Synthesis of Bicyclic Furan Derivatives (1)

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Acid catalyzed reaction of cyclododecane-1,2-dione VI with dimethyl 3-ketoglutarate II led to the formation of methyl (E)-6,7,8,9,10,11,12,13-octahydro-3-(methoxycarbonyl)cyclododeca-[b]furan-2-acetate IX, presumably formed through the dihydrodihydroxyfuran VIII. This dihydrofuran intermediate VIII was shown to be characteristic of the reaction of 2-substituted carbonyl-compounds with II for both α-chlorocyclohexanone and α-chlorocyclopentanone furnished furans XVIa and XX, respectively, when treated with II. The effect of dihydrodihydroxyfuran intermediates on the course of such reactions is discussed.

The reaction of 1,2-dicarbonyl compounds I with dimethyl 3-ketoglutarate II in aqueous acidic (2a-c) or alkaline (3a-e) media has been studied in some detail. Several possible intermediates have been proposed (3e) to occur early in this sequence; those of most interest to the present work are III and IV (see Scheme I). Repeated

Scheme I

II   III   IV
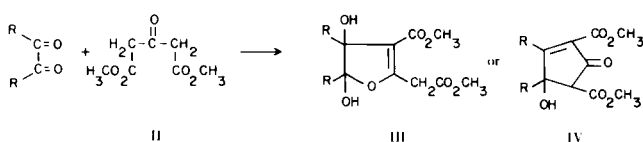
attempts to-isolate a simple, 1:1 intermediate in this sequence were unsuccessful; for example, when either cyclohexane-1,2-dione or cyclododecane-1,2-dione was stirred with II, no 1:1 adduct was isolated; although use of a sterically hindered 1,2-dione, camphorquinone, did lead to the formation of the 4,5-dihydrodihydroxyfuran V of type III (3e).

We would now like to report here that reaction of cyclododecane-1,2-dione VI and II under different conditions: heating in the presence of p-toluenesulfonic acid, has provided a new compound in moderate yield which appears to be derived from an intermediate similar to III. The empirical formula ($C_{19}H_{26}O_5$) of this adduct

V   VII
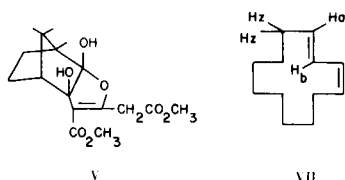
was established by microanalysis and mass spectrometry (M^+ at m/e 334.1788; Calcd. 334.1733). This white crystalline solid (m.p. 85-86°) contained saturated and unsaturated ester functions as evidenced by bands in the ir spectrum at 1740 and 1715 cm^{-1}. The 220 M Hz nmr spectrum indicated the presence of 2 vinyl protons in this compound [δ 6.07 (d of t, J_1 = 15 Hz, J_2 = 5 Hz), and δ 6.25 (d, J = 15 Hz)]. Chemical shifts and J values of the 2 vinyl signals are very similar to those of the signals from

protons H_a and H_b of cis,trans-1,3-cyclododecadiene VII reported by Gassman (4). Two methoxyl singlets were observed at δ 3.73 and 3.80 in the spectrum of the adduct while an absorption due to an isolated methylene function was found at δ 4.02. Comparison with the proton spectrum of V was revealing (3e), since the chemical shifts of the methoxyl signals of this compound were almost identical with those found in the spectrum of the adduct from II and VI. This suggested that the reaction product might be derived from a dihydrodihydroxyfuran intermediate of type III ($C_{19}H_{30}O_7$) by loss of 2 molecules of water. A reasonable possibility would arise from condensation of the 1,2-dione VI and II to generate the diol VIII, as illustrated in Scheme II, loss of 2 molecules of water from

