new compounds. [b] Neat film. [c] Parts per million downfield; TMS, 0.0.

chased from the 3M Co. and converted to its anhydride with P_2O_5.[22] Nonafluorobutanesulfonyl fluoride was kindly supplied by Farbenfabriken Bayer. Proton Sponge, 1,8-bis(dimethylamino)naphthalene, and 2,6-lutidine were purchased from Aldrich Chemical Co. Oxygen-18 enriched H_2O containing 1.75 atom % ^{18}O was purchased from BioRad and the one containing 25 atom % ^{18}O from Firma Roth, West Germany, and diluted to 12.5 atom % ^{18}O. o-Methoxyphenol, 2,6-dimethoxyphenol, 3,5-dimethoxyphenol, and 2,6-diisopropylphenol were purchased from Aldrich Chemical Co. o-Cyclopropylphenol was kindly provided by Dr. P. Cagniant, University of Metz, France; 3,5-dicyclopropylphenol, 2,4,6-tricyclopropylphenol, 2,4,6-triisopropylphenol, and 3,5-(2-methylcyclopropyl)phenol were prepared according to Effenberger et al.[23]

Aryl triflates were prepared by a procedure similar to the preparation of alkyl tosylates[24] by addition of an equivalent amount of triflic anhydride to a pyridine phenol mixture of 0 °C. In most instances pyridine triflate precipitated from the reaction mixture during a 24-h period while the mixture was kept in a refrigerator. The reaction mixture was poured into ether and washed several times with water, the ether solution was dried over $MgSO_4$, and the solvent evaporated. The crude aryl triflates were purified first by column chromatography on silica gel and then by preparative GC.

Aryl nonaflates were prepared similarly, as previously reported,[25] using triethylamine as the base. Physical and spectral properties of previously unknown aryl triflates and nonaflates are reported in Table VI; for 4 and 5 see ref 18 and for 11 and 12 see ref 23.

Solvolysis and Product Identification. Solvolyses of sulfonate esters 3–14 were carried out on a 10-mmol scale or less under the conditions given in Tables II–V in thick-walled glass ampules. Analysis was by means of either direct injection into the GC and use of authentic samples or by workup as follows. Most of the solvent was removed by aspirator and the residue dissolved in ether. The ether layer was washed with 5% NaOH (4 × 20 ml) and the phenol regenerated by acidification with ice-cold dilute HCl and extracted with ether, and identified with the aid of authentic samples. The NaOH-insoluble portion was separately worked up by washing the ether layer, from which the phenol was extracted, with ether, drying over Na_2SO_4, and removing the solvent. In all instances no or only negligible amounts of residue was observed.

The 3,5-dimethoxyphenyl trifluoroethyl ether from the reaction of 10 in CF_3CH_2OH was identified by spectral means as follows: mass spectrum m/e 236 (M^+); ir (CCl_4) 1250, 1160 cm^{-1}; NMR (CCl_4) δ 3.75 (6 H, OCH_3), 4.3 (2 H, q, OCH_2CF_3), 6.1 (m, 3 H).

Anal. Calcd: C, 50.84; H, 4.70. Found: C, 50.69; H, 4.75.

Preparation of 3,5-Di-$CH_3OC_6H_3{}^{18}OH$. Three grams (0.02 mol) of 3,5-dimethoxyaniline was mixed with 11 ml of 6 N sulfuric acid. The slurry was cooled to 0 °C in an ice–salt bath and stirred. Then 4 ml of 5 N sodium nitrite solution was added dropwise at a rate which kept the temperature of the reaction mixture between 0 and 5 °C. After addition was completed, the mixture was stirred at 0 °C for 20 min and filtered through glass filter. The filtrate was kept in ice–salt bath for 15 min. When forming the diazonium salt, 4 ml of concentrated sulfuic acid was added to 100 ml of ^{18}O-enriched water. The solution was divided equally into two flasks and heated to boiling. The liquid from diazotization was added to the refluxing acidified ^{18}O-enriched water at such a rate that the mixture boiled very vigorously. After addition was completed, the reaction mixture was refluxed for 5 min and cooled to room temperature. The two portions of the reaction mixture were combined and extracted with ether. The ethereal solution was then dried ($MgSO_4$) and evaporated. The crude product was purified by silica gel column chromatography to give 350 mg of phenol. Mass spectrometric analysis indicated an ^{18}O content for phenol of 1.55 atom %. The ^{18}O content of the ether generated by solvolysis of the labeled triflate in CF_3CH_2OH was analyzed by GC/mass spectrum. The results from two demonstrations indicate an ^{18}O content for the product ether of 1.6 ± 0.3 atom % ^{18}O.

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Registry No.—**3**, 17763-67-6; **4**, 25628-11-9; **5**, 42096-33-3; **6**, 60319-06-4; **7**, 59099-58-0; **8**, 60319-07-5; **9**, 60319-08-6; **10**, 60319-09-7; **11**, 41381-28-6; **12**, 41381-29-7; **13**, 60319-10-0; **14**, 60319-11-1; phenol, 108-95-2; o-methoxyphenol, 90-05-1; 2,6-dimethoxyphenol, 91-10-1; 2,6-diisopropylphenol, 2078-54-8; 3,5-dimethoxyphenol, 500-99-2; 3,5-dicyclopropylphenol, 41381-26-4; bis(1-methylcyclopropyl)-phenol, 41381-27-5; 2,4,6-tricyclopropylphenol, 60319-12-2; 2,4,6-triisopropylphenol, 2934-07-8; triflic anhydride, 358-23-6; 3,5-dimethoxyphenyl trifluoroethyl ether, 60319-13-3.

Reference and Notes

(1) Institute of Organic Chemistry, University of Erlangen-Nürnberg, 8520 Erlangen, West Germany.
(2) For reviews see L. R. Subramanian and M. Hanack, *J. Chem. Educ.*, **52**, 80 (1975); P. J. Stang, *Prog. Phys. Org. Chem.*, **10**, 205 (1973); G. Modena and U. Tonellato, *Adv. Phys. Org. Chem.*, **9**, 185 (1971); M. Hanack, *Acc. Chem. Res.*, **3**, 209 (1970); H. G. Richey, Jr., and J. M. Richey, "Carbonium Ions", Vol. II, G. A. Olah and P. v. R. Schleyer, Ed., Interscience, New York, N.Y., 1970.
(3) (a) T. M. Su, W. F. Sliwinski, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **91**, 5386 (1969); (b) L. R. Subramanian and M. Hanack, *Chem. Ber.*, **105**, 1465 (1972); (c) A. Streitwieser, Jr., and A. Dafforn, *Tetrahedron Lett.*, 1435 (1976).
(4) (a) J. L. Beauchamp, *Adv. Mass. Spectrom.*, **6**, 717 (1974); (b) J. L. Franklin, J. G. Dillard, H. M. Rosenstock, J. T. Herron, K. Draxl, and F. H. Field, "Ionization Potentials, Appearance Potentials and Heats of Formation of Gaseous Positive Ions", U.S. Department of Commerce, National Bureau of Standards, NSRDS-NBS 26, 1969.
(5) (a) H. Zollinger, *Acc. Chem. Res.*, **6**, 335 (1973); (b) J. Miller, "Aromatic Nucleophilic Substitution", Elsevier, Amsterdam, 1968; (c) R. W. Alder, R. Baker, and J. M. Brown, "Mechanism in Organic Chemistry", Wiley-Interscience, New York, N.Y., 1971.
(6) C. G. Swain, J. E. Sheats, and K. G. Harbison, *J. Am. Chem. Soc.*, **97**, 783, 791, 796 (1975).
(7) N. Kamigata, M. Kobayashi, and H. Minto, *Bull. Chem. Soc. Jpn.*, **45**, 2047 (1972); R. A. Abramovitch and F. F. Gadallah, *J. Chem. Soc., B*, 497 (1968).
(8) J. I. G. Cadogan, *Acc. Chem. Res.*, **4**, 186 (1971).
(9) E. S. Lewis et al., *J. Am. Chem. Soc.*, **91**, 419, 426, 430 (1969); R. A. Abramovitch and J. G. Saha, *Tetrahedron*, **21**, 3297 (1965).
(10) R. G. Bergstrom, G. H. Wahl, Jr., and H. Zollinger, *Tetrahedron Lett.*, 2975 (1974).
(11) (a) W. D. Pfeifer, C. A. Bahn, P. v. R. Schleyer, S. Bocher, C. E. Harding, K. Hummel, M. Hanack, and P. J. Stang, *J. Am. Chem. Soc.*, **93**, 1513 (1971); (b) E. Lamparter and M. Hanack, *Chem. Ber.*, **105**, 3789 (1972); (c) R. J. Hargrove and P. J. Stang, *Tetrahedron*, **32**, 37 (1976).
(12) (a) J. D. Dill, P. v. R. Schleyer, and J. A. Pople, *Tetrahedron Lett.*, 2857 (1975); (b) J. D. Dill, P. v. R. Schleyer, J. A. Pople, and E. Haselbach, *J. Am.*

Chem. Soc., in press; (c) J. D. Dill, P. v. R. Schleyer, and J. A. Pople, *ibid.*, in press; (d) H. H. Jaffe and G. F. Koser, *J. Org. Chem.*, **40**, 3082 (1975).
(13) R. W. Taft, *J. Am. Chem. Soc.*, **83**, 3350 (1961).
(14) R. Gleiter, RHoffmann, and W. D. Stohrer, *Chem. Ber.*, **105**, 8 (1972).
(15) R. J. Cox, P. Bushnell, and E. M. Evleth, *Tetrahedron Lett.*, 207 (1970); E. M. Evleth and P. M. Horowitz, *J. Am. Chem. Soc.*, **93**, 5636 (1971).
(16) J. L. Derocque, F. Effenberger, and W. Kurtz, submitted for publication.
(17) Many of the compounds chosen for study were based on the work of Gleiter, Hoffmann, and Stohrer,[14] which dealt principally with "through-bond effects". Subsequent ab initio calculations[12] on a wider range of substituents revealed, however, that through-bond effects are relatively minor in importance. However, the compounds reported in the present paper are representative. The ab initio calculations indicate that the greatest stabilization of singlet forms to be expected is from a planar *p*-NH_2 group but the magnitude of the stabilization is relat vely small and should not be enough to overcome the inherent instability of a singlet phenyl cation.
(18) M. Hanack and H. J. Schneider, *Angew. Chem.*, **79**, 709 (1967); J. Haywood Farmer, *Chem. Rev.*, **74**, 315 (1974).
(19) M. Hanack, T. Bassler, W. Eymann, W. E. Heyd, and R. Kopp, *J. Am. Chem. Soc.*, **96**, 6686 (1974).
(20) C. A. Bunton and Y. F. Frei, *J. Chem. Soc.*, 1872 (1951); S. Oae, T. Fukumoto, and R. Kiritani, *Bull. Chem. Soc. Jpn.*, **36**, 346 (1963); S. Oae and R. Kiritani, *ibid.*, **38**, 765 (1965); R. H. Summerville, C. A. Senkler, P. v. R. Schleyer, T. E. Dueber, and P. J. Stang, *J. Am. Chem. Soc.*, **96**, 1100 (1974).
(21) P. E. Peterson and F. J. Waller, *J. Am. Chem. Soc.*, **94**, 991 (1972); T. W. Bentley, F. L. Schadt, and P. v. R. Schleyer, *ibid.*, **94**, 992 (1972).
(22) T. Burdon, I. Farazmand, M. Stacey, and J. C. Tatlow, *J. Chem. Soc.*, 2574 (1957); P. J. Stang and T. E. Dueber, *Org. Synth.*, **54**, 79 (1974).
(23) W. Kurtz, P. Fischer, and F. Effenberger, *Chem. Ber.*, **106**, 525 (1973).
(24) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. I, Wiley, New York, N.Y., 1967.
(25) L. R. Subramanian, H. Bentz, and M. Hanack, *Synthesis*, 293 (1973).

Notes

The Structure of Cacalone

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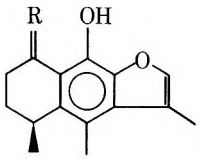
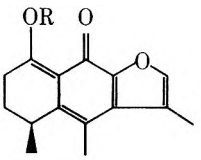
Cacalol and cacalone are two apparently related sesquiterpenes which have been isolated from the roots of *Cacalia decomposita*.[1,2] The present structures are **1a** and **2a**, respectively, which have evolved through a series of revisions.[2-4]

We have synthesized the ketone **1b**,[5] which is an aromatic tautomer of the previously proposed structure of cacalone **2a**.[4] The physical properties of compound **1b** were different from those reported for the natural cacalone,[1,2] as can be perceived from the data in Table I.

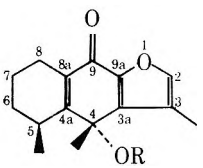
We describe here the chemical and spectroscopical data which demand alteration of the presently accepted structure of cacalone, and which strongly support structure **3a** instead.



