A Remarkable Methyl Substituent Effect in a Twistane Aldol Synthesis

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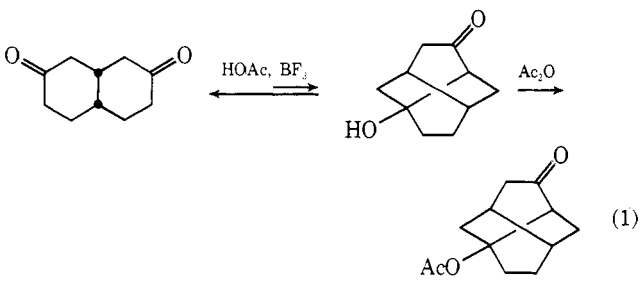
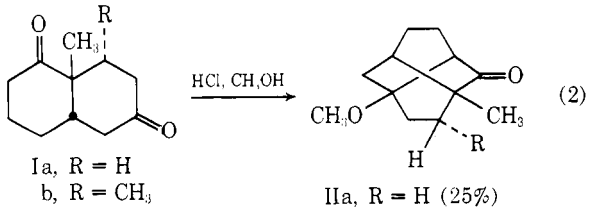
An internal aldol cyclization of 1-methyl-*cis*-bicyclo[4.4.0]decane-2,8-dione derivatives (I) to substituted twistanones (II) is described. The presence of a *trans*-methyl substituent at C-10 enhances this cyclization in a striking manner. Indeed, the resulting aldol product (III) predominates in the base-catalyzed equilibrium. The *p*-bromobenzenesulfonate derivative of III was analyzed by X-ray diffraction.

The twistane ring system (the tricyclo[4.4.0.0^{3,8}]decane system) has intrigued organic chemists since its initial synthesis by Whitlock in 1962.[1] Because of its D_2 symmetry, twistane is an ideal model for studying the chiroptical properties of twist-boat structures.[2] Furthermore, twistane is a highly efficient precursor to adamantane,[3] and its 4-keto derivative is reported to be an antiviral agent.[4] For these and other reasons, effective methods for synthesizing twistane and its derivatives have been sought and developed by many research groups. One of the most interesting new methods for preparing such compounds involves the intramolecular aldol condensation of *cis*-bicyclo[4.4.0]decane-3,9-dione discovered by Deslongchamps and coworkers.[5,6] In their approach an unfavorable aldol equilibrium was displaced by derivatization of the aldol hydroxyl function.



(1)

In this paper we report our investigations of a similar intramolecular aldol condensation of the 1-methyl-*cis*-bicyclo[4.4.0]decane-2,8-dione system (eq 2), and call attention to a remarkable methyl substituent effect on the aldol equilibrium. The C-1 angular methyl substituent in these diketones is necessary to maintain a cis configuration of the fused six-membered rings. However, we find that other methyl groups may exert profound but less easily explained influences.



(2)

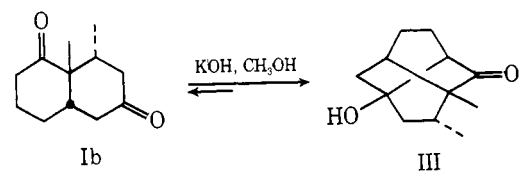
Ia, R = H
b, R = CH_3

IIa, R = H (25%)
b, R = CH_3 (98%)

On treatment with a methanolic potassium hydroxide solution, Ia remained unchanged insofar as TLC analysis could determine. Although the trapping procedure used by Deslongchamps (eq 1) did not work well in this case, we were able to obtain a methyl ether derivative of the twistane aldol (IIa) in modest yield by treating Ia with a solution of hydrogen chloride in anhydrous methanol (eq 2). A sample of pure IIa was obtained by preparative GLC and identified by comparing its characteristic ir, NMR, and mass spectra (Experimental Section) with those of the methyl homolog IIb.

The introduction of a second methyl substituent at C-10 resulted in a surprising enhancement of twistane ether formation when this methyl was oriented trans to the angular methyl, but not when it was cis. Thus Ib was converted to IIb in almost quantitative yield by treatment with methanolic hydrogen chloride. Both IIa and IIb exhibited a characteristic carbonyl absorption at 1726 cm^{-1} and displayed parent ions at *m/e* 194 and 208 in their respective mass spectra. It proved possible to crystallize IIb from wet ether, mp 45–46°, but the product appeared to be a hydrate (infrared absorption at 3410 cm^{-1}).