Scheme II

VI   VIII

IX
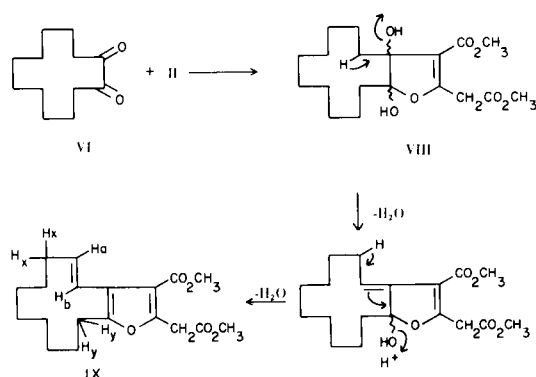
VIII would yield methyl (E)-6,7,8,9,10,11,12,13-octahydro-3-(methoxycarbonyl)cyclododeca[b]furan-2-acetate IX. The coupling constant observed for the vinyl protons of IX, J_{ab} = 15 Hz, agrees well with that reported (4) for the trans-protons (H_a, H_b) of VII and its trans,trans-isomer, indicating similar stereochemistry for the double bond in our compound. The 3 singlets in the region δ 3.50 to 4.10 in the proton spectrum of the new compound are consistent with a structure such as IX, but more important are the signals from the methylene protons of IX denoted as H_x and H_y. The quartet at δ 2.20 (2H, J = 5 Hz) in the spectrum of IX has been assigned to the protons of H_x, for these hydrogens are coupled to the adjacent

methylene function, as well as to H_a, and are similar to the signals from H_z (δ 2.15) of the diene VII (4). A triplet from the hydrogens designated H_y appeared at δ 2.75; this simple splitting pattern would be expected, since this methylene is adjacent to only one hydrogen-bearing carbon. Furthermore, the absorption from a methylene group in a similar environment has been reported to occur at δ 2.68 in the spectrum of 2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydrobenzofuran (5,6).

Several reactions were carried out to confirm the structure of this furan derivative IX. Treatment with sodium borohydride in refluxing methanol led to reduction of the saturated ester function, while the conjugated ester remained intact. Similar borohydride reductions of esters have been reported by Brown and Rapoport (7). The alcohol X obtained from this reduction was a white solid (m.p. 92-95°) whose 220 M Hz nmr spectrum contained 2 new signals at δ 3.25 (t, J = 6 Hz) and δ 3.90 (t, J = 6 Hz), while the methoxy and methylene absorptions at δ 3.73 and 4.02, respectively, had disappeared. Furthermore, the band at 1740 cm^{-1} in the ir spectrum of IX was not present in the spectrum of X.

Reduction of IX with lithium aluminum hydride provided the diol XI (m.p. 77-80°) in good yield, while acid catalyzed hydrolysis and decarboxylation of IX gave (E)-6,7,8,9,10,11,12,13-octahydro-3-(methoxycarbonyl)-2-methylcyclododeca[b]furan XII via a pathway illustrated at the bottom of Scheme III. All spectral data obtained
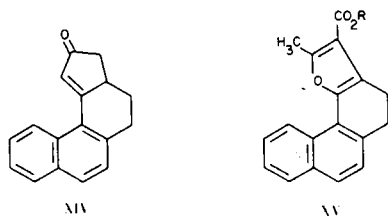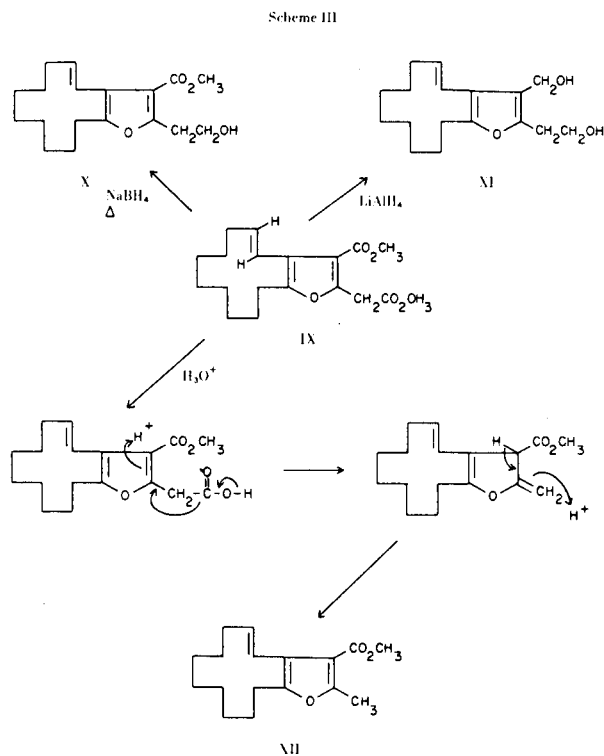
for furans X, XI, and XII clearly supported structure IX.

