cis-1-Benzoyl-2,3-diphenylaziridine (25) was prepared in the same manner as 16[9] in 75% yield. Recrystallization from petroleum ether gave 25 melting at 139–141°.

Anal. Calcd for $C_{21}H_{17}NO$: C, 84.23; H, 5.72; N, 4.68. Found: C, 84.10; H, 5.53; N, 4.69.

Registry No.—1, 13866-50-7; 2, 13866-51-8; 3, 13866-52-9; 4, 13866-53-0; 5, 13866-54-1; 6, 13866-06-3; 7, 13866-07-4; 8, 13866-08-5; 9, 13866-09-6; 10, 13866-10-9; 12, 13866-11-0; 13, 13866-12-1; 15, 13866-13-2; 25, 13866-14-3.

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A Total Synthesis of 8-Isoestrone *via* Novel Intermediates. The Unique Salt Formation of 2-Methylcyclopentane-1,3-dione with Strong Acids

R. D. HOFFSOMMER, D. TAUB, AND N. L. WENDLER

Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., Rahway, New Jersey

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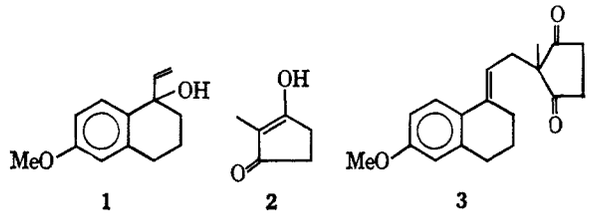
Condensation of 4-acetoxy-2-methylcyclopentane-1,3-dione with the isothiouronium salt derived from 1-vinyl-1-hydroxy-1,2,3,4-tetrahydro-6-methoxynaphthalene yielded the enedione 6. The latter cyclized under acidic conditions to the unstable hexaene 7, which on hydrogenation and demethylation afforded 8-isoestrone 8b. 2-Methylcyclopentane-1,3-dione was observed to yield highly crystalline salts with strong acids, notably hydrogen halides and fluorosulfonic acid.

Since the original discovery by the Russian workers of the unique and facile condensation of cyclic β-diketones with 1-vinyl-1-hydroxy-1,2,3,4-tetrahydro-6-methoxynaphthalene 1 leading to steroid end products,[1] a great deal of activity in this area has resulted relative to the condensation of 1 with 2 to give 3.[2]



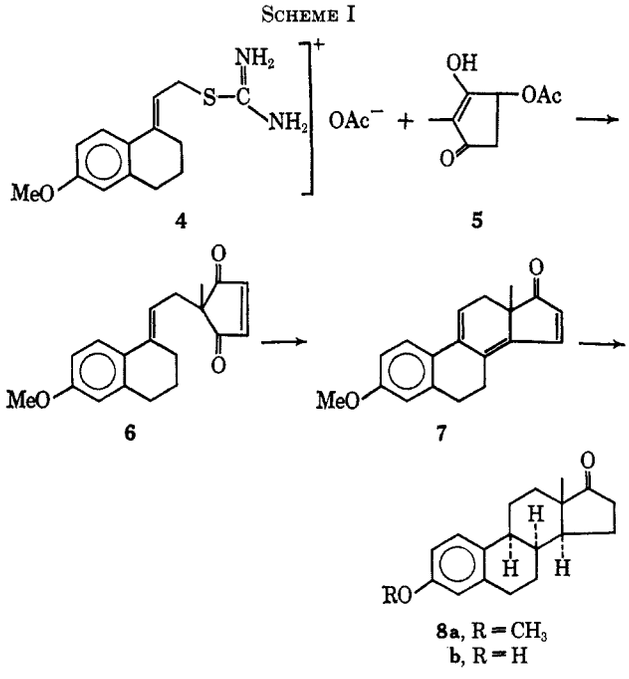
1 2 3

We had observed that 1 can be advantageously as well as nearly quantitatively converted into the crystalline isothiouronium salt 4, which in turn spontaneously couples with 2-methylcyclopentane-1,3-dione (2) in high yield to give the estrone precursor 3.[3] In this connection we were interested in examining other β-dicarbonyl systems insofar as they might provide alternative or superior routes to the steroid skeleton.