An even more striking influence of the methyl substituent in Ib was observed in its reaction with base, a mixture of Ib (29%) and its internal aldol isomer III (71%) being generated by treatment of either pure Ib or III with methanolic potassium hydroxide (eq 3).



(3)

Ib III

A pure sample of III, obtained by GLC, proved to be a crystalline solid, mp 106–107° having spectroscopic properties consistent with the assigned structure (Experimental Section). Pure III proved to be sensitive to moisture and decomposed in part to Ib on silica gel chromatography. Treatment of III with a benzene solution of *p*-toluenesulfonic acid also gave Ib.

A crystalline *p*-bromobenzenesulfonate derivative of III, mp 124–125°, gave excellent single crystals, having the space group $P\bar{1}$-cell constants a = 11.949 (2), b = 12.475 (2), c = 6.683 (1) Å, α = 108.48 (1), β = 100.86 (1), γ = 108.48 (1)°, with two molecules per unit cell. Analysis of such a crystal by means of a Picker FACS-1 four-circle diffractometer established the twistane configuration of III,[7] as shown in Figure 1. Interestingly, the carbonyl bond angle (C-1–C-2–C-3) disclosed by this study is 108.9 (4)°, indicating a degree of angle strain also reflected in the infrared stretching frequency of this function (1725 cm^{-1}).

The influence of the C-10 methyl substituent on the internal aldol cyclization of Ib appears to be due in part to extreme nonbonded interactions in one of the decalin conformations (eq 4).

Methyl substituents in other locations on the *cis*-bicyclo[4.4.0]decane-2,8-dione system may also influence the course of intramolecular aldolization. For example, our initial investigation of the 7-methyl derivative IV suggests that four-membered aldol products such as V and VI are formed. No products having ^{1}H NMR, ir, and mass spectra consistent with a twistane structure were obtained.

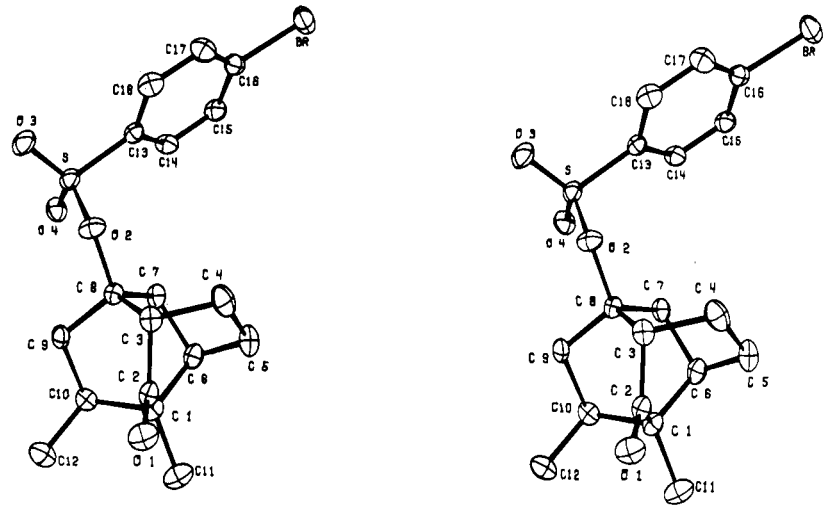
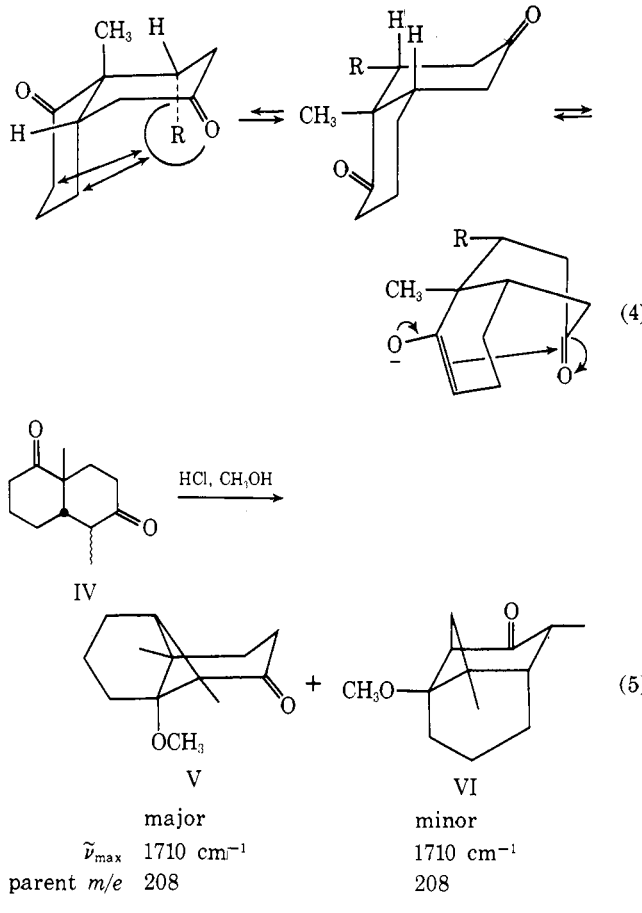