Since the isolation of IX indicated that dihydrodihydroxyfurans such as III, V, or VIII were indeed intermediates in these reactions, it was desirable to determine whether this observation might have some predictive value for the direction of reaction of II with other carbonyl compounds. The two ketones initially chosen as substrates were α-chlorocyclohexanone XIIIa and α-chlorocyclopentanone XIIIb, since activated methylene compounds have been reported (8a-d) to combine with α-halo-ketones [see, for example, the reaction of ethyl acetoacetate with 3-bromo-4-ketotetrahydrophenanthrene to yield XIV and XV (8a,b)].

When α-chlorocyclohexanone XIIIa was stirred with II at room temperature in aqueous buffer (pH = 5.6 or 8.4), reaction was extremely slow, if occurring at all. Heating the solution merely led to decomposition of the chloroketone. However, stirring XIIIa with the sodium salt of II in DMF at 64° for several days did provide a 50% yield of

Scheme III

methyl 4,5,6,7-tetrahydro-3-(methoxycarbonyl)-2-benzofuranacetate XVIa in addition to lesser amounts of XVII and XVIII as outlined in Scheme IV. The diol XVII is known to arise from self-condensation of α-hydroxycyclohexanone (9), while dimerization of dimethyl 3-ketoglutarate II leads to the aromatic species XVIII (10).

It is important to note that the chemical shifts of the protons on the methylene carbon and ester functions attached to positions 2 and 3 of the furan XVIa were almost identical with those from the corresponding protons of furan IX (see above). Furthermore, acid-catalyzed hydrolysis and decarboxylation of XVIa under vigorous conditions provided both 4,5,6,7-tetrahydro-3-(methoxycarbonyl)-2-methylbenzofuran XVIc and 4,5,6,7-tetrahydro-3-carboxy-2-methylbenzofuran XVId (8c), presumably by a pathway analogous to that proposed for the origin of XII illustrated in Scheme III. Mild hydrolysis of the diester XVIa produced the mono-ester XVIb.

Analogous reaction of XIIIb should provide access to derivatives of cyclopenta[b]furans. However, conflicting reports have appeared in the literature regarding both the ease (8d) and even the feasibility (11) of the preparation of 4,5-cyclopentylfurans because of the strain encountered in this bicyclic ring system. It was therefore not surprising that heating a mixture of α-chlorocyclopentanone XIIIb and the sodium salt of II in dimethylformamide yielded the alcohol XIX rather than the desired furan. The structure of XIX was deduced from ir, nmr, and mass spectral data. The nmr spectrum was especially informative: a quartet (1H) was located at δ 4.08, indicative of a methine

Scheme IV

a. R_1 = Me, R_2 = CO$_2$Me
b. R_1 = Me, R_2 = COOH
c. R_1 = Me, R_2 = H
d. R_1 = R_2 = H
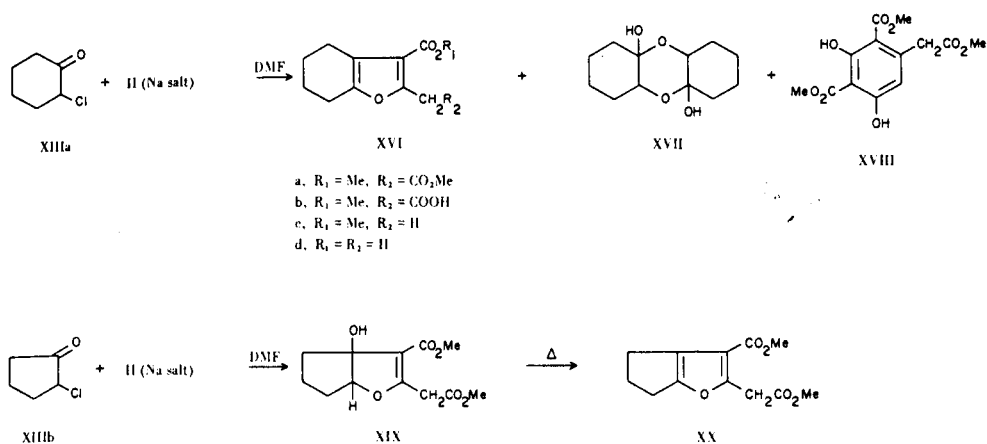
hydrogen adjacent to oxygen (12), while a broad hydroxyl singlet (deuterium oxide-exchangeable) appeared at δ 4.80. The six methylene protons of the cyclopentane ring were observed as a broad multiplet at δ 1.90, while the 2 ester functions and the methylene group (adjacent to ester) all appeared as overlapping singlets centered at δ 3.67. When this alcohol XIX (M$^+$ at m/e 256) was subjected to electron impact mass spectrometry, a facile loss of water was observed to generate an ion at m/e 238, suggesting that perhaps the furan XX would result from thermal dehydration of the alcohol XIX. Indeed, when the alcohol XIX was pyrolyzed at 220°, a compound was obtained, whose ir spectrum contained a band at 1570 cm^{-1} characteristic of furans (13); moreover, the hydroxyl absorption had disappeared. Comparison of the nmr and ir spectra of the tetrahydrobenzofuran XVIa with this new derivative demonstrated that the loss of water on heating had indeed generated the desired methyl 5,6-dihydro-3-(methoxycarbonyl)-4H-cyclopenta[b]furan-2-acetate XX.