2-Methylcyclopentane-1,3-4-trione,[4] the precursor of 2-methylcyclopentane-1,3-dione (2) by the Panouse and Sannié synthesis,[5] had been catalytically reduced to 4-hydroxycyclopentane-1,3-dione by Orchin and Butz.[6] Neither 2-methylcylopentane-1,3,4-trione nor 4-hydroxycyclopentane-1,3-dione gave useful products on reaction with vinyl carbinol 1. However, the corresponding acetate derivative 5, available by controlled acetylation, did undergo condensation (see below).

Condensation of 2-methyl-4-acetoxycyclopentane-1,3-dione (5) with vinyl carbinol 1 under a variety of conditions gave at best 18% of the pentaene 6 after chromatography. However, reaction of 5 with isothiouronium salt 4 in water–ether at room temperature gave by direct crystallization 48% of adduct 6 with substantial additional amounts in the mother liquors (Scheme I). In this condensation, elimination of

SCHEME I



acetic acid appears to occur more or less spontaneously since the reaction conditions are extremely mild. The fact that β elimination does not occur with comparable facility in 5 itself is probably ascribable to the enolic character of 5 and the inherent instability of a resultant cyclopentadienone system.

(1) I. N. Nazarov, S. N. Ananchenko, and I. V. Torgov, *Izv. Akad. Nauk SSSR*, 103 (1959); S. N. Ananchenko and I. V. Torgov, *Dokl. Akad. Nauk SSSR*, **127**, 153 (1959); and related articles.

(2) (a) S. N. Ananchenko and I. V. Torgov, *Tetrahedron Letters*, 1553 (1963); (b) T. B. Windholz, J. H. Fried, and A. H. Patchett, *J. Org. Chem.*, **28**, 1092 (1963); (c) G. H. Douglas, J. M. H. Groves, D. Hartley, G. A. Hughes, B. J. McCoughlin, J. Siddall, and H. Smith, *J. Chem. Soc.*, 5072 (1963); (d) T. Miki and K. Hiraga, *Proc. Chem. Soc.*, 139 (1963); (e) D. J. Crispin and J. S. Whitehurst, *ibid.*, 22 (1963).

(3) C. H. Kuo, D. Taub, and N. L. Wendler, *Angew. Chem.*, **77**, 1142 (1965); *Angew. Chem. Intern. Ed. Engl.*, **4**, 1083 (1965); *Chem. Ind.* (London), 1340 (1966).

(4) O. Diels, S. Sielisch, and E. Müller, *Ber.*, 39, 1328 (1906).

(5) J. J. Panouse and C. S. Sannié, *Bull. Soc. Chim. France*, 1036 (1955).

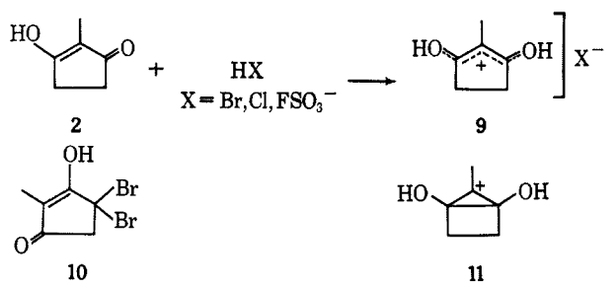
(6) M. Orchin and L. W. Butz, *J. Am. Chem. Soc.*, **65**, 2296 (1943).

Hydrogenation of **6** in benzene in the presence of the soluble catalyst tris(triphenylphosphine)rhodium chloride[7] resulted in selective saturation of the Δ^{15} double bond to give the tricyclic dione **3** in good yield.

The enedione **6** on treatment with *p*-toluenesulfonic acid in benzene smoothly cyclized in 80–85% yield to a noncrystalline product, the spectral characteristics of which were in complete conformity with the hexaene **7**. This substance exhibited ultraviolet absorption with λ_{max} 377, 313, 288, and 251 mμ. The nmr spectrum of **7** showed vinyl proton bands for the C_{11} H, τ 3.52 (quartet), C_{15} H, τ 1.99 (d, J = 5.5 cps), and C_{16} H τ 3.75 (d, J = 5.5 cps). The hexaene **7** was grossly unstable; even when stored cold in an inert atmosphere it deteriorated rapidly with development of an intense purple coloration. It was essential to submit **7** to further transformation immediately after preparation and to this end it was hydrogenated with palladium in benzene to yield 8-isoestrone methyl ether (**8a**)[8] which was demethylated by pyridine hydrochloride fusion to 8-isoestrone (**8b**).[8] By carrying out this reaction at 180°, the yield of **8b** was improved to over 70% compared with 50% obtained when the fusion was carried out conventionally at *ca.* 210–220°.[9]