Figure 1. Stereodrawings illustrating the brosylate of III as determined by X-ray analysis. The 30% probability ellipsoids represent the thermal motions of each nonhydrogen atom.



	major	minor
$\tilde{\nu}_{max}$	1710 cm^{-1}	1710 cm^{-1}
parent *m/e*	208	208

Experimental Section[8]

***cis*-8a-Methyl-3,4,4a,7,8,8a-hexahydronaphthalene-1,6(2*H*,5*H*)-dione Derivatives (I).** The Wieland–Miescher ketone[9] and its 8-methyl derivatives[10] were prepared by established variations of the Robinson annelation procedure.[10,11] Reduction of the Wieland–Miescher ketone over a palladium catalyst yielded Ia.[12] Reduction of an ethanol solution of *trans*-8,8a-dimethyl-3,4,8,8a-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione[10] over palladium on charcoal (10%) with 50 psi of hydrogen gave 94% Ib as a colorless oil: ir (CCl_4) 1720, 1705, 1085 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (3 H, d, J = 6.0 Hz), 1.43 (3 H, s), 1.52–3.20 (12 H); mass spectrum (70 eV) *m/e* (rel intensity) 194 (35), 179 (3), 161 (10), 123 (20), 110 (91), 95 (28), 81 (29).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19, H, 9.34. Found: C, 74.11; H, 9.20.

(1*R,3*R**,6*S**,8*R**,10*R**)-8-Methoxy-1,10-dimethyltricyclo-[4.4.0.0^{3,8}]decan-2-one (IIb).** A solution of 22.5 mg (0.108 mmol) of Ib in 4 ml of absolute methanol was maintained at 0° while anhydrous hydrogen chloride was added over a 2-min period. The reaction mixture was then allowed to warm to room temperature with stirring, and an hour later the solvent was removed at reduced pressure. The residue was dissolved in ether, washed sequentially with saturated sodium chloride solution and saturated sodium bicarbonate solution, and dried. The resulting solution was passed through a short silica gel column, and subsequent removal of the solvent gave 23.8 mg (98%) of IIb as an oil with the following physical properties: ir (neat) 1726, 1451, 1135, 1110, 1090, and 1074 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (3 H, d, J = 6.0 Hz), 0.91 (3 H, s), 1.00–2.42 (11 H), 3.23 (3 H, s); mass spectrum (70 eV) *m/e* (rel intensity) 208 (13), 193 (4), 176 (8), 110 (100), 99 (63).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.96, H, 9.72.

The oil thus obtained could be crystallized from wet ether (mp 45–46°); however, ir absorption at 3410 cm^{-1} suggested that water was incorporated in the crystal lattice. The carbonyl absorption appeared unchanged.