1a, R = 2H
b, R = O



2a, R = H
b, R = Ac



3a, R = H
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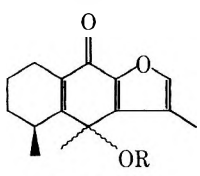
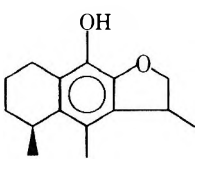
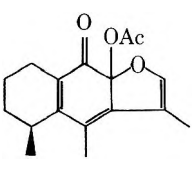


3c, R = H
d, R = Me



4



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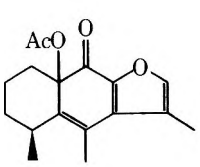
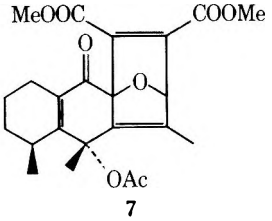


6



7

Dehydration of cacalone using a variety of dehydration agents has been ineffective or has produced polymeric products. Hydrogenation of cacalone acetate (5% Pd/C, AcOEt) or pyrolysis through a heated tube[7] at 480 °C yielded cacalol **1a**. Cacalone hydrogenation (10% Pd/C in MeOH) has afforded dihydrocacalol **4**.[1] On the basis of these data and spectroscopic studies (see below) the structure **3a** (4-hydroxy-5,6,7,8-tetrahydro-3,4,5-trimethylnaphtho[2,3-*b*]furan-9(4*H*)-one) has been assigned to natural cacalone.

Among the three alternative structures (**3b**, **5**, and **6**) for cacalone acetate, which are conceivable as products of oxidation of cacalol **1a**, **5** was eliminated according to the following considerations.

Cacalone acetate affords a Diels–Alder adduct **7** when reacted with dimethyl acetylenedicarboxylate in boiling xylene. The adduct structure was established from its NMR spectrum, exhibiting a single peak at δ 5.96 for the proton at C-2 instead of the vinylic proton of cacalone acetate at 7.3 ppm. There also appear two singlets (3 H each) at 3.71 and 3.85 ppm corresponding to nonequivalent methyl ester groups. The fact that cacalone acetate forms a methyl ether **3d** (HCl_{aq}–MeOH) provides additional evidence for structure **3b** and further eliminates structure **5**, since the latter one has a ketal function. While these evidences do not distinguish between structures **3b** and **6**, structure **3b** has been selected on the basis of (1) ^1H NMR and shift reagent experiments, (2) ^{13}C NMR, (3) mass spectrometry.

1. ^1H NMR. The NMR data are shown in Table II. The comparison of the proton spectrum of **3a** and **3b** with synthetic **1b** is self-explanatory. The main differences between **1b** and **3a** consist in the absorption of the methyl in the 4 position, the OH chemical shift (there is H bonding at 13.35 ppm in **1b**), the two other methyl signals, and the very small chemical shift difference observed for H-6 and H-7 protons

Table I. Comparisons of the Properties of the Ketones

	Ketone **1b**[a]	Cacalone[b]
Mp, °C	115	140–143
Ir, cm^{-1}	ν_{max} ($CHCl_3$) 3500–2700 and 1650	ν_{max} ($CHCl_3$) 3550 and 1660
NMR, δ	1.27 (d, J = 7 Hz, 3 H), ca. 2.0 (m, 2 H), 2.40 (d, J = 1 Hz, 3 H), 2.53 (s, 3 H), ca. 2.75 (m, 2 H), 3.42 (m, 1 H), 7.55 (q, J = 1 Hz, 1 H), and 14.2 ppm (s, 1 H, interchangeable with D_2O)[c]	1.26 (d, J = 7 Hz, 3 H), 1.66 (s, 3 H), ca. 1.80 (m, 5 H), 2.21 (d, J = 1 Hz, 3 H), ca. 2.40 (m, 2 H), 3.15 (m, 1 H), and 7.29 ppm (q, J = 1 Hz, 1 H)[c,d]
$FeCl_3$	Positive reaction (green)	Negative

[a] Reference 5. [b] References 1 and 2. [c] Taken in $CDCl_3$ using Me_4Si as internal reference. [d] From an authentic sample kindly provided by Dr. J. Romo.

Table II. A Nuclear Magnetic Resonance Comparison of Compounds 3a, 3b, and 1b[a]

Compd	H-2	H-5	H-6 H-7	H-8	CH_3-3	CH_3-4	CH_3-5	OH	CH_3CO
3a	6.95 q (1)	3.16 m	1.59 m	2.50 m	2.08 d (1)	1.53 s	1.12 d (7)	2.85 br	
3b[b]	6.85 q (1)	2.53 m	1.65 m	2.61 m	1.72 d (1)	1.38 s	1.05 d (7)		1.67 s
δ 0.12	6.95	2.65	2.00	3.14	1.81	1.55	1.15		1.76
δ 0.22	7.20	2.82	2.40	3.58	1.95	1.69	1.25		1.85
δ 0.36	7.37	2.96	2.70	4.10	2.01	1.91	1.35		1.94
1b	7.00 q (1.3)	2.95 m	1.47 m, 2.41 m		1.92 d (1.3)	2.14 s	0.92 d (7)	13.00 s	

[a] Spectra were determined on a Varian HA-100 spectrometer in C_6D_6 solutions using Me_4Si as internal standard. Values are given in δ units. Multiplicity of signals are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Numbers in parentheses denote coupling constant in hertz. [b] δ 0.12, 0.22, and 0.36, after addition of 0.12, 0.22, and 0.36 mol of $Eu(fod)_3$, respectively.

Table III. ^{13}C Chemical Shifts for 1b, 3a, and 3b[a]

Carbon	1b	3a	3b
2	145.8	140.5 (d)	139.3 (d)
3	112.1	120.2 (s)	118.5 (s)
3a	140.0	145.3 (s)	145.9 (s)
4	117.4	72.3 (s)	77.4 (s)
4a	135.2	144.3 (s)	144.5 (s)
5	28.8	28.0 (d)	28.4 (d)
6	28.9	21.6 (t)	21.6 (t)
7	33.0	16.0 (t)	16.2 (t)
8	200.5	30.3 (t)	30.5 (t)
8a	117.9	130.7 (s)	132.7 (s)
9	142.0	175.0 (s)	174.8 (s)
9a	148.7	161.6 (s)	158.2 (s)
CH_3-3	11.1	8.8 (q)	8.6 (q)
CH_3-4	13.8	27.2 (q)	28.0 (q)
CH_3-5	19.1	21.4 (q)	20.8 (q)
$OCOCH_3$			168.6 (s), 20.7 (q)

[a] Varian XL-100 in $CDCl_3$ solutions, using Me_4Si as internal standard; letters in parentheses denote multiplicity in off-resonance experiments.

in **3a**. The shift reagents experiments on the acetate **3b** have shown that the H-8 signal has a much bigger shift (0.42 slope) and the other protons H-2 (0.10 slope) and CH_3-4 (0.14 slope) have the induced shift in a normal range. If cacalone acetate had structure **2b**, the acetate and the H-7 protons would be shifted more than observed as the favorite coordination site would be on the carbonyl at C-9. In addition, small homoallylic coupling (0.6 Hz) has been observed between protons 5 and 8.

The conformation of the cyclohexene part of **3a** is half chair and the relative position of CH_3-4 and CH_3-5 is cis. The absolute configuration of the C-5 asymmetric center of cacalone was established previously[2] as β. The orientation of the C-4 methyl group in **3a** was determined on the basis of the pyridine-induced solvent shifts[8] that were observed when the NMR spectrum of this compound and of its epimer in chloroform solution were compared with spectra determined in pyridine solution. Product **3a** does not show appreciable solvent effect on the signal corresponding to the C-5 methyl ($\Delta = \delta_{CDCl_3} - \delta_{C_5D_5N} = +0.04$), while its epimer exhibits substantial deshielding ($\Delta = -0.15$) for this methyl signal. On the other hand, the proton signal at C-5 in **3a** shows considerable deshielding ($\Delta = -0.20$), but in its epimer the shift of the proton is not so large ($\Delta = -0.10$).

2. ^{13}C NMR. The identification of all carbon signals of compounds **1b, 3a,** and **3b** has been done with the help of the off-resonance experiments (Table III). The ensemble of signals for **1b** and **3a,b** confirms our proposition of structures for both furan[9] and the unsaturated ketone[10] parts of the molecule.

The comparison of spectra on these series has shown that the only possible structure for natural cacalone is in fact **3a.** The spectra exhibit some particularities. The signal at 72 ppm corresponding to C-4 of the alcohol is shifted to 77 ppm after acetylation ($\Delta\delta$ = 5 ppm). The furan C-2 carbon is shifted by 5 ppm in **1b** compared to **3a.** The carbonyl C-8 signal of **1b** is around 200 ppm; however, for the 3 series the carbonyl C-9 absorption is in the 175-ppm range.

The prediction of the methyl chemical shift of the CH_3-4 and CH_3-5 trying a number of gauche and nonbonded interaction calculations,[11] using benzoquinones[12] or unsaturated ketones models,[13] confirms again our propositions. In spite of a zig-zag configuration of the oxygen lone pair to C-4, this methyl absorption is at 28 ppm only, because the lone pairs are oriented anti and eclipsed at the same time.[14]

3. Mass Spectrometry. The interpretation of the mass spectrum of natural cacalone and its acetate, done by Romo et al.,[4] was based on the assumption of the existence of a $M^+ + 2$ ion. The supposed $M^+ + 2$ ion is in reality the M^+ ion. Incidentally, o-benzoquinone type of structures lead to $M^+ + 2$ ions but, according to Djerassi, "caution must be exercised

Table IV. Mass Spectral Data of 1b and 3a[a]

1b	3a
244 (94%, M^+)	246 (66%, M^+)
230 (36%)	231 (32%)
229 (100%)	228 (42%)
215 (28%)	213 (48%)
201 (37%)	200 (56%)
187 (21%)	191 (100%)
173 (10%)	185 (25%)
128 (7%)	91 (30%)

[a] Spectra were determined on a Hitachi Perkin-Elmer RMU-7H spectrometer, 70 eV, 150 °C.

in the interpretation of such spectra in order to avoid misleading conclusions".[15]

The comparison of the mass spectra of **1b** and **3a** is done in Table IV. For the major fragmentation pathways (leading to 100% ions with the loss of CH_3 or C_4H_7 unit, respectively) the metastable ions have been observed. The corresponding acetates show a similar fragmentation pattern and loss of acetic acid has replaced dehydration.

Experimental Section

Melting points were taken on a Culatti capillary melting point apparatus and are uncorrected. The preparative TLC plates were Merck silica F-254. In order to follow the progress of the reactions or the purity of the compounds, Merck F-254 thin layer plates (250 μm), cut into small slides (5 by 2.5 cm), were used. Infrared spectra were taken on 521 or 567 Perkin-Elmer spectrophotometers. ^1H NMR spectra were obtained on Varian A-60A or HA-100 spectrometers in different solvents as indicated, with tetramethylsilane as internal reference, and are expressed as δ values, with the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. In double resonance experiments, a Hewlett-Packard audio oscillator Model 200 AB was used. The lanthanide shift reagent Eu(fod)$_3$ source was Bio-Rad Laboratories, Richmond, Calif. Carbon magnetic resonance data were obtained at 25.2 MHz with a Varian XL-100 spectrometer using tetramethylsilane as internal reference; *m/e* determinations were made on a Hitachi Perkin-Elmer RMU 7H mass spectrometer.

Oxidation of Cacalol 1a. To a solution of 2.3 g (10 mmol) of cacalol **1a** in 30 ml of benzene was added 3.22 g (7.2 mmol) of lead tetraacetate. The solution was stirred at 25 °C for 12 h. The lead acetate formed was filtered on Celite and washed with benzene. Excess of reagent was reduced by the addition of 2 ml of ethylene glycol and then 50 ml of water was added. The organic layer was washed with water and dried. Evaporation of the solvent gave an oily residue. The crude product was crystallized from acetone–hexane to afford 2.1 g (73%) of cacalone acetate **3b:** mp 168–169 °C; uv (95% EtOH) 211, 256, and 316 nm (ε 6100, 9900, and 7200); ir ($CHCl_3$) 1740 and 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.29 (d, 3 H, J = 7 Hz, C-5 Me), ca. 1.65 (m, 4 H, C-6 and C-7 protons), 1.68 (s, 3 H, C-4 Me), 2.05 (d, 3 H, J = 1 Hz, C-3 Me), 2.08 (s, 3 H, OAc), ca. 2.45 (m, 3 H, C-5 and C-8 protons), and 7.30 ppm (q, 1 H, J = 1 Hz, C-2 proton); MS *m/e* 288 (M^+, 9%), 246 (100%), 228 (12%), 213 (21%), 191 (72%), 185 (10%), 43 (20%).