In light of a recent and superior synthesis of 2-methylcyclopentane-1,3-dione,[10] we wished to convert the latter into **5**, if possible, by a bromination–acetoxylation sequence. We observed that the bromination of **2** in acetic acid solution with 1 mole of bromine resulted in the separation of a highly crystalline substance which proved to be the hydrobromide salt of 2-methylcyclopentane-1,3-dione (**9**, X = Br). The same compound was formed on passing dry hydrogen bromide into an acetic acid solution of the dione. Similarly, dione **2** formed crystalline salts **9** (X = Cl, FSO_3) with hydrogen chloride and fluorosulfonic acid, respectively. On contact with water the salts were immediately hydrolyzed with regeneration of **2**. The infrared spectrum (Nujol mull) of **9** (X = Br) was completely different from that of **2**. The spectrum of the latter had a weak band at 5.90 μ and strong absorbtion at 6.34–6.40 μ due to the enol double bond and H-bonded carbonyl, whereas the spectrum of **9** (X = Br) showed only weak 6.10- and 6.40-μ absorption and a strong band at 6.70 μ. Major differences were present in the respective fingerprint regions. Quite clearly the hydrobromide salt is structurally distinct from **2** and the cation is reasonably formulated as the delocalized allylic cation **9**. There is no evidence for a 1,3-bridged contributing structure **11** which would place partial positive charge on C-2 with an attendant downfield shift of the 2-methyl band in the nmr spectrum.[11] The latter band in the spectrum of **2** or **9** (X = Br) appeared in the τ 8.1–8.3 region when the spectrum was taken in pyridine, trifluoracetic acid, or fluorosulfonic acid. Protonation of **2** therefore does not significantly alter its nmr spectrum.

The seemingly unique ability of 2-methylcyclopentane-1,3-dione[12] to form a crystalline hydrobromide under anhydrous conditions bespeaks a high onium ion stabilization not reflected normally in β-dicarbonyl systems. The fact that the pentad–enol system of **2** is held essentially planar in virtue of its incorporation in a five-ring system probably enhances the capacity of charge delocalization in its conjugate acid with consequent greater stabilization.[13]



2 **9**

10 **11**

The second product from the original bromination proved to be a dibromide formulated as 2-methyl-4,4-dibromocyclopentane-1,3-dione (**10**) on the basis of analysis and spectral information. This compound was enolic, exhibiting a positive ferric chloride test, characteristic hydrogen-bonding absorption in the infrared region at 2.8–4.3 μ, and ultraviolet absorption at λ_{max} 266 mμ. The nmr spectrum of the dibromide **10** showed the presence of one methylene group at τ 5.04 and a methyl singlet at 8.28.[14]

Experimental Section[15]

4-Hydroxy-2-methylcyclopentane-1,3-dione was prepared according to the procedure of Orchin and Butz,[6] with the modification that a tenfold increase in the amount of catalyst was employed, resulting in a fourfold reduction of the time required for the hydrogenation. The crude product, after washing with cold ethyl acetate, was obtained in 70% yield and had mp 157–160, λ_{max}^{MeOH} 248 mμ (ε 15,515), and an equivalent weight of 132 (calcd 128).

4-Acetoxy-2-methylcyclopentane-1,3-dione (**5**).—A solution of 6.21 g (0.0484 mole) of 4-hydroxy-2-methylcyclopentane-1,3-dione in 60 ml of dry pyridine was treated with 12 ml of acetic anhydride at room temperature overnight. The reaction mixture was taken to dryness under reduced pressure at 35–40°.

The residual noncrystalline enol diacetate was dissolved in 60 ml of glacial acetic acid; 60 ml of water was added and the mixture heated on a steam bath for 1.5 hr and taken to dryness under reduced pressure. The brown oily residue was allowed to stand overnight in 100 ml of a 60:40 benzene–chloroform mixture. Filtration of this mixture yielded 675 mg of starting material (10.7% recovery). The filtrate was taken to dryness under vacuum and the residual oil on trituration with ether afforded 4.43 g (60.2% corrected yield) of 4-acetoxy-2-methylcyclopentane-1,3-dione (**5**), mp 96–100°.