(1*R,3*R**,6*S**,8*R**10*R**)-8-Hydroxy-1,10-dimethyltricyclo-[4.4.0.0^{3,8}]decan-2-one (III).** To 2 ml of methanol–water (50:50) which contained one pellet of potassium hydroxide was added 20 mg (0.10 mmol) of Ib. This solution was stirred overnight at room temperature and then diluted with water and extracted with benzene. The organic extract was washed with water and evaporated at reduced pressure, giving a quantitative recovery of an oil. GLC analysis (4% QF-1, 195°) of this oil indicated that it was a mixture of ketol III (71%) and unreacted starting material (29%). Preparative GLC gave an analytical sample (mp 106–107°) which rapidly lost its crystalline properties on exposure to the air and which could not be recrystallized. The spectroscopic properties of III were observed to be ir (CCl_4) 3590, 3400, 1725, 1455, 1378, 1315, and 1070 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.67 (3 H, d, J = 6.5 Hz), 0.81 (3 H, s), 0.85–2.40 (11 H), 4.96 (1 H, s); mass spectrum (70 eV) *m/e* (rel intensity) 194 (35), 110 (91), 95 (28), 81 (29), 69 (75), 55 (47), 41 (100).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.14; H, 9.51.

Overnight treatment of a benzene solution of III with *p*-toluenesulfonic acid gave a 92% yield of Ib, identified by ir spectroscopy and GLC retention time.

Preparation of a *p*-Bromobenzenesulfonate Derivative of III. A solution of 90 mg (0.22 mmol) of ketol III in 2 ml of dry pyridine was treated at 0° with a large excess of *p*-bromobenzenesulfonyl chloride. After complete dissolution the resulting solution was stirred at room temperature for 3 days and then poured into water at 0°, stirred, and extracted with ether. The organic phase was washed sequentially with dilute hydrochloric acid, water, and saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate. Careful evaporation gave 133 mg (70%) of white crystals. A portion of these were dissolved in ether and placed in a closed vial from which very slow evaporation of the solvent gave

excellent single crystals appropriate for collecting three-dimensional X-ray data. An analytical sample had mp 124–125°; ir (CCl_4) 1734, 1325–1380, 1178, 920, 868 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3 H, d, J = 6.5 Hz), 0.92 (3 H, s), 1.20–2.86 (11 H), 7.78 (4 H, s); mass spectrum (70 eV) m/e (rel intensity) 414 (3), 412 (3), 221 (6), 219 (6), 193 (45), 176 (24), 157 (14), 155 (14), 148 (28), 133 (12), 120 (12), 110 (100), 93 (17), 81 (41), 69 (21), 55 (21).

Anal. Calcd for $C_{18}H_{21}BrO_4S$: C, 52.31, H, 5.12. Found: C, 52.29; H, 5.21.

(1*R,3*R**,6*S**,8*R**)-8-Methoxy-1-methyltricyclo-[4.4.0.0^{3,8}]decan-2-one (IIa).** A solution of 194 mg (1.0 mmol) of Ia in 5 ml of absolute methanol saturated with hydrogen chloride was stirred overnight and worked up by quenching with saturated sodium bicarbonate solution. The ether extracts of this solution yielded an oil which GLC analysis showed to be a mixture of Ia, IIa, and several other components. The component assigned structure IIa (about 20% of the mixture) was collected by preparative GLC (4% QF-1 at 170°): ir (neat) 2930, 2855, 2820, 1730, 1460, 1325, 1135, 1115, 1100 cm^{-1}; mass spectrum (70 eV) m/e 194, 179, 95, 85, 55. The parent ion (m/e 194) exhibited isotope peaks at m/e 195 (14.5% P) and 196 (ca. 2% P); the isotopic abundance calculated for $C_{12}H_{18}O_2$ is 14.45 and 1.37%, respectively.

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Registry No.—Ia, 4707-05-5; Ib, 55090-34-1; IIa, 55090-35-2; IIb, 55090-36-3; III, 55090-37-4; III brosylate, 55090-38-5; *trans*-8,8a-dimethyl-3,4,8,8a-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione, 17566-22-2; *p*-bromobenzenesulfonyl chloride, 95-58-8.