Alkaline Hydrolysis of Cacalone Acetate. A solution of 350 mg (3.5 mmol) of $KHCO_3$ in 5 ml of water and 20 ml of methanol was added to a solution of 1 g (3.47 mmol) of cacalone acetate **3b** in 50 ml of methanol. The resulting solution was heated to reflux for 20 h. After the methanol was evaporated, water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried, and concentrated to give 700 mg (82%) of the oily mixture **3c**, epimeric at C-4 (ca. 1:1 by NMR). This mixture was chromatographed on eight preparative chromatoplates using benzene–ethyl acetate (98:2) as developing solvent. The plates were developed eight times. The more polar isomer was identical with the natural cacalone **3a:** mp 140–143 °C; uv (95% EtOH) 212, 250, and 320 nm; NMR (C_5D_5N) δ 1.22 (d, 3 H, J = 7 Hz, C-5 Me), ca. 1.60 (m, 4 H, C-6 and C-7 protons), 1.75 (s, 3 H, C-4 Me), 2.28 (d, 3 H, J = 1 Hz, C-3 Me), ca. 2.55 (m, 2 H, C-8 protons), ca. 3.35 (m, 1 H, C-5 proton), and 7.50 ppm (q, 1 H, J = 1 Hz, C-2 proton). For other spectroscopic data see Tables I–IV.

The less polar isomer shows spectroscopic constants identical with those of its epimer except the methyl signals at C-5 and at C-4 and the proton signal at C-5 in its NMR spectrum: mp 120–121 °C; NMR ($CDCl_3$) δ 1.29 (d, 3 H, J = 7 Hz, C-5 Me), 1.63 (s, 3 H, C-4 Me), ca. 1.80 (m, 5 H, C-6 and C-7 protons and OH), 2.21 (d, 3 H, J = 1 Hz, C-3 Me), ca. 2.40 (m, 2 H, C-8 protons), 2.90 (m, 1 H, C-5 proton), and 7.29 ppm (q, 1 H, J = 1 Hz, C-2 proton); NMR (C_5D_5N) δ 1.44 (d, 3 H, J = 7 Hz, C-5 Me), ca. 1.65 (m, 4 H, C-6 and C-7 protons), 1.70 (s, 3 H, C-4 Me), 2.26 (d, 3 H, J = 1 Hz, C-3 Me), ca. 2.60 (m, 2 H, C-8 protons), ca. 3.00 (m, 1 H, C-5 proton), and 7.53 ppm (q, 1 H, J = 1 Hz, C-2 proton).

Hydrogenation of Cacalone Acetate. A solution of 115 mg (0.4 mmol) of cacalone acetate **3b** in 25 ml of ethyl acetate was hydrogenated over 25 mg of 5% Pd/C at 25 °C for 12 h. The product was purified by chromatography in two preparative chromatoplates giving 100 mg (97%) of an oil. Crystallization of the product from acetone–hexane afforded cacalol **1a** as colorless crystals, mp 90–91 °C (lit.[1] 92–94 °C). For spectroscopic constants see ref 1, 2, and 5.

Pyrolysis of Cacalone Acetate. A solution of 144 mg (0.5 mmol) of cacalone acetate in 20 ml of toluene was injected through a pyrolysis tube heated at 480 °C. The hot emerging gases were condensed in a trap cooled by dry ice. Evaporation of the toluene and recrystallization of the residue (acetone–hexane) gave 110 mg (95%) of cacalol **1a.**[1,2,5]

Hydrogenation of Cacalone. A solution of 170 mg (0.74 mmol) of cacalone **3a** in 40 ml of methanol was hydrogenated over 75 mg of 10% Pd/C at 25 °C until hydrogen absorption ceased. After filtration of the catalyst, the filtrate was concentrated and the product purified by TLC using benzene–ethyl acetate (95:5) as developing solvent. Elution with acetone yielded 75 mg (45%) of dihydrocacalol **4**[1] as a yellow oil which did not crystallize.

Formation of Adduct 7. A solution containing 300 mg (1.04 mmol) of cacalone acetate **3b,** 1.1 g (10 mmol) of dimethyl acetylenedicarboxylate, and 30 ml of xylene was heated at reflux for 12 h. Excess of reagent was evaporated under vacuum and the residue was chromatographed on six preparative chromatoplates using benzene–ethyl acetate (90:10) as developing solvent. The acetone eluates gave 180 mg (40%) of the adduct **7** as an oil: uv (95% EtOH) 218 and 330 nm (ε 11 500 and 4650); ir ($CHCl_3$) 1740 (b, OAc and methyl esters) and 1675 cm^{-1} (α,β-unsaturated ketone); NMR ($CDCl_3$) δ 1.12 (d, 3 H, J = 7 Hz, C-5 Me), ca. 1.71 (m, 4 H, C-6 and C-7 protons), 1.80 (s, 3 H, C-4 Me), 2.06 (s, 6 H, C-3 Me and OAc), ca. 2.40 (m, 2 H, C-8 protons), ca. 2.85 (m, 1 H, C-5 proton), 3.71 and 3.85 (s, 3 H each, nonequivalent methyl ester groups), and 5.96 ppm (s, 1 H, C-2 proton).

Methanolysis of Cacalone Acetate. A solution of 70 mg (0.24 mmol) of cacalone acetate **3b** in a mixture of 20 ml of methanol and 1 ml of 10% hydrochloric acid was heated at reflux for 30 min. The methanol was evaporated, water was added, and the product was extracted with ethyl acetate. The organic layer was washed with water, dried, and concentrated. The crude product was purified by TLC, obtaining 50 mg (87%) of the oily mixture **3d** (ca. 1:1 by NMR): ir ($CHCl_3$) 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.26 and 1.29 (d, 3 H, J = 7 Hz, C-5 Me), 1.65 (s, 3 H, C-4 Me), ca. 1.70 (m, 4 H, C-6 and C-7 protons), 2.19 (d, 3 H, J = 1 Hz, C-3 Me), ca. 2.55 (m, 3 H, C-5 and C-8 protons), 2.90 and 2.93 (s, 3 H, OMe), and 7.40 ppm (q, 1 H, J = 1 Hz, C-2 proton).

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Registry No.—**1a,** 24393-79-1; **3a,** 26294-92-8; **3a** epimer, 60428-00-4; **3b,** 60428-01-5; 4*R*-**3d,** 60428-02-6; 4*S*-**3d,** 60428-03-7; **4,** 60428-04-8; **7,** 60428-05-9; dimethyl acetylenedicarboxylate, 762-42-5.

References and Notes

(1) J. Romo and P. Joseph-Nathan, *Tetrahedron*, **20,** 2331 (1964).
(2) P. Joseph-Nathan, J. J. Morales, and J. Romo, *Tetrahedron*, **22,** 301 (1966).
(3) (a) H. Kakisawa, Y. Inouye, and J. Romo, *Tetrahedron Lett.*, 1929 (1969); (b) P. M. Brown and R. H. Thomson. *J. Chem. Soc. C,* 1184 (1969).
(4) M. P. González, P. Joseph-Nathan, and J. Romo, *Rev. Latinoam. Quim.*, **2,** 5 (1971).
(5) F. Yuste and F. Walls, *Aust. J. Chem.*, in press.
(6) R. Criegee in "Oxidations in Organic Chemistry", Part A, K. B. Wiberg, Ed., Academic Press, New York, N.Y., 1965, pp 288–292.
(7) F. Walls, *Chem. Ind. (London)*, 681 (1972).
(8) P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Am. Chem. Soc.*, **90,** 5480 (1968).
(9) A. Kiewiet, J. de Wit, and W. D. Weringa, *Org. Magn. Reson.*, **6,** 461 (1974).
(10) R. Hollenstein and W. von Philipsborn, *Helv. Chim. Acta*, **55,** 2030 (1972).

(11) H. Beierbeck and J. K. Saunders, *Can. J. Chem.*, **53**, 1307 (1975).
(12) R. Hollenstein and W. von Philipsborn, *Helv. Chim. Acta*, **56**, 320 (1973).
(13) A. Rieker and S. Berger, *Org. Magn. Reson.*, **4**, 857 (1972).
(14) K. Jankowski, *J. Org. Chem.*, submitted.
(15) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds", Holden-Day, San Francisco, Calif., 1967, p 118.

Novel Formation of Anti-Bredt Olefins from 2,3,4,5,6,7-Hexahydro-1,6-methano-1*H*-4-benzazonin-7-ols

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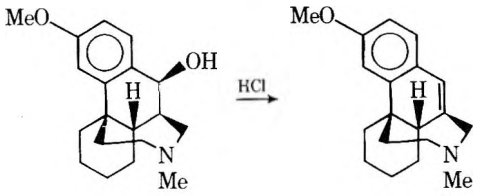
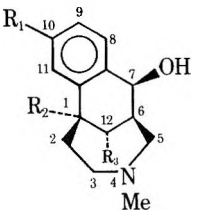
While there are many examples of formation of anti-Bredt olefins[1] by Hofmann elimination[2] or dehydrohalogenation[3] of the corresponding bridgehead substituted compounds or by dehalogenation[4] of 1,2-dihalo compounds, formation by elimination of compounds substituted adjacent to the bridgehead carbon is less common.[5] Recently, we reported that *B/C-cis*-6-methoxy-12-methyl-1,3,4,9,10,10a-hexahydro-2*H*-10,4a-methanoiminoethano-9β-phenanthrol (**1**), when treated with HCl, gave an olefinic compound **2** in violation of Bredt's rule.[6] This interesting result, which may be not only a new example of formation of anti-Bredt olefin but the first instance of the formation of anti-Bredt olefin under acidic condition, prompted us to examine reaction of the closely related 2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonin-7β-ol[7] derivatives **3a–d** with HCl which might be expected to give similar results.

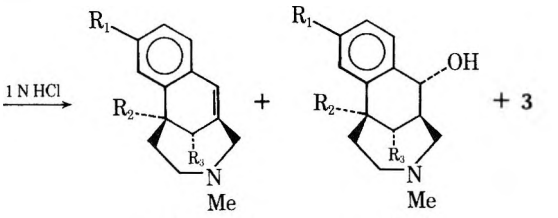


1 **2**

When 1,4,12α-trimethyl-10-methoxy-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonin-7β-ol (**3d**)[8] was refluxed with 1 N HCl for 1.5 h, anti-Bredt olefin **4d** was afforded in high yield. The structure of **4d** was confirmed from its NMR and mass spectra. In the NMR spectrum **4d** exhibited an olefinic proton signal at δ 6.16 (singlet). The mass spectrum showed a M^+ peak at *m/e* 257.1778 ($C_{17}H_{23}NO$). Treatment of 4-methyl- (**3a**),[9] 1,4-dimethyl- (**3b**), and 1,4-dimethyl-10-methoxy-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonin-7β-ol (**3c**)[8] with 1 N HCl gave the corresponding olefins **4a–c**, 7α-hydroxy[4] **5a–c**, and 7β-hydroxy compounds **3a–c** (product ratios are summarized in Table I), respectively. Each of the products was isolated by column chromatography and identified by NMR and/or mass spectrometry. The olefins **4a–c** exhibited, in the NMR, olefinic proton signals as singlets at δ 6.24 for **4a**, 6.25 for **4b**, and 6.27 for **4c**, respectively. The mass spectra showed M^+ at *m/e* 199.1370 ($C_{14}H_{17}N$) for **4a**, 213.1525 ($C_{15}H_{19}N$) for **4b**, and 243.1631 ($C_{16}H_{21}NO$) for **4c**,



3a, 3b, 3c, 3d



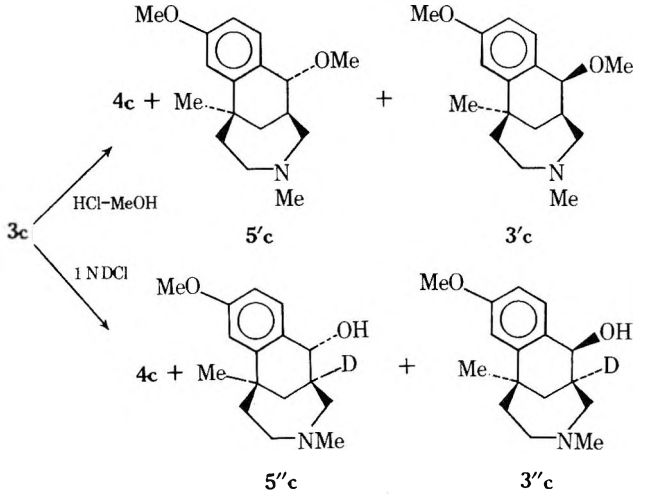
4a, 4b, 4c, 4d **5a, 5b, 5c,**

a, $R_1 = R_2 = R_3 = H$
b, $R_1 = R_3 = H$; $R_2 = Me$
c, $R_1 = OMe$; $R_2 = Me$; $R_3 = H$
d, $R_1 = OMe$; $R_2 = R_3 = Me$

respectively. The 7α-hydroxy isomers **5a–c** and the 7β-hydroxy isomers **3a–c** were easily distinguishable by NMR spectrometry, since the coupling constants of the C-7 proton with the C-6 proton of the former should be smaller than those of the latter (**5a**, 2.2 Hz at δ 4.26, vs. **3a**, 4.0 Hz at δ 4.88; **5b**, 2.8 Hz at δ 4.28, vs. **3b**, 5.5 Hz at δ 4.87; **5c**, 3.5 Hz at δ 4.26, vs. **3c**, 5.0 Hz at δ 4.83).