Apparently the strain of the cyclopenta[b]furan system is sufficient to prevent its direct formation in a manner similar to formation of XVIa.

Numerous attempts to convert α-chloro or α-bromo-cyclododecanone to the dihydro analog of IX were unsuccessful. It appears that elimination of HX is occurring in the α-halocyclododecanone, followed by condensation reactions which lead to inseparable mixtures. Furthermore, no spectroscopic evidence for the formation of any furan was obtained in these cases (14).

The difference in reactivity of the saturated ester (position 2) vs. the unsaturated carbomethoxy group (position 3) of IX is noteworthy. Presumably, stabilization of the ester carbonyl at position 3 of the furan ring renders this carbonyl less reactive to hydride or hydroxide attack than the saturated ester carbonyl at position 2, for formation of the tetrahedral intermediate would destroy the resonance overlap with the π bond.

It does appear that dihydroxyfuran intermediates such

as III are present in most of the reactions of II with 1,2-dicarbonyl compounds. Furthermore, the assumption that dimethyl 3-ketoglutarate tends to form intermediates of this type does have some predictive value, as evidenced by the reactions of α-haloketones and II described herein.

EXPERIMENTAL

Microanalyses were performed on an F and M Scientific Corp. Carbon, Hydrogen, Nitrogen Analyzer Model 185. 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 M Hz spectrometers. Infrared spectra were taken on a Beckman Acculab-1 instrument, and mass spectra were recorded on a Hitachi RMU-6 mass spectrometer. Analytical tlc plates used were E. Merck Brinkman uv active silica gel or alumina on plastic. Cyclododecane-1,2-dione, α-chlorocyclopentanone, α-chlorocyclohexanone, and dimethyl 3-ketoglutarate were purchased from Aldrich Chemical Company.

Acid Catalyzed Reaction of Cyclododecane-1,2-dione VI and Dimethyl 3-Ketoglutarate II in Refluxing Benzene to Provide IX.

Cyclododecane-1,2-dione VI (3.0 g., 0.015 mole), dimethyl 3-ketoglutarate II (5.32 g., 0.030 mole) and p-toluenesulfonic acid (200 mg.) were dissolved in benzene (70 ml.). The solution was refluxed for 24 hours, while the water was removed by means of a Dean-Stark trap. Evaporation of the benzene afforded an oil (6 g.) which was found to be a mixture of starting materials and a new compound IX (R$_f$ = 0.42 in 10% ethylacetate/benzene). The oil was chromatographed on silica gel to furnish a small amount of the furan IX (1.0 g., 20% yield) which was crystallized from methanol to provide white crystals, m.p. 85-86°; ir (carbon tetrachloride): 2940 and 2870 (C-H), 1740, 1715 with a shoulder at 1700 (saturated and unsaturated ester functions) and 1560 cm^{-1}; nmr (deuteriochloroform): δ 220 M Hz 1.21-1.91 (12H, broad multiplet), 2.20 (1H, q, J = 5 Hz), 2.75 (1H, t, J = 6 Hz), 3.73 (3H, s), 3.80 (3H, s), 4.02 (2H, s), 6.07 (1H, d of t, J$_1$ = 15 Hz, J$_2$ = 5 Hz), and 6.25 (1H, d, J = 15 Hz); mass spectrum: M$^+$ at m/e 334.1788; Calcd. for C$_{19}$H$_{26}$O$_5$, 334.1733; m/e 334 (M$^+$, 100), 306 (14), 302 (57), 291 (81.6), 276 (20), 275 (100), 274 (40), 280 (14), 251 (14), 246 (10.7), 245 (15), 231 (15), 238 (16), 219 (23), 218 (24), 205 (34), 203 (34), 192 (35), 191 (61.3), 189 (57), 173 (30), 159 (51), 149 (54), 145 (35), and 131 (65).