References and Notes

(1) H. W. Whitlock, *J. Am. Chem. Soc.*, **84**, 3412 (1962).
(2) (a) K. Adachi, K. Naemura, and M. Nakazaki, *Tetrahedron Lett.*, 5467 (1968); (b) M. Tichy, *Ibid.*, 2001 (1972).
(3) H. W. Whitlock and M. Siefken, *J. Am. Chem. Soc.*, **90**, 4929 (1968).
(4) P. Deslongchamps, Canadian Patent 800,003 (1968); *Chem. Abstr.*, **70**, 96254e (1969).
(5) J. Gauthier and P. Deslongchamps, *Can. J. Chem.*, **45**, 297 (1967); **47**, 795 (1969).
(6) A. Belanger, J. Poupart, and P. Deslongchamps, *Tetrahedron Lett.*, 2127 (1968).
(7) This appears to be the first reported X-ray structure determination of a twistane derivative. Full details of this work (with Dr. B. L. Barnett) have been submitted: *J. Cryst. Mol. Struct.*, in press.
(8) All reactions were conducted under a nitrogen or argon atmosphere. Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Proton magnetic spectra were obtained using a Varian T-60 high-resolution spectrometer. Mass spectra were obtained by Mrs. Lorraine Guile with a Hitachi RMU-6 mass spectrometer. Gas–liquid partition chromatography (GLC) was carried out using Varian Aerograph 1200 and A-90P3 instruments. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.
(9) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **33**, 2215 (1950).
(10) R. M. Coates and J. E. Shaw, *J. Am. Chem. Soc.*, **92**, 5657 (1970).
(11) S. Ramachandran and M. S. Newman, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 486.
(12) S. Swaminathan and M. S. Newman, *Tetrahedron*, **2**, 88 (1958).

Synthesis and Substituent Effects in the Nuclear Magnetic Resonance and Mass Spectra of Dimethyl- and Dihaloxanthones

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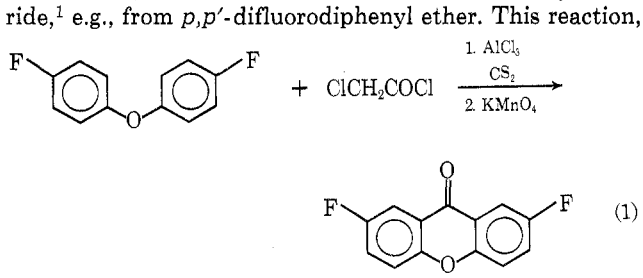
Halogen- and methyl-substituted xanthones have been prepared by three routes. The main approach has been Friedel–Crafts acylation–cyclization of aromatic ethers with oxalyl chloride or with chloroacetyl chloride followed by permanganate oxidation. The substituent shifts in the ^1H NMR spectra of the compounds studied are in good agreement with those predicted for substituted benzene derivatives. The typical electron-impact-induced CO expulsion from the molecular ion of xanthone decreases or even disappears in the halogenated derivatives owing to the competing halogen elimination.

In a preliminary communication by one of us, it was shown that the Friedel–Crafts acylation–cyclization reaction can be used to synthesize substituted xanthones (xanthen-9-ones) from aromatic ethers and chloroacetyl chloride,[1] e.g., from *p,p'*-difluorodiphenyl ether. This reaction,



(1)

which is a variation of a similar procedure using oxalyl chloride,[2–4] has also been used to prepare phenoxaphosphines[5] and phenothiaphosphines,[6] starting with phosphorus trichloride and aromatic ethers and sulfides, respectively. Whereas these earlier papers have dealt with the synthesis of substituted xanthones,[2–4] practically no comparative studies which might demonstrate the generality of this reaction have appeared. With this goal in mind, we have synthesized ten xanthone derivatives, some of which are new, and studied their properties by mass spectrometry, nuclear magnetic resonance spectrometry, and infrared absorption spectroscopy. This report provides syntheses of xanthones and some correlations of various spectral parameters with the structures of the xanthone derivatives.

Experimental Section

Melting points were taken with a Thomas-Hoover capillary apparatus and are uncorrected. Proton NMR spectra were run in $CDCl_3$ with Me_4Si and $CHCl_3$ as internal standards with a Jeol C-60 HL high-resolution spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6 instrument at 70 eV using the direct insertion probe and a source temperature of 150–200°. Peaks with intensities greater than 10% of the base peak are