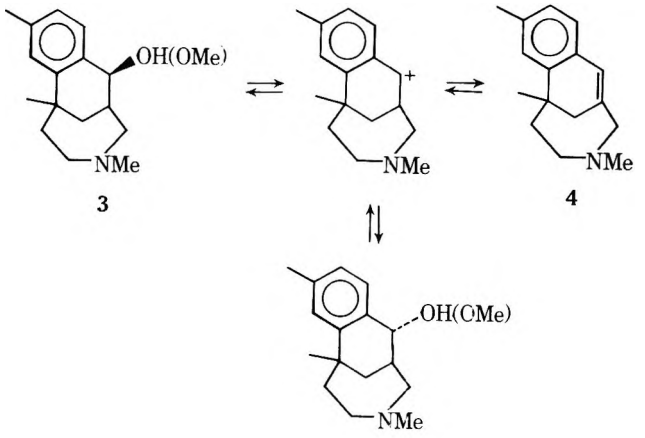
Reaction of 7α-hydroxy compound **5a** with 1 N HCl for 1.5 h gave a mixture of **3a**, **4a**, and **5a**. Similarly, **5b** gave **3b**, **4b**, and **5b**. Olefin **4a**, when refluxed with 1 N HCl, gave a mixture of **3a**, **4a**, and **5a**. Similarly, **4b** gave **3b**, **4b**, and **5b**. Under these conditions **4d**, however, was recovered unchanged.

When the reaction of compound **3c** with HCl was carried out in methanol a mixture of **4c**, 7β-methoxy **3'c**, and 7α-methoxy derivative **5'c** was afforded in the ratio 1:3:3 (by GLC). The structures of **3'c** and **5'c** were established by the NMR spectra and elemental analysis. We observed further that reaction of **3c** in 1 N DCl gave a mixture of olefin **4c**, 6-deuterio-7β-hydroxy **3''c**, and 6-deuterio-7α-hydroxy derivative **5''c** in the ratio 1:2:4 (by NMR). The incorporation of deuterium at the C-6 position was confirmed by the change of C-7 proton signals of **3c** and **5c** from doublet to singlet.



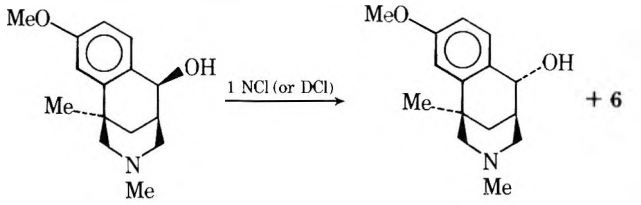
These experimental results made it evident that anti-Bredt olefins **4** are easily formed from the corresponding 7-hydroxy- (or methoxy-) 2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine derivatives **3** and **5** by treatment with acid, and that 7-hydroxy (or methoxy) derivatives **3** and **5** are formed, under these conditions, not by a simple substitution of the

Scheme I



corresponding isomers but by hydration (or addition of methanol) of the anti-Bredt olefins. Thus, it may be suggested that these three compounds, **3, 4,** and **5,** are in equilibrium as shown in Scheme I. In the case of **4d,** attack of hydronium ion at C-6 (the first step of the hydration) is greatly hindered by 12α-methyl, so that no C-7 hydroxy compound is formed.

For comparison, 1,3-dimethyl-9-methoxy-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocin-6β-ol (**6**) was refluxed with



6 7

1 N HCl. From the reaction mixture no olefinic compound was detected but only 6β-hydroxy **6** and 6α-hydroxy derivative **7** (ratio 1:4) were obtained. The reaction of **6** in 1 N DCl gave no C-5 deuterio compound, which suggested that no anti-Bredt olefin is formed, even as an intermediate, from compound **6** (or **7**) under these conditions. The failure of **6** to form the corresponding olefin may be caused by the great strain to form an eight-membered trans cyclic olefin.

Experimental Section

General Comments. The following compounds were prepared by known procedure: **3a**,[9] **3c,** and **3d**.[8]

The melting points were determined on a micro melting point apparatus (Yanagimoto) and are uncorrected. The NMR ($CDCl_3$, δ, Me_4Si as internal standard) were recorded, at 60 MHz, on a JEOL PMX-60 spectrometer or at 100 MHz on a JEOL PS-100 spectrometer. Ir spectra were taken on a Hitachi 215 grating infrared spectrometer. Mass spectra were recorded on a JEOL JMS-01SG mass spectrometer. GLC analyses were performed on a Shimadzu GC-4B PTF flame-ionization chromatograph using an internal standard method (**4a, 4b,** and **4c** previously isolated were used as standard). The column contained SE-30 (20% on Shimalite, 1 m × 3 mm), and the column temperature was 250 °C. Nitrogen was used as carrier.

Preparation of 3b. A solution of $ClCO_2Et$ (43.2 g) in benzene (200 ml) was added to a refluxing solution of 4-methyl-4-(2-dimethylaminoethyl)-3,4-dihydronaphthalen-1(2*H*)-one[10] (60 g) in benzene (800 ml) over 45 min. The mixture was refluxed for 2 h. The cooled mixture was washed with 5% HCl and H_2O and dried ($MgSO_4$). After evaporation of the benzene, the residue (pale yellow syrup, 61 g) was refluxed with 12 M HCl (900 ml) for 18 h. Evaporation of the solvent gave 37 g of a crystalline mass, which was recrystallized from MeOH to give a pure sample of 4-methyl-4-(2-methylaminoethyl)-3,4-dihydronaphthalen-1(2*H*)-one hydrochloride, mp 206–208 °C. Anal. Calcd for $C_{14}H_{19}NO$·HCl: C, 66.25; H, 7.95; N, 5.52. Found: C, 66.23; H, 8.11; N, 5.68.

The above amino ketone HCl (35 g) was dissolved in MeOH (780 ml) and Formalin (74 ml). The mixture was kept at 40 °C for 3 days.

Table I. Products and Ratios in Reaction of 2,3,4,5,6,7-Hexahydro-1,6-methano-1*H*-4-benzazonine Derivatives

Registry no.	Compd	Reflux in 1 N HCl, h	Product ratio[a] 3	4	5
60384-67-0	**3a**	1.5	2.5	1	2.5
60384-68-1	**3b**	1.5	2.5	1	2.5
59122-63-3	**3c**	1.5	2.0	1	2.6
59122-62-2	**3d**	1.5	0	1	0
60363-75-9	**4a**	3.5	0.63	1	0.63
60363-76-0	**4b**	3.0	2.5	1	2.5
60363-77-1	**4d**	2.0	0	1	0
60384-69-2	**5a**	3.5	1.7	1	1.7
60384-70-2	**5b**	3.0	2.5	1	2.5

[a] Obtained by gas chromatography.

After evaporation to dryness, the residue was dissolved in H_2O, washed with benzene, basified with 10% NaOH, extracted with Et_2O, and dried (K_2CO_3). The residue (16.3 g) from the ethereal solution was dissolved in MeOH and added to a solution of picric acid (16 g) in MeOH to give 21.5 g of 1,4-dimethyl-2,3,4,5-tetrahydro-1,6-methano-1*H*-4-benzazonin-7(6*H*)-one picrate, mp 188–195 °C. From the picrate 9.7 g of the free base was obtained: bp 140–150 °C (1 mmHg); ir (neat) 1675 cm^{-1} (C=O). Hydrochloride: mp 174–180 °C (from MeOH); NMR (CD_3OD) δ 1.60 (3 H, s, C-1 Me), 2.95 (3 H, s, N-Me), 7.30–7.90 (3 H, m, C-9, 10, 11 H), 8.04 (1 H, double d, J = 7.5, J' = 1.5 Hz, C-8 H). Anal. Calcd for $C_{15}H_{19}NO$·HCl: C, 67.79; H, 7.58; N, 5.27. Found: C, 67.90; H, 7.50; N, 5.48.

To a solution of the free base of the above ketone (8.7 g) in MeOH (200 ml) was added $NaBH_4$ (5 g) over 30 min under ice cooling. After stirring for 3 h at room temperature, the mixture was acidified with AcOH, evaporated to dryness, dissolved in H_2O, made alkaline with 20% NaOH, extracted with $CHCl_3$, and dried (K_2CO_3). Evaporation of the solvent gave 8 g of crude **3b** as a solid mass, which was recrystallized from Et_2O to give 5.5 g of pure sample: mp 102–105 °C; ir (Nujol) 3300 cm^{-1} (OH); NMR δ 1.27 (3 H, s, C-1 Me), 2.23 (3 H, s, N-Me), 2.70 (1 H, s, exchangeable with D_2O, OH), 4.87 (1 H, d, J = 5.5 Hz, C-7 H), 7.10–7.25 (3 H, m, C-9, 10, 11 H), 7.45–7.75 (1 H, m, C-8 H). Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 78.03; H, 8.86; N, 5.86.

Preparation of 6. To a stirred mixture of 1,3-dimethyl-9-methoxy-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine[11] (1.6 g) and $Na_2Cr_2O_7$ (3.1 g) in 100 ml of 1 N H_2SO_4 was added 10 N H_2SO_4 (215 ml) with ice cooling during 2 h. After stirring for 15 h at room temperature, the mixture was cooled (ice bath), basified with 12 M NH_4OH, extracted with Et_2O, and dried (K_2CO_3). Evaporation of the ether gave 1 g of 1,3-dimethyl-9-methoxy-1,2,3,4-tetrahydro-1,5-methano-3-benzazocin-6(5*H*)-one as a viscous syrup: ir (neat) 1690 cm^{-1} (C=O); NMR δ 1.36 (3 H, s, C-1 Me), 2.05 (3 H, s, N-Me), 3.82 (3 H, s, O-Me), 6.75 (1 H, double d, J = 9.0, J' = 2.0 Hz, C-8 H), 6.77 (1 H, d, J = 2.0 Hz, C-10 H), 7.96 (1 H, d, J = 9.0 Hz, C-7 H), 1.50–3.27 (7 H, m). Picrate: mp 140–144° (from MeOH). Anal. Calcd for $C_{15}H_{19}NO_2$·$C_6H_3N_3O_7$: C, 53.17; H, 4.67; N, 11.81. Found: C 53.07; H, 4.65; N, 11.61.

A mixture of the ketone (1.0 g) and $LiAlH_4$ (1.0 g) in dioxane (40 ml) was refluxed for 6.5 h. After cooling, the mixture was treated with aqueous Rochelle salt solution, extracted with $CHCl_3$, and dried (K_2CO_3). Evaporation of the solvent gave 1.0 g of crude **6.** Distillation under reduced pressure gave pure sample as a colorless oil: bp 145–165 °C (5 mmHg) (bath temperature); ir (neat) 3420 cm^{-1} (OH); NMR δ 1.23 (3 H, s, C-1 Me), 2.01 (3 H, s, N-Me), 3.73 (3 H, s, O-Me), 2.75 (1 H, broad d, exchangeable with D_2O, OH), 4.79 [1 H, broad t, changed to doublet (J = 7.0 Hz) by treatment with D_2O, C-6 H], 6.65 (1 H, d, J = 2.5 Hz, C-10 H), 6.66 (1 H, double d, J = 9.0, J' = 2.5 Hz, C-8 H), 7.38 (1 H, d, J = 9.0 Hz, C-7 H). Picrate: mp 217–219 °C (from MeOH). Anal. Calcd for $C_{15}H_{21}NO_2$·$C_6H_3N_3O_7$: C, 52.94; H, 5.08; N, 11.76. Found: C, 52.60; H, 5.07; N, 11.69.

Reaction of 3a, 3b, 3c, 3d, 4a, 4b, 4d, 5a, 5b, and 6 with 1 N HCl. As an example, we will describe the reaction of **3c** with 1 N HCl. All other reactions were done following a similar procedure and we will report the experimental and spectroscopic data related to the compounds which were not already published.

I. Reaction of 3c. A solution of **3c** (800 mg) in 1 N HCl (50 ml) was refluxed for 1.5 h. After cooling, the mixture was basified with 10% NaOH, extracted with $CHCl_3$, and dried (Na_2SO_4). Evaporation of

the solvent gave 500 mg of **3c + 4c + 5c** as a yellow, viscous syrup, which was chromatographed on silica gel (Wakogel C-200). Elution with $CHCl_3$–MeOH–12 M NH_4OH (150:10:1) gave pure samples of **3c** (150 mg), **4c** (80 mg), and **5c** (200 mg).

3c: NMR δ 1.28 (3 H, s, C-1 Me), 2.35 (3 H, s, N-Me), 3.83 (3 H, s, O-Me), 4.83 (1 H, d, J = 5.0 Hz, C-7 H), 6.78 (1 H, d, J = 3.0 Hz, C-11 H), 6.88 (1 H, double d, J = 8.0, J' = 3.0 Hz, C-9 H), 7.60 (1 H, d, J = 8.0 Hz, C-8 H), 1.55–3.25 (10 H, m).