Anal. Calcd. for C$_{19}$H$_{26}$O$_5$: C, 68.30; H, 7.80. Found: C, 68.00; H, 8.02.

Reduction of IX with Sodium Borohydride.

The furan IX (50 mg., 1.5 x 10^{-4} mole) was dissolved in methanol (30 ml.) and sodium borohydride (200 mg.) was added to the solution. The mixture was refluxed until the starting material disappeared (monitored by tlc). After cooling to room temperature, the methanol was removed under reduced pressure, and sodium hydroxide was added to the residue to dissolve the salts. Extraction of the solution with ether, followed by removal of solvent provided a white solid X (38 mg., 83%) of m.p. 92-95° (from methanol); R_f = 0.22 (10% ethylacetate/benzene); uv λ max (methanol); 267 nm; ir (carbon tetrachloride): 3440, 2940, 2870, 1710 cm^{-1} with a shoulder at 1720 and 1560 cm^{-1}; nmr (deuteriochloroform): δ (220 M Hz) 1.21-1.65 (12H, broad multiplet), 2.20 (1H, q, J = 5 Hz), 2.75 (1H, t, J = 6 Hz), 3.25 (2H, t, J = 6 Hz), 3.80 (3H, s), 3.90 (2H, t, J = 6 Hz), 6.07 (1H, d of t, J_1 = 15 Hz, J_2 = 5 Hz) and 6.25 (1H, d, J = 15 Hz); mass spectrum: m/e 306 (M^+, 52), 288 (70.4), 278 (31), 275 (100), 247 (96), 231 (14), 219 (15), 217 (14), 205 (14), 191 (32), 189 (14), 163 (20), 159 (20), 145 (21), 131 (21).

Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.58; H, 8.49. Found: C, 70.30; H, 8.30.

Reduction of IX with Lithium Aluminum Hydride.

The furan IX (30 mg., 9 x 10^{-5} mole) was dissolved in dry tetrahydrofuran (50 ml.). To this solution, lithium aluminum hydride (100 mg.) was added and the resulting mixture was refluxed for 3 hours. The slurry was next treated with cold hydrochloric acid (1N, 25 ml.) to dissolve the lithium salts. Extraction of the aqueous layer with diethyl ether (5 x 25 ml.) and removal of the solvent under reduced pressure, afforded a white solid XI (25 mg., 80% yield), m.p. 77-80°; uv λ max (methanol): 277.5 nm; ir (carbon tetrachloride): 3460, 2920, 2880, and 1595 cm^{-1}; mass spectrum: m/e 278 (33), 260 (5), 247 (100), 230 (10), 221 (5).

Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.38; H, 9.34. Found: C, 73.21; H, 9.17.

Acid-Catalyzed Hydrolysis and Decarboxylation of IX to yield (*E*)-6,7,8,9,10,11,12,13-octahydro-3-(methoxycarbonyl)-2-methyl-cyclododeca[*b*]furan (XII).

The furan IX (10 mg., 3 x 10^{-5} mole) was dissolved in hydrochloric acid (3 ml., 6N) and the mixture was refluxed for 4 hours. The solution was cooled and extracted with chloroform (5 x 20 ml.). The combined extracts were washed with potassium carbonate solution (2 x 25 ml. of a 10% solution), followed by water and dried with sodium sulfate. Removal of solvent under reduced pressure provided 4.2 mg. of an oil; uv λmax (methanol): 274.2 nm; R_f = 0.54 (10% ethyl acetate/benzene); ir (carbon tetrachloride): 2960, 2930, 2600, 1710 and 1560 cm^{-1}; mass spectrum: m/e 276 (M^+, 100), 248 (33), 236 (33), 233 (33), 219 (66), 211 (49), 207 (50), 206 (43), 205 (38), 196 (66), 194 (100), 167 (100).