4c: bp 110–120 °C (0.01 mmHg) (bath temperature); ir (neat) 1670 cm^{-1} (C=C); NMR δ 1.36 (3 H, s, C-1 Me), 2.36 (3 H, s, N-Me), 3.16 and 3.28 (2 H, AB, J_{AB} = 10.0 Hz, C-5 H_2), 3.84 (3 H, s, O-Me), 6.27 (1 H, s, C-7 H), 6.73 (1 H, double d, J = 8.5, J' = 2.5 Hz, C-9 H), 6.88 (1 H, d, J = 2.5 Hz, C-11 H), 7.17 (1 H, d, J = 8.5 Hz, C-8 H), 1.45–2.70 (6 H, m); mass spectrum m/e 243.1631 (M^+, calcd for $C_{16}H_{21}NO$, 243.1632).

5c: mp 73–75 °C (from hexane); ir (Nujol) 3350 cm^{-1} (broad, OH); NMR δ 1.31 (3 H, s, C-1 Me), 2.21 (3 H, s, N-Me), 2.63 (1 H, s, exchangeable with D_2O, OH), 3.82 (3 H, s, O-Me), 4.26 (1 H, d, J = 3.5 Hz, C-7 H), 6.76 (1 H, double d, J = 8.0, J' = 2.5 Hz, C-9 H), 6.82 (1 H, d, J = 2.5 Hz, C-11 H), 7.24 (1 H, d, J = 8.0 Hz, C-8 H), 1.45–3.20 (9 H, m). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.26; H, 8.88; N, 5.30.

II. Reaction of 3a. 3a gave an 80% yield of **3a + 4a + 5a. 4a:** bp 105–110 °C (0.02 mmHg) (bath temperature); ir (neat) 1680 cm^{-1} (C=C); NMR δ 2.36 (3 H, s, N-Me), 2.95 and 3.61 (2 H, AB, J_{AB} = 10.0 Hz, C-5 H_2), 6.24 (1 H, s, C-7 H), 1.17–2.95 (7 H, m), 7.13 (4 H, m, aromatic H); mass spectrum m/e 199.1370 (M^+, calcd for $C_{14}H_{17}N$, 199.1361).

5a: mp 108–109 °C (from hexane); ir (Nujol) 3270 cm^{-1} (OH); NMR δ 2.20 (3 H, s, N-Me), 2.47 (1 H, s, exchangeable with D_2O, OH), 4.26 (1 H, d, J = 2.2 Hz, C-7 H), 1.50–3.25 (10 H, m), 7.18 (4 H, m, aromatic H). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.37; H, 8.81; N, 6.45. Found: C, 77.03; H, 8.64; N, 6.50.

III. Reaction of 3b. 3b gave a 70% yield of **3b + 4b + 5b. 4b:** bp 110–115 °C (0.02 mmHg) (bath temperature); ir (neat) 1680 cm^{-1} (C=C); NMR δ 1.37 (3 H, s, C-1 Me), 2.34 (3 H, s, N-Me), 3.13 and 3.50 (2 H, AB, J_{AB} = 10.0 Hz, C-5 H_2), 4.25 (1 H, s, C-7 H), 7.17 (4 H, m, aromatic H), 1.20–2.70 (6 H, m); mass spectrum m/e 213.1525 (M^+, calcd for $C_{15}H_{19}N$, 213.1517).

5b: mp 103–104 °C (from hexane); ir (Nujol) 3250 cm^{-1} (OH); NMR δ 1.34 (3 H, s, C-1 Me), 2.22 (3 H, s, N-Me), 4.28 (1 H, d, J = 2.8 Hz, C-7 H), 7.27 (4 H, m, aromatic H), 1.20–3.30 (10 H, m). Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.06. Found: C, 77.68; H, 9.03; N, 6.28.

IV. Reaction of 3d. 3d gave a 75% yield of **4d. 4d:** bp 120–130 °C (0.01 mmHg) (bath temperature); ir (neat) 1670 cm^{-1} (C=C); NMR δ 0.79 (3 H, d, J = 7.0 Hz, C-12 Me), 1.31 (3 H, s, C-1 Me), 2.37 (3 H, s, N-Me), 3.05 and 3.45 (2 H, AB, J_{AB} = 10.0 Hz, C-5 H_2), 3.80 (3 H, s, O-Me,), 6.16 (1 H, s, C-7 H), 6.63 (1 H, double d, J = 8.0, J' = 2.5 Hz, C-9 H), 6.78 (1 H, d, J = 2.5 Hz, C-11 H), 7.06 (1 H, d, J = 8.0 Hz, C-8 H), 1.50–2.73 (5 H, m); mass spectrum m/e 257.1778 (M^+, calcd for $C_{17}H_{23}NO$, 257.1780).

V. Reaction of 4a. Reflux of **4a** with 1 N HCl for 3.5 h gave a 90% yield of **3a + 4a + 5a.**

VI. Reaction of 4b. Reflux of **4b** with 1 N HCl for 3 h gave an 85% yield of **3b + 4b + 5b.**

VII. Reaction of 4d. Reflux of **4d** with 1 N HCl for 3 h gave a 95% yield of recovery of **4d.**

VIII. Reaction of 5a. Reflux of **5a** for 3.5 h gave an 85% yield of **3a + 4a + 5a.**

IX. Reaction of 5b. Reflux of **5b** with 1 N HCl for 3 h gave a 90% yield of **3b + 4b + 5b.**

X. Reaction of 6. Reflux of **6** (211 mg) with 1 N HCl (20 ml) for 1 h gave a mixture of **6** and **7** (185 mg). The mixture was chromatographed on a silica gel column. Elution with $CHCl_3$–MeOH (150:10) gave pure samples of **6** and **7.** Compound **6** was identified by comparison of ir spectrum with that of the authentic sample.

7: colorless, viscous oil; ir (neat) 3340 cm^{-1} (OH); NMR δ 1.27 (3 H, s, C-1 Me), 2.00 (3 H, s, N-Me), 3.75 (3 H, s, O-Me), 4.47 (1 H, s, C-6 H), 6.67 (1 H, double d, J = 9.0, J' = 2.5 Hz, C-8 H), 6.70 (1 H, d, J = 2.5 Hz, C-10 H), 7.15 (1 H, d, J = 9.0 Hz, C-7 H). Picrate: mp 197–203 °C (from MeOH). Anal. Calcd for $C_{15}H_{21}NO_2 \cdot C_6H_3N_3O_7$: C, 52.94; H, 5.08; N, 11.76. Found: C, 53.14; H, 5.06; N, 11.57.

Reaction of 3c with HCl in MeOH. A solution of **3c** (500 mg) and 12 M HCl (1 ml) in MeOH (10 ml) was refluxed for 2 h, the solvent, evaporated, diluted with H_2O, basified with 10% NaOH, and extracted with $CHCl_3$. After drying (Na_2SO_4), the solvent was evaporated to give 300 mg of **3'c + 4c + 5'c** (3:1:3). The mixture was chromatographed on silica gel (Wakogel C-200). Elution with $CHCl_3$–MeOH–12 M NH_4OH (150:10:1) gave pure samples of **3'c** (110 mg), **4c** (30 mg, identified by comparison of ir spectrum with that of the authentic sample) and **5'c** (100 mg).

3'c: bp 150–160 °C (1.5 mmHg) (bath temperature); NMR δ 1.22 (3 H, s, C-1 Me), 2.24 (3 H, s, N-Me), 3.48 (3 H, s, C-7 O-Me), 3.76 (3 H, s, C-10 O-Me), 4.28 (1 H, d, J = 4.0 Hz, C-7 H), 6.69 (1 H, double d, J = 8.0, J' = 2.8 Hz, C-9 H), 6.62 (1 H, d, J = 2.8 Hz, C-11 H), 7.43 (1 H, d, J = 8.0 Hz, C-8 H), 1.56–2.88 (9 H, m). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 73.88; H, 8.91; N, 4.70.

5'c: bp 150–160 °C (1.5 mmHg) (bath temperature); NMR 1.28 (3 H, s, C-1 Me), 2.22 (3 H, s, N-Me), 3.33 (3 H, s, C-7 O-Me), 3.76 (3 H, s, C-10 O-Me), 3.68 (1 H, d, J = 2.5 Hz, C-7 H), 6.64 (1 H, double d, J = 8.0, J' = 2.5 Hz, C-9 H), 6.72 (1 H, d, J = 2.5 Hz, C-11 H), 7.07 (1 H, d, J = 8.0 Hz, C-8 H). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.29; H, 9.15; N, 5.09.

Reaction of 3c with 1 N DCl. A solution of **3c** (101 mg) in 1 N DCl (6 ml) was refluxed for 1 h. After cooling, the mixture was basified with 10% NaOH, extracted with $CHCl_3$, and dried (K_2CO_3). Evaporation of the solvent gave 99 mg of a yellow oil. The NMR showed that it was a mixture of olefin **4c,** 6-deuterio-7β-hydroxy **3"c,** and 6-deuterio-7α-hydroxy compound **5"c** in the ratio 1:2:4 [C-7 proton signal of **4c,** δ 6.20 (singlet); C-7 proton signal of **3"c,** δ 4.78 (singlet); C-7 proton signal of **5"c,** δ 4.25 (singlet)].

Reaction of 6 with 1 N DCl. Reflux of **6** (90 mg) in 1 N DCl (6 ml) gave a mixture of **6** and **7** (70 mg). The NMR showed that substitution of C-5 hydrogen of **6** and **7** with deuterium did not occur at all.

Registry No.—**3'c,** 60363-78-2; **3"c,** 60363-79-3; **4c,** 60363-80-6; **5c,** 60409-21-4; **5'c,** 60409-20-3; **5"c,** 60384-71-6; **6,** 60363-81-7; **7,** 60384-72-7; **7** picrate, 60409-18-9; 4-methyl-4-(2-dimethylaminoethyl)-3,4-dihydronaphthalen-1(2*H*)-one, 60363-82-8; 4-methyl-4-(2-methylaminoethyl)-3,4-dihydronaphhalen-1(2*H*)-one HCl, 54782-00-2; 1,4-dimethyl-2,3,4,5-tetrahydro-1,6-methano-1*H*-4-benzazonin-7(6*H*)-one picrate, 60384-73-8; 1,4-dimethyl-2,3,4,5-tetrahydro-1,6-methano-1*H*-4-benzazonin-7(6*H*)-one, 54782-07-9; 1,4-dimethyl-2,3,4,5-tetrahydro-1,6-methano-1*H*-4-benzazonin-7(6*H*)-one HCl, 60384-74-9; 1,3-dimethyl-9-methoxy-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine, 37639-69-3; 1,3-dimethyl-9-methoxy-1,2,3,4-tetrahydro-1,5-methano-3-benzazocin-6(5*H*)-one, 60363-83-9.

References and Notes

(1) (a) G. L. Buchanan, *Chem. Soc. Rev.*, **3**, 41 (1974); (b) R. Keese, *Angew. Chem., Int. Ed. Engl.*, **14**, 528 (1975).
(2) (a) J. R. Wiseman, H.-K. Foon, and C. J. Ahola, *J. Am. Chem. Soc.*, **91**, 2812 (1969); (b) J. R. Wiseman and J. A. Chong, *ibid.*, **91**, 7775 (1969); (c) M. Kim and J. D. White, *ibid.*, **97**, 451 (1975).
(3) (a) N. Takanishi, Y. Fujikura, Y. Inamoto, H. Ikeda, and K. Aigami, *J. Chem. Soc., Chem. Commun.*, 372 (1975); (b) C. B. Quinn and J. R. Wiseman, *J. Am. Chem. Soc.*, **95**, 1342, 6120 (1973); (c) H. O. Krabbenfoft, J. R. Wiseman, and C. B. Quinn, *ibid.*, **96**, 258 (1974).
(4) J. R. Wiseman and W. A. Pletcher, *J. Am. Chem. Soc.*, **92**, 956 (1970).
(5) W. Carruthers and M. I. Qureshi, *J. Chem. Soc. C*, 2238 (1970).
(6) S. Shiotani, *J. Org. Chem.*, **40**, 2033 (1975).
(7) The α and β designations used in this paper are with respect to the hydroaromatic ring. The compounds **3a–d** and **6** were prepared from the corresponding C-7 (C-6 for **6**) keto compounds by reduction with $LiAlH_4$ or $NaBH_4$. These reactions should give the 7β-hydroxy (6β- for **6**) derivatives, since the reagents attack from the less hindered side of the molecule.
(8) S. Shiotani, T. Kometani, K. Mitsuhashi, T. Nozawa, A. Kurobe, and O. Futsukaichi, *J. Med. Chem.*, **19**, 803 (1976).
(9) S. Shiotani and T. Kometani, *Chem. Pharm. Bull.*, **21**, 1053 (1973).
(10) E. L. May and J. G. Murphy, *J. Org. Chem.*, **20**, 257 (1955).
(11) S. Shiotani, T. Kometani, and K. Mitsuhashi, *J. Med. Chem.*, accepted.

(*E*)- and (*Z*)-4-Methyl-5-[5-(2,6,6-trimethylcyclohexen-1-yl)-3-methyl-2(*E*),4(*E*)-pentadienylidene]-2(5*H*)-furanone. Synthesis and Spectral Properties

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In the course of some other research on vitamin A and its derivatives, we became interested in the preparation of the

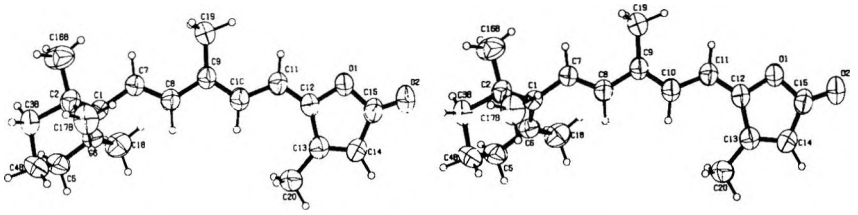
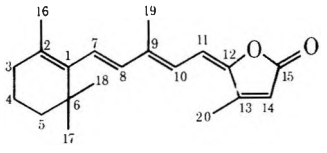


Figure 1. Stereodrawing of 1 showing one of the two conformers which are present in the crystal. Atoms C(3)B, C(4)B, C(16)B, and C(17)B are the half-weight carbon atoms of the "B" conformer. The thermal ellipsoids scaled to the 50% probability level and the hydrogen atoms are shown as spheres of an arbitrary size.

(*E*)- and (*Z*)-2(5*H*)furanones, **1** and **2**, respectively, related to retinoic acid.[1]



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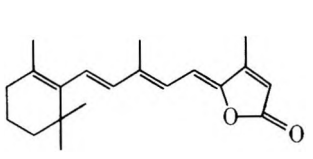

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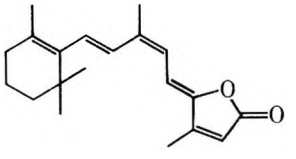
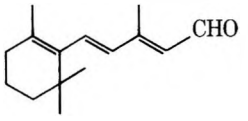


3

During the progress of this work, reports of the x-ray crystal structure determinations of **2** and its 9-cis isomer **3** appeared.[2,3] Although these papers stated that these compounds resulted from the reaction of *trans*-β-ionylideneacetaldehyde (**4**) and 3-methylbut-2-enolide (**5a**), no synthetic details could



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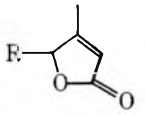

5

6

R
a H
b Br
c $^{+}PPh_3Br^{-}$

be found in the chemical literature. This paper reports the synthesis and spectral characterization including ^{13}C NMR of **1** and **2**, and the x-ray structure analysis of **1**, which was not previously reported.

The synthetic approach was analogous to the synthesis of freelingyne,[4,5] which utilized a Wittig reagent prepared from the isomeric butenolide **6**.[6]

The lactone **5a** and bromolactone **5b** were prepared as previously described.[7] The bromolactone **5b** was reacted immediately with triphenylphosphine to give the phosphonium bromide **5c**. Wittig reaction of **5c** and *all-trans*-β-ionylidineacetaldehyde[8] (**4**) in dimethylformamide with sodium hydride as base afforded a mixture of **1** and **2**. Chromatographic purification and crystallization afforded a less polar, higher melting compound. After being stored at −20 °C for 3 days, the mother liquors afforded a crystalline fraction consisting of two crystal forms which could be separated manually. One corresponded to the less polar compound; the second could be further purified by recrystallization from cold (−20 °C) pentane to give a more polar, lower melting isomer. Although the isomers displayed slightly different spectral properties, the unambiguous assignment of structure on this basis was not possible. Thus the structure of the crystalline less polar isomer **1** was determined by single-crystal x-ray diffraction analysis. The conformation of the molecule is shown in Figure 1. The C(6)–C(1)–C(7)–C(8) torsion angle is −53° (see Figure 1 for the atom labeling scheme).

Table I. Crystal Data for 1 and 2[a]

		2	
	1	Data from ref 2	Measured crystal data
Space group	$P2_1/a$	$P\bar{1}$	$P\bar{1}$
a	15.218 (2) Å	6.87 (1)	6.870 (2)
b	10.347 (3) Å	7.51 (1)	7.528 (6)
c	11.934 (2) Å	18.67 (1)	18.835 (8)
α		81.04 (12)	80.37 (5)
β	108.60 (1)°	83.77 (12)	83.51 (3)
γ		68.96 (12)	69.05 (7)
Z	4	2	2
d_{calcd}	1.115 g cm^{-3}	1.12	
μ (Cu Kα)	5.5 cm^{-1}		

[a] The formula and formula weight for **1** and **2** are $C_{20}H_{26}O_2$ and 298.43.

The crystal data are given in Table I. The intensity data were measured on a Hilger-Watts diffractometer. The size of the crystal used for data collection was approximately 0.25 × 0.40 × 0.75 mm. No absorption correction was made. Of the 3621 accessible reflections with $\theta < 76°$, 3014 had intensities which were significantly greater than background. The structure was solved by a multiple solution procedure[9] and was refined by full-matrix least squares.

During the preliminary refinement it became apparent that the crystals were disordered. The disorder arises from a 1:1 mixture of the two possible puckered conformations of the cyclohexene ring. To account for the disorder the atoms C(3), C(4), C(16), and C(17) were each replaced by two atoms of half weight, corresponding to the two conformations of the cyclohexene ring.

The preliminary refinement was continued with anisotropic temperature factors for all atoms. A difference Fourier calculated at the end of this refinement had peaks at reasonable positions for all of the ordered hydrogens. The positions of all hydrogen atoms were calculated. Two sets of half-weighted hydrogen atoms were used for the carbons involved in the disorder and also for C(5). In the final refinement the hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final difference Fourier has no peaks or holes greater than ±0.2 e A^{-3}. The final discrepancy index is R = 0.057 for the 3014 observed reflections.

The crystal data for the more polar isomer **2** were measured and compared with the previously published values (Table I). The unit cell given by Thackeray and Gafner[2] is related to the cell given in Table I by the transformation (0,0,1/0,−1,0/1,0,0). Intensity data were measured for the isomer **2**. There were 1560 observed reflections with $\theta < 57°$. Three cycles of full-matrix least squares, starting with the published atomic parameters, resulted in a discrepancy index of R = 0.119 for the 1560 observed reflections (all atoms anisotropic,

Table II. ^{13}C NMR Spectral Data for 1 and 2[c]

Carbon atom	Multiplicity[a]	δc 1	δc 2
15	s	168.5	168.8
13	s	152.4	153.7
12	s	149.1	149.4
9	s	143.0	141.9
1	s	137.4	137.3
8	d	136.9	136.8
2	s	130.3	130.8
7	d	130.1	130.1
10	d	121.7	122.4
14	d	118.1	115.1
11	d	113.0	107.5
5	t	39.5	39.6
6	s	34.2	34.2
3	t	33.0	33.2
17, 18[b]	q	28.9	28.9
16	q	21.7	21.7
4	t	19.1	19.2
20	q	15.7	12.8
19	q	12.3	11.6

[a] Single frequency off-resonance multiplicity. [b] Two-carbon peak. [c] See 1 for numbering of carbon atoms.

no hydrogens), thus conclusively confirming the structure of **2**.

The ^{13}C NMR spectral data for compounds **1** and **2** are given in Table II. The chemical shifts for these two compounds are very similar to those of *all-trans*-retinoic acid and its isomers,[10] and the majority of peaks can be readily assigned. However, there are three carbon atoms—carbon atoms 10, 11, and 12—which differ significantly in chemical shift from those of the retinoic acids and cannot be assigned by direct comparison. The unassigned carbon atoms due to C-10 and C-11 are found in the spectral region from ~107 to 123 ppm. In both **1** and **2**, the chemical shifts of C-11 would be expected at higher field than those of C-10, since C-11 is closer to the lactone ring. In addition, a larger chemical shift difference would also be expected for C-11 than for C-10 in going from **1** to **2**. The chemical shifts of C-10 and C-11 in *all-trans*-retinal occur at 129.4 and 132.4 ppm, respectively.[10] Thus, the peaks found for **1** and **2** at 113.0 and 107.5 ppm were assigned to C-11 (upfield shift of ~21 ppm; Δδ 5.5 ppm); the peaks at 121.7 and 122.4 ppm were assigned to C-10 (upfield shift of ~9 ppm; Δδ 0.7 ppm). Because it is directly bonded to oxygen, C-12 should exhibit a large downfield shift in both compounds when compared to the retinoic acids; the downfield shift should be approximately the same in both compounds. Thus, C-12 is assigned to the carbon atoms at 149.1 and 149.4 ppm for **1** and **2**, respectively.

Experimental Section

Melting points were determined on a Kofler micro hot stage and are corrected values. The ^{13}C NMR spectra were recorded on 100 mg of each compound in deuteriochloroform solution on a Varian XL-100 NMR spectrometer at 25.2 MHz in the Fourier transform mode. The spectra were obtained using a 5000-Hz sweep width and an 8K data table. Elemental and spectral analyses and x-ray structure determinations were carried out by the Physical Chemistry Department, Hoffmann-La Roche Inc.

(2,5-Dihydro-3-methyl-5-oxofuran-2-yl)triphenylphosphonium Bromide (5c). A mixture of 13.28 g (0.135 mol) of the butenolide **5a**,[7] 26.4 g (0.149 mol) of *N*-bromosuccinimide, and 200 ml of carbon tetrachloride was heated to the reflux with a light source for 2 h. The mixture was allowed to cool and was filtered; the filtrate was concentrated in vacuo to give 23.3 g (0.131 mol) of crude 4-bromobutenolide **5b**. Without further purification, this was combined with 38 g (0.145 mol) of triphenylphosphine and 250 ml of benzene and heated to the reflux for 5 h. The mixture was allowed to cool to room temperature overnight and then was filtered to give 41.4 g (0.094 mol) of phosphonium salt **5c**. This material was used in the next step without further purification.

(*E*)-4-Methyl-5-[5-(2,6,6-trimethylcyclohexen-1-yl)-3-methyl-2(*E*),4(*E*)-pentadienylidene]-2(5*H*)-furanone (1). To a cooled (5 °C) suspension of 17.2 g (78.2 mmol) of C_{15} aldehyde **4**, 41.4 g (94 mmol) of phosphonium salt **5c**, and 150 ml of dry dimethylformamide, 2.26 g (94 mmol) of sodium hydride (56.6% in mineral oil) was added. After the addition was completed, the reaction mixture was stirred at room temperature for 2 h, then heated to 60 °C for 16 h. The mixture was cooled and then poured into 500 ml of ice water. The aqueous layer was saturated with sodium chloride and extracted with three 250-ml portions of chloroform. The combined extract was washed twice with saturated sodium chloride solution and dried over sodium sulfate. Evaporation of the solvent gave 32.6 g of an oil, which was purified by chromatography on 900 g of silica gel packed in hexane. Elution with hexane containing 2% ether, and gradually increasing to 15% ether, gave 5.5 g of an isomeric mixture. This was purified by repeated recrystallization from pentane to give 2.4 g (10.2%) of the less polar furanone **1** as yellow crystals: mp 129–137 °C; NMR (CCl_4) δ 1.04 (s, 6 H), 1.71 (s, 3 H), 2.01 (s, 3 H), 2.40 (s, 3 H), 5.88 (m, 1 H), 6.1 (d, J = 16 Hz, 1 H), 6.3 (d, J = 16 Hz, 1 H), 6.37 (d, J = 12 Hz, 1 H), and 6.60 (d, J = 12 Hz, 1 H); mass spectrum *m/e* 298 (M^+), 283, 265, and 255; uv λ_{max} (2-propanol) (ε) 388 nm (39 130); ir ($CHCl_3$) 1747, 1587, and 1574 cm^{-1}. The material was found to be 94.5% isomerically pure by liquid chromatographic analysis.

Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.54; H, 8.96.

(*Z*)-4-Methyl-5-[5-(2,6,6-trimethylcyclohexen-1-yl)-3-methyl-2(*E*),4(*E*)-pentadienylidene]-2(5*H*)-furanone (2). The mother liquors from the above pentane recrystallization were combined and stored at −20 °C for 3 days. The resulting crystals were filtered and the two crystal forms were separated manually. Repeated recrystallization of the lower melting, more polar substance from cold pentane gave 350 mg of **2** as yellow crystals: mp 90–95 °C; NMR (CCl_4) δ 1.02 (s, 6 H), 1.21 (s, 3 H), 1.99 (s, 3 H), 2.18 (s, 3 H), 5.81 (m, 1 H), 6.01 (d, J = 12 Hz, 1 H), 6.24 (s, 2 H), and 6.53 (d, J = 12 Hz, 1 H); mass spectrum *m/e* 298 (M^+), 283, and 265; uv λ_{max} (2-propanol) (ε) 385 nm (26 820) and 242 (7900); ir ($CHCl_3$) 1750 and 1575 cm^{-1}.