Anal. Calcd. for $C_{17}H_{24}O_3$: C, 73.91; H, 8.69. Found: C, 74.10; H, 8.50.

Methyl 4,5,6,7-Tetrahydro-3-(methoxycarbonyl)-2-benzofuran-acetate (XVIa).

The sodium salt (15) of II (10.88 g., 0.055 mole) was dissolved in dry DMF and α-chlorocyclohexanone XIIIa (6.6 g., 5 x 10^{-2} mole) was added to the solution. The mixture was stirred at 64° for 3 days. The DMF was then removed under vacuum and the oily residue taken up in chloroform. The organic layer was washed with hydrochloric acid (0.1 N), dried (sodium sulfate) and the solvent removed under reduced pressure. Chromatography of the

oily residue was carried out on neutral alumina to provide the furan XVIa (6.2 g., 48% yield), b.p. 143° at 0.6 mm Hg; ir (potassium bromide): 1748 (C=O), 1712 (C=O), 1640 and 1585 cm^{-1} (furan ring); nmr (deuteriochloroform): δ 1.73 (4H, m), 2.65 (4H, m), 3.70 (3H, s), 3.76 (3H, s), and 4.00 (2H, s); mass spectrum: M^+ at m/e 252.

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.90; H, 6.40. Found: C, 61.75; H, 6.25.

In addition, the diol XVII [m.p. 133°, lit. value 132.5° (9)] and the triester XVIII [m.p. 142-143°, lit. 144-145° (10)] were obtained in 15 and 10% yield, respectively.

Hydrolysis of XVIa to Generate 4,5,6,7-Tetrahydro-3-(methoxy-carbonyl)-2-benzofuranacetic Acid (XVIb).

The tetrahydrobenzofuran derivative XVIa (2.52 g., 0.01 mole) was heated for 2 hours in hydrochloric acid with acetic acid added as a cosolvent. The mixture was neutralized with sodium carbonate and extracted with ether (3 x 50 ml.). Evaporation of solvent furnished XVIb as a white crystalline solid (1.90 g., 80%), m.p. 140°(from ether); ir (potassium bromide): 3200-2600 (OH), 1728 (C=O), 1715 (C=O) and 1580 cm^{-1}; nmr (deuteriochloroform): δ 1.80 (4H, m), 2.52 (4H, m), 3.83 (3H, s), 4.05 (2H, s), 10.9 (1H, s); mass spectrum: M^+ at m/e 238.

Anal. Calcd. for $C_{12}H_{14}O_5$: C, 60.50; H, 5.85. Found: C, 60.30; H, 5.65.

Hydrolysis of XVIa to Furnish 4,5,6,7-Tetrahydro-3-(methoxy-carbonyl)-2-methylbenzofuran (XVIc) and 4,5,6,7-Tetrahydro-3-carboxy-2-methylbenzofuran (XVId).

The furan XVIa (2.42 g.) was treated in the way described in the previous experiment; however, the solution was refluxed for 4 hours. After workup and column chromatography [silica gel, gradient elution (petroleum ether/benzene)] the first few fractions yielded a small amount of an amorphous oil, which crystallized on standing. This solid was identified as XVIc. Later fractions yielded a white solid which was found to be the mono acid XVId. XVIc, m.p. 166° (from ether); ir (potassium bromide): 1717 (C=O), and 1585 cm^{-1}; nmr (deuteriochloroform): δ 1.65 (4H, m), 2.50 (4H, m), 2.52 (3H, s), 3.85 (3H, s); mass spectrum: M^+ at m/e 194.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.04; H, 7.16. Found: C, 67.90; H, 7.00.

Compound XVId.