Anal. Calcd for $C_{20}H_{26}O_2$: C 80.50; H, 8.78. Found: C, 80.60; H, 8.79.

Registry No.—**1**, 60305-11-5; **2**, 10035-29-7; **3**, 55177-16-7; **4**, 3917-41-7; **5a**, 6124-79-4; **5b**, 60270-03-3; **5c**, 60270-04-4; triphenylphosphine, 603-35-0.

Supplementary Material Available. Tables of positional and thermal parameters for the structure of **1** (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Compounds **1** and **2** are named as derivatives of 2(5*H*)-furanone. However, because of their relationship to retinoic acid, this numbering system has been employed in this paper for purposes of discussion.
(2) M. M. Thackeray and G. Gafner, *Acta Crystallogr., Sect. B*, **30**, 711 (1974).
(3) M. M. Thackeray and G. Gafner, *Acta Crystallogr., Sect. B*, **31**, 335 (1975).
(4) C. F. Ingham and R. A. Massy-Westropp, *Aust. J. Chem.*, **27**, 491 (1974).
(5) D. W. Knight and G. Pattenden, *J. Chem. Soc., Chem. Commun.*, 188 (1974); *J. Chem. Soc., Perkin Trans. 1*, 641 (1975).
(6) J. E. T. Corrie, *Tetrahedron Lett.*, 4873 (1971).
(7) W. J. Conradie, C. F. Garbers, and P. S. Steyn, *J. Chem. Soc.*, 594 (1964).
(8) H. Mayer and O. Isler in "Carotenoids", O. Isler, Ed., Basel and Stuttgart, Birkhauser Verlag, 1971, p 347 ff.
(9) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. B*, **26**, 274 (1970).
(10) G. Englert, *Helv. Chim. Acta*, **58**, 2367 (1975).

Carbohydrate Thio Ortho Esters. Synthesis and Characterization

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Carbohydrate ortho esters have been used extensively during the last 10 years for synthesis of 1,2-trans glycosides.[1]

Table I. Yield and Product Composition for the Formation of Thio Ortho Esters (cf. Scheme I)

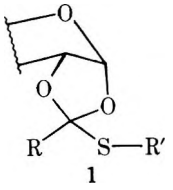
Registry no.	Starting material[a] (configuration)	Yield[b] (%)	Product composition[c] (exo/endo, %)
572-09-8	D-gluco	**2** (79)	71/29
3068-32-4	D-galacto	**3** (72)	70/30
3068-31-3	D-xylo	**4** (77)	80/20
4753-07-5	D-"lacto"	**5** (55)	100/0
21085-72-3	D-glucurono[d]	**6** (89)	56/44

[a] Per-O-acetylated α-D-glycopyranosyl bromide. [b] Isolated product. [c] Determined from NMR integrals. [d] Methyl ester.

Table II. ^{13}C NMR Chemical Shifts (ppm, Me_4Si) for the Exo (2a) and Endo (2b) Gluco Thio Ortho Esters and the β-Thioglucoside (2c)

Compd	C_1	C_{2-6}	CH_3CO	CH_3CO	Arom C	CH_3Ph	CH_3CS	CH_3CS
Exo (**2a**)	97.32	73.21	20.78	170.52	139.11	21.26	26.46	117.93
		69.80		169.55	135.62			
		68.26		169.14	129.70			
		66.88			128.24			
		62.98						
Endo (**2b**)	97.87	75.53	20.63	170.63	139.45	21.28	28.34	118.25
		72.20		169.74	136.36			
		70.66		169.50	129.70			
		67.98			127.35			
		62.21						
Glucoside (**2c**)	85.79	75.73	20.61	170.44	138.70	21.18		
		74.02		170.03	133.76			
		69.88		169.14	129.62			
		68.18			127.50			
		62.09						

Thio ortho esters (**1**), however, have not been reported although they should have potential in carbohydrate synthesis (glycoside synthesis, protective group, reduction to acetals, oxidation to sulfoxides and sulfones, S-alkylation, transformation by heavy metal ions, etc.).



1

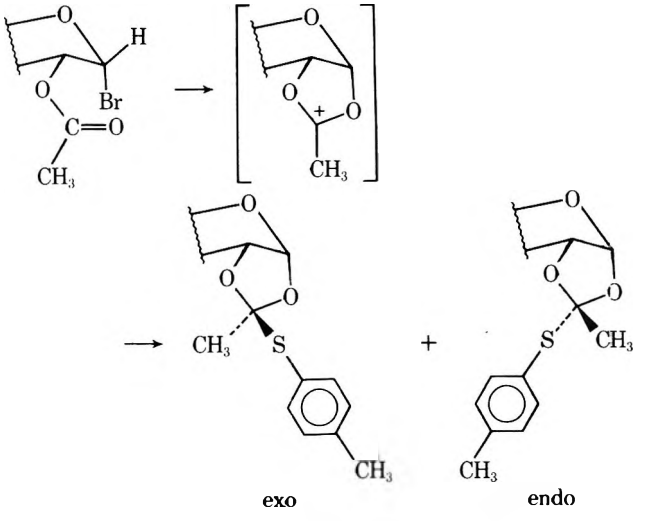
I now wish to report the synthesis and characterization of *p*-methylthiophenyl ortho esters[2] of some representative mono- and disaccharides (peracetylated). The synthesis consists of heating equimolar amounts of the appropriate acetobromo sugar, *p*-methylthiophenol, and 2,4,6-trimethylpyridine in nitromethane. Chromatography of the reaction mixture gave the thio ortho esters in good yields together with small amounts of di-*p*-methyl phenyl disulfide and β-thioglycoside (see Table I). The mechanism of the reaction probably involves initial solvent attack[3] on the acetobromo sugar followed by acetoxonium ion formation. This will then react with the thiol to give the thio ortho ester (see Scheme I).

A mixture of exo and endo isomers was obtained using acetobromo monosaccharides but only the exo compound was formed from acetobromo lactose. Probably the galactose residue hinders thiol attack at the endo side of the intermediate acetoxonium ion.

In order to determine the structures of these compounds, the gluco isomers (exo and endo thio ortho esters and the β-thioglucoside) were isolated in pure (NMR) form and investigated by spectroscopic methods.

The ^1H NMR spectra showed the following significant features: a low-field (ca. 5.7 ppm) rough doublet with a splitting of ca. 5 Hz for the thio ortho ester anomeric protons.

Scheme I



Further, *C*-methyl group singlets (1.82 and 1.63 ppm) were found for the exo and endo thio ortho esters (absent for the β-thioglucoside). This is in accordance with normal ortho esters.[4]

The ^{13}C NMR spectra of the thio ortho esters (see Table II) showed high-field signals for the *C*-methyl group carbons and low-field signals for the quaternary carbons of the ortho ester group. These signals were absent with the β-thioglucoside.

All the thio ortho esters reported here showed a low-intensity molecular ion peak in the mass spectrum. Other significant features were a strong M − 123 peak for the acetoxonium ion (cf. Scheme I) and base peak at 169 mass units.

Since sulfur is less basic than oxygen, one could expect thio ortho esters of the present type to be more acid stable than normal ortho esters. The latter are completely hydrolyzed by dilute sulfuric acid in acetone within ca. 30 min.[3] With the thio ortho esters, approximately 50% hydrolysis occurred after 3 h under the same conditions.

The relative hydrolytic stability of this new type of compound and the possibility of utilizing the unique properties of sulfur for selective transformations suggest that thio ortho esters should be versatile intermediates in synthetic sugar chemistry.

Experimental Section

Melting points are uncorrected. Ir spectra were run as KBr tablets. ^1H and ^{13}C NMR spectra were run in $CDCl_3$ (Me_4Si) on JEOL PMX-60 and JEOL FX-60 spectrometers, respectively. Mass spectra were run on a Varian MAT 311 spectrometer.

General Procedure for Preparation of the Thio Ortho Esters. The appropriate acetobromo sugar (2.5 mmol) and *p*-methylthiophenol (2.5 mmol, recrystallized from petroleum ether) were dissolved in dry nitromethane (3 ml) containing 2,4,6-trimethylpyridine (2.55 mmol). The solution was stirred (magnet) under N_2 at 50 °C for ~5 h (compound **6**, 15 h). The reaction was followed by TLC (SiO_2, ethyl acetate–light petroleum). 2,4,6-Trimethylpyridinium bromide was formed as a white precipitate. The reaction mixture was cooled and ether (10 ml) was added to complete the precipitation. Filtration and evaporation of the filtrate gave a colorless syrup which was chromatographed on silica (100 g, Merck Kieselgel 60, 0.063–0.200 mm) with ethyl acetate–light petroleum as eluent (1:2 for monosaccharide and 1:1 for disaccharide thio ortho esters). This gave as the first fraction a few milligrams of **di-*p*-methyl phenyl disulfide** [ir 1490, 798 cm^{-1}; NMR δ 7.34, 7.04 (rough AB q, 4 H each, J_{AB} = 8.3 Hz, aromatic H), 2.27 ppm (s, 6 H, CH_3Ph); mass spectrum *m/e* (rel intensity) 246 (M^+, 100, base peak), 123 (80). Anal. Calcd for $C_{14}H_{14}S_2$: mol wt, 246.0537. Found: mol wt, 246.0541] followed by a second fraction of pure exo thio ortho ester and a third fraction of exo plus endo thio ortho esters (for monosaccharides). Trace amounts of the thioglycosides could be isolated in some cases from a fourth fraction (verified for the gluco compound). The composition (exo/endo) was determined from NMR integrals of the CH_3CS signals (see Table I). Yields are not optimized.

3,4,6-Tri-*O*-acetyl-1,2-*O*-*p*-methylthiophenoxyethylidene-α-D-glucopyranose (2). Yield 79% (exo plus endo isomer; see Table I).

Exo Isomer (2a): syrup;[6] $[\alpha]^{25}_{578}$ +78.9° (*c* 0.735, $CHCl_3$); ir 1750, 810 cm^{-1}; NMR δ 7.41, 7.15 (rough AB q, 2 H each, J_{AB} = 7.8 Hz, aromatic H), 5.77 (d, 1 H, 5.0 Hz splitting, OCHO), 3.76–5.35 (m, 6 H, OCH), 2.36 (s, 3 H, CH_3Ph), 2.15, 2.08 (s, 9 H, CH_3COO), 1.82 ppm (s, 3 H, CH_3CS); ^{13}C NMR, see Table II; mass spectrum *m/e* (rel intensity) 454 (M^+, 0.3, $C_{21}H_{26}O_9S$), 331 (70), 271 (6), 229 (6), 211 (7), 187 (6), 169 (100, base peak).

Anal. Calcd for $C_{14}H_{19}O_9$: mol wt, 331.1029. Found: mol wt, 331.1029 ($M - C_7H_7S$).

Endo Isomer (2b). Rechromatography of the exo/endo mixture gave the pure endo compound **(2b)**: syrup; $[\alpha]^{25}_{578}$ +107.9° (*c* 0.410, $CHCl_3$); ir 1755, 810 cm^{-1}; NMR δ 7.56, 7.16 (rough AB q, 2 H each, J_{AB} = 8.1 Hz, aromatic H), 5.69 (d, 1 H, 5.6 Hz splitting, OCHO), 4.00–5.80 (m, 6 H, OCH), 2.37 (s, 3 H, CH_3Ph), 2.09, 2.05 (s, 9 H, CH_3COO), 1.63 (s, 3 H, CH_3CS); ^{13}C NMR, see Table II; mass spectrum *m/e* (rel intensity) 454 (M^+, 0.06, $C_{21}H_{26}O_9S$), 331 (8), 271 (6), 229 (3), 211 (8), 187 (6), 169 (100, base peak).

Anal. Calcd for $C_{14}H_{19}O_9$: mol wt, 331.1029. Found: mol wt, 331.1028 ($M - C_7H_7S$).

***p*-Methylphenyl 2,3,4,6-Tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (2c):** mp 116–117 °C; $[\alpha]^{24}_{578}$ −19.8° (*c* 2.90, $CHCl_3$) [lit.[5] mp 118 °C; $[\alpha]_D$ −21° (c 2.0, $CHCl_3$)]; ir 1748, 919, 820, 810 cm^{-1}; NMR δ 7.38, 7.12 (rough AB q, 2 H each, J_{AB} = 8.0 Hz, aromatic H), 3.51–5.43 (m, 7 H, OCH), 2.34 (s, 3 H, CH_3Ph), 2.07 (s, 6 H, CH_3COO), 2.00, 1.97 ppm (s, 3 H each, CH_3COO); mass spectrum *m/e* (rel intensity) 454 (M^+, 0.1, $C_{21}H_{26}O_9S$), 331 (35), 271 (9), 229 (3), 211 (6), 187 (3), 169 (100, base peak).

Anal. Calcd for $C_{14}H_{19}O_9$: mol wt, 331.1029. Found: mol wt, 331.1026 ($M - C_7H_7S$).

3,4,6-Tri-*O*-acetyl-1,2-*O*-*p*-methylthiophenoxyethylidene-α-D-galactopyranose (3). Yield 72% (exo plus endo isomer; see Table I).

Exo Isomer: syrup; $[\alpha]^{25}_{578}$ +118.5° (*c* 0.287; $CHCl_3$); ir 1757, 810 cm^{-1}; NMR δ 7.41, 7.13 (rough AB q, 2 H each, J_{AB} = 8.0 Hz, aromatic H), 5.85 (d, 1 H, 5 Hz splitting, OCHO), 4.00–5.46 (m, 6 H, OCH), 2.35 (s, 3 H, CH_3Ph), 2.09, 2.06, 2.03 (s, 3 H each, CH_3COO), 1.77 ppm (s, 3 H, CH_3CS); mass spectrum *m/e* (rel intensity) 454 (M^+, 0.1, $C_{21}H_{26}O_9S$), 331 (59), 271 (6), 229 (4), 211 (6), 187 (3), 169 (100, base peak).

Anal. Calcd for $C_{14}H_{19}O_9$: mol wt, 331.1029. Found: mol wt, 331.1020 ($M - C_7H_7S$).

Endo Isomer: NMR δ 1.66 ppm (s, 3 H, CH_3CS).

3,4-Di-*O*-acetyl-1,2-*O*-*p*-methylthiophenoxyethylidene-α-D-xylopyranose (4): yield 77% (exo plus endo isomer; see Table I).

Exo Isomer: syrup; $[\alpha]^{25}_{578}$ +71.8° (*c* 0.490, $CHCl_3$); ir 1749, 810 cm^{-1}; NMR δ 7.38, 7.10 (rough AB q, 2 H each, J_{AB} = 7.6 Hz, aromatic H), 5.58 (d, 1 H, 4.4 Hz splitting, OCHO), 3.37–5.32 (m, 5 H, OCH), 2.31 (s, 3 H, CH_3Ph), 2.08, 2.00 (s, 3 H each, CH_3COO), 1.77 ppm (s, 3 H, CH_3CS); mass spectrum *m/e* (rel intensity) 382 (M^+, 0.1, $C_{18}H_{22}O_7S$), 259 (30), 246 (17) 217 (20), 199 (29), 170 (20), 157 (74), 149 (55), 128 (76), 124 (40), 115 (75), 97 (100, base peak).

Anal. Calcd for $C_{11}H_{15}O_7$: mol wt, 259.0818. Found: mol wt, 259.0809 ($M - C_7H_7S$).

Endo Isomer: NMR δ 1.59 ppm (s, 3 H, CH_3CS).

3,6-Di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-1,2-*O*-*p*-methylthiophenoxyethylidene-α-D-glucopyranose (5): yield 55% (pure exo isomer; see Table I). Recrystallization from ethanol gave an analytical sample: mp 142–143 °C; $[\alpha]^{25}_{578}$ +47.5° (*c* 1.12, $CHCl_3$); ir 1752, 810 cm^{-1}; NMR δ 7.44, 7.20 (rough AB q, 2 H each, J_{AB} = 8.0 Hz, atomatic H), 5.73 (d, 1 H, 5.0 Hz splitting, OCHOCS), 3.69–5.66 (m, 13 H, OCH), 2.37 (s, 3 H, CH_3Ph), 2.17, 2.10, 2.06, 1.96 (s, 18 H, CH_3COO), 1.83 ppm (s, 3 H, CH_3CS); mass spectrum *m/e* (rel intensity) 742 (M^+, 0.05, $C_{33}H_{42}O_{17}S$), 619 (7), 576 (4), 559 (8), 516 (2), 499 (1), 457 (3), 331 (80), 317 (6), 288 (21), 271 (10), 229 (12), 211 (31), 169 (100, base peak).

Anal. Calcd for $C_{26}H_{35}O_{17}$: mol wt, 619.1873. Found: mol wt, 619.1926 ($M - C_7H_7S$). Calcd for $C_{33}H_{42}O_{17}S$: C, 53.4; H, 5.7; S, 4.3. Found: C, 53.1; H, 5.9; S, 4.1.

Methyl 3,4-Di-*O*-acetyl-1,2-*O*-*p*-methylthiophenoxyethylidene-α-D-glucopyranuronate (6). Reaction time was 15 h; yield 89% (exo plus endo isomer; see Table I).

Exo Isomer: syrup; $[\alpha]^{25}_{578}$ +55.7° (*c* 0.445; $CHCl_3$); ir 1752, 827, 810 cm^{-1}; NMR δ 7.37, 7.11 (rough AB q, 2 H each, J_{AB} = 8.0 Hz, aromatic H), 5.84 (d, 1 H, 5.0 Hz splitting, OCHO), 4.16–5.36 (m, 4 H, OCH), 3.75 (s, 3 H, OCH_3), 2.36 (s, 3 H, CH_3Ph), 2.12, 2.06 (s, 3 H each, CH_3COO), 1.83 ppm (s, 3 H, CH_3CS); mass spectrum *m/e* (rel intensity) 440 (M^+, 0.1, $C_{20}H_{24}O_9S$), 317 (7), 259 (24), 257 (11), 199 (24), 197 (8), 157 (53), 155 (59), 97 (100, base peak).

Anal. Calcd for $C_{13}H_{17}O_9$: mol wt, 317.0872. Found: mol wt, 317.0893 ($M - C_7H_7S$).

Endo Isomer: NMR δ 1.61 ppm (s, 3 H, CH_3CS).

Acknowledgments. I am grateful to Birgit Boman for technical assistance and to Lennart Holmquist for running the mass spectra.

Registry No.—**2a**, 60426-93-9; **2b**, 60410-57-3; **2c**, 28244-94-2; *exo*-**3**, 60410-58-4; *endo*-**3**, 60439-00-1; exo-**4**, 60410-59-5; *endo*-**4**, 60410-60-8; *exo*-**5**, 60410-61-9; *exo*-**6**, 60410-62-0; *endo*-**6**, 60410-63-1; *p*-methylthiophenol, 106-45-6; 2,4,6-trimethylpyridine, 108-75-8; 2,4,6-trimethylpyridinium bromide, 60410-64-2; di-*p*-methylphenyl disulfide, 103-19-5.

References and Notes

(1) G. Wulff and G. Röhle, *Angew. Chem.*, **86**, 173 (1974).
(2) *p*-Methylthiophenol was chosen for several reasons: it is easily visualized on TLC plates by uv irradiation, the smell is quite tolerable, making its use outside a hood possible, and it can be easily purified by recrystallization from petroleum ether.
(3) N. K. Kochetkov, A. J. Khorlin, and A. F. Bochkov, *Tetrahedron*, **23**, 693 (1967).
(4) R. U. Lemieux and A. R. Morgan, *Can. J. Chem.*, **43**, 2199 (1965).
(5) M. Cerny, D. Zachystalova, and J. Pacak, *Collect. Czech. Chem. Commun.*, **26**, 2206 (1961).
(6) **Note Added in Proof.** Crystals were obtained after several months: mp 115–115.5 °C (from EtOH); $[\alpha]^{25}_{578}$ +85.9° (*c* 0.66, $CHCl_3$).

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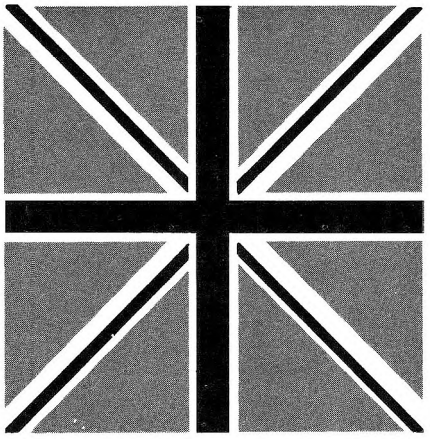

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GOT A WHALE OF A PROBLEM?

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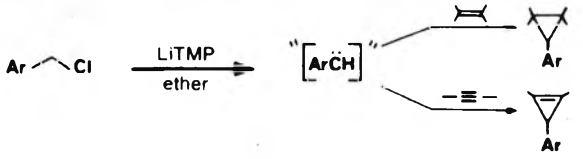
PROTON-SELECTIVE BASE

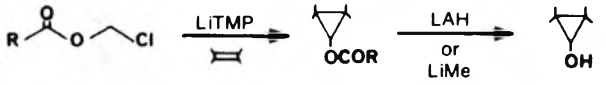
As the goals of synthetic and mechanistic chemistry become increasingly complex, the need for highly selective reagents becomes more critical. The quest for **non-nucleophilic strong bases**, for example, has sparked the research of many workers.

One of the most effective new proton-selective reagents is lithium 2,2,6,6-tetramethylpiperidide **(LiTMP)**, a member of the class of strong bases which Olofson[1] has termed **"H⁺arpoons."** **LiTMP** is conveniently prepared by treating an ethereal solution of **2,2,6,6-tetramethylpiperidine (HTMP)** with methyl- or butyllithium.[2]

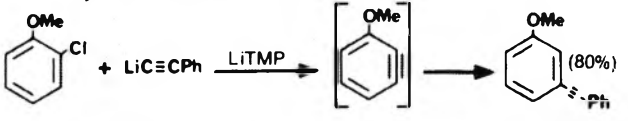
LiTMP has been found to be superior to NaOEt, KO-*t*-Bu, NaH, $NaNH_2$, LiAr, LiR, $NaCPh_3$, $LiN(SiMe_3)_2$, $LiN(i\text{-}Pr)_2$, and $BrMgN(i\text{-}Pr)_2$ for the practical synthesis of arylcyclopropanes and cyclopropenes from benzyl chlorides.[1,2]



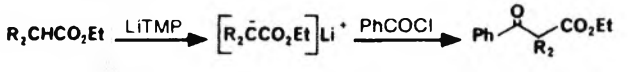
Very recently, Olofson reported a useful synthesis of cyclopropyl esters (and ultimately cyclopropanols) from chloromethyl esters, **LiTMP**, and a variety of olefins.[3]



LiTMP is a highly effective base for generating benzynes from aryl chlorides:[1]

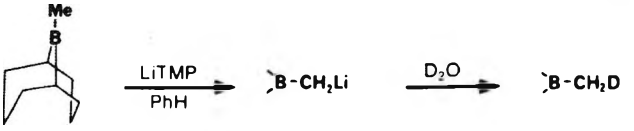


This particular **H⁺arpoon** has been used to effect difficult carbonyl condensations in cases where more conventional bases have failed.[1]



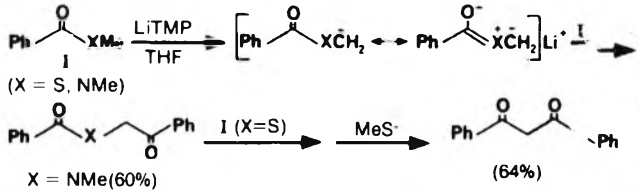
R=Me(89%), Et(86%)

Early work by Rathke and Kow[4] provided the "first example of base-promoted α proton removal from an organoborane."

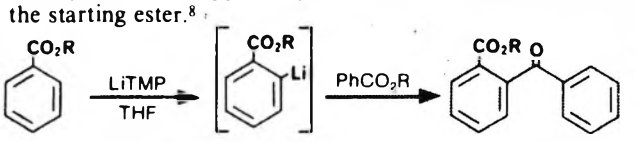


In subsequent findings,[5] the authors demonstrated the superiority of **LiTMP** over bases such as $LiN(i\text{-}Pr)_2$ and $LiN(i\text{-}Pr)(c\text{-}Hex)$ for producing boron-stabilized carbanions from vinylboranes, effective precursors for 3-silylated aldehydes and ketones.

LiTMP has been used by Beak to generate transient dipole-stabilized carbanions *via* deprotonation of aromatic thioesters[6] and amides.[6,7]



Unless additional stabilization of the incipient carbanion is provided (*e.g.*, by unsaturation), the analogous reaction for *esters* does not occur. Thus, alkyl benzoates afford *o*-benzoylbenzoates, apparently the result of ortho lithiation of the starting ester.[8]



References:

1) R.A. Olofson and C.M. Dougherty, *J. Amer. Chem. Soc.*, **95**, 582 (1973).
2) R.A. Olofson and C.M. Dougherty, *ibid.*, **95**, 581 (1973).
3) R.A. Olofson, K.D. Lotts, and G.N. Barber, *Tetrahedron Lett.*, 3381 (1976).
4) M.W. Rathke and R. Kow, *J. Amer. Chem. Soc.*, **94**, 6854 (1972).
5) R. Kow and M.W. Rathke, *ibid.*, **95**, 2715 (1973).
6) P. Beak and R. Farney, *ibid.*, **95**, 4771 (1973).
7) P. Beak, G.R. Brubaker, and R.F. Farney, *ibid.*, **98**, 3621 (1976).
8) C.J. Upton and P. Beak, *J. Org. Chem.*, **40**, 1094 (1975).

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