This compound had m.p. 159-161° (from ether), lit. value 156° (8c); ir (potassium bromide): 3200-2600(OH), 1665 (C=O), and 1570 cm^{-1}; nmr (deuteriochloroform): δ 1.70 (4H, m), 2.50 (4H, m), 2.52 (3H, s), and 10.9 (1H, s); mass spectrum: M^+ at m/e 180.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.66; H, 6.66. Found: C, 66.46. H, 6.50.

Methyl 5,6-Dihydro-3-(methoxycarbonyl)-4*H*-cyclopenta[*b*]furan-2-acetate (XX).

The sodium salt of II (23.52 g., 0.12 mole) was suspended in dry dimethoxyethane (400 ml.) and α-chlorocyclopentanone XIIIb (11.95 g., 0.1 mole) was added. The mixture was stirred at 45° for 2 weeks. The DME was removed under reduced pressure and the residue taken up in chloroform. The solution was washed with dilute hydrochloric acid (0.1 N) and the organic layer was dried (sodium sulfate). The solvent was removed under reduced pressure to furnish an oil which was purified by column chromatography, first over silica gel and then repurified on alumina. The yield of oily alcohol XIX (1.25 g.) was only 5.2%; however, repeating the reaction in DMF increased the yield of XIX to 30%; ir (neat):

3230 (OH), 1745 (C=O), 1695 (C=O), and 1635 cm^{-1} (O-C=C). No band was found in the region of 1570 cm^{-1}; nmr (deuterio-chloroform): δ 1.90 (6H, m), 3.65 (2H, s), 3.67 (3H, s), 3.68 (3H, s), 4.08 (1H, q), and 4.80 (broad OH, disappeared on treatment with deuterium oxide); mass spectrum: M$^+$ at m/e 256, base peak (M$^+$ - 18) m/e 238.

This alcohol XIX was not purified further but was heated to 220° for 40 minutes and then distilled under vacuum to provide methyl 5,6-dihydro-3-(methoxycarbonyl)-4H-cyclopenta[b]furan-2-acetate XX (1 g.) in 80% yield, b.p. (oil bath) 180° at 0.6 mm Hg; ir (neat): 1745 (C=O), 1710 (C=O), and 1570 cm^{-1} (furan); nmr (deuteriochloroform): δ 2.60 (6H, m), 3.68 (3H, s), 3.72 (3H, s), and 3.90 (2H, s).

Anal. Calcd. for $C_{12}H_{14}O_6$: C, 60.50; H, 5.85. Found: C, 60.40; H, 5.75.

REFERENCES AND NOTES

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(6) In the nmr spectrum of 3-methylfuran the signal for the methyl group appears at δ 1.97, while the analogous absorption for 2-methylfuran is located at lower field (δ 2.22). In addition, methylene functions next to oxygen at the 2 position of a furan

have been reported to occur in the proton nmr spectrum at δ 2.62 (2-ethylfuran) and δ 2.72 (5-ethyl-2-furaldehyde). These data are consistent with structure IX, for the methylene function adjacent to oxygen (deshileded) in the spectrum of this molecule can be found at δ 2.72; nmr of 2-methylfuran, Sadtler Standard Spectra, Sadtler Research Laboratories, 6662 (1969); nmr of 3-methyl-furan, D. Miller, *J. Chem. Soc.* (C), 12 (1969); nmr of 2-ethyl-furan, Sadtler Standard Spectra 23890; nmr of 5-ethyl-2-fur-aldehyde, Sadtler Standard Spectra 23891.

Further support for structure IX can be obtained by examination of the splitting pattern for the allylic, methylene protons present in the nmr spectrum of *trans,trans*-1,3-cyclododecadiene (see Reference 4): the protons appeared as a complex signal (doublets of triplets) at δ 2.09, again consistent with the signal assigned to the protons of H_X in the spectrum of IX.

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(13) Furans are known to contain a band in the aromatic region of the ir spectrum between 1550 and 1600 cm^{-1}. For the ir spectra of a series of furan derivatives see J. Pouchert, "The Aldrich Library of Infrared Spectra," Aldrich Chemical Co., 1970, pp. 882-884.

(14) Preliminary experiments on the reaction of cyclohexane-1,2-dione and II in benzene in the presence of p-toluenesulfonic acid, were also not promising; complex mixtures were obtained.

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(16) This work was supported by a grant from the National Heart and Lung Institute.