(7) J. W. Young, J. A. Osborn, F. H. Jardine, and G. Wilkinson, *Chem. Commun.*, 131 (1965); A. J. Birch and K. A. M. Walker, *J. Chem. Soc., Sect. C*, 1894 (1966).

(8) W. S. Johnson, I. A. Davis, H. C. Dehm, R. J. Highet, E. W. Warnhoff, W. D. Wood, and E. T. Jones, *J. Am. Chem. Soc.*, **80**, 661 (1958).

(9) See R. D. Hoffsommer, D. Taub, and N. L. Wendler, *Chimia* (Aarau), **29**, 251 (1966), for discussion of naphthalenoid by-product formation on pyridine hydrochloride fusion in the estrone series.

(10) V. J. Grenda, G. W. Lindberg, N. L. Wendler, and S. H. Pines, *J. Org. Chem.*, **32**, 1236 (1967). See also H. Schick, G. Lehmann, and G. Hilgetag, *Angew. Chem.*, **79**, 97 (1967).

(11) In allylic cations studied by Deno, *et al.*, the band due to methyl on partially positive carbon occurred in the τ 7.1–7.2 region: N. C. Deno, H. G. Richey, Jr., N. Friedman, J. D. Hodge, J. J. Houser, and C. U. Pittman, Jr. *J. Am. Chem. Soc.*, **85**, 2991 (1963).

(12) Under the conditions examined, 2-methylcyclohexane-1,3-dione did not yield crystalline salts.

(13) Deno, *et al.*, have observed enhanced stability of the allylic carbonium ion when the latter is incorporated in a cyclopentene ring: N. C. Deno, J. Bollinger, N. Friedman, K. Hafer, J. D. Hodge, and J. J. Houser, *ibid.*, **85**, 2998 (1963).

(14) Bromination of **2** in a chloroform–water mixture has been reported to yield 2-bromo-2-methylcyclopentane-1,3-dione, mp 56–58°: G. V. Kondrateva, G. A. Kogan, T. Fadeeve, and S. I. Zavialov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1648 (1964).

(15) Melting points were taken on a microscope hot-stage apparatus and are uncorrected. Nmr spectra were recorded on a Varian A-60 spectrometer using tetramethylsilane as an internal standard.

This material was contaminated with a small quantity of 2-methylcyclopentane-1,3-dione (**2**) as indicated by thin layer chromatography on alumina-impregnated glass fiber sheets (Gelman ITLC, Type A) developed with chloroform. Dione **2** was removed by dissolving the product in 50 ml of water followed by chloroform extraction. Trituration of the residue with hexane now gave **5** with mp 106–109°; λ_{max}^{chf} 3.1–3.4 (br), 5.75, 5.90, 6.02–6.10, 7.20, 7.38, and 8.01 μ; λ_{max}^{MeOH} 247.5 mμ (ϵ 15,635).

Anal. Calcd for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C, 56.80; H, 6.08.

3-Methoxy-8(14)-secoestra-1,3,5(10),9(11),15-pentaene-14,17-dione (6).—A slurry of 1 g (3.1 mmoles) of the isothiouronium salt **4**[3] in 20 ml of water in a 100-ml flask under nitrogen was treated with 527 mg (3.1 mmoles) of 4-acetoxy-2-methylcyclopentane-1,3-dione (**5**) and 20 ml of diethyl ether. The reaction mixture was stirred at room temperature for 45 min. The aqueous layer changed from a slurry to a cloudy solution within the first 5 min. The aqueous layer was extracted with two 10-ml portions of ether; the combined ether layer and extracts were washed with two 10-ml portions of 5% potassium bicarbonate and 10 ml of saturated salt solution, dried over magnesium sulfate, and taken to dryness *in vacuo* to yield 460 mg of crude **6**. Continued stirring of the aqueous mother liquor with another 20-ml portion of ether for 3 hr yielded an additional 140 mg of product. Both crops were combined and triturated with hexane to afford 453 mg (48%) of **6**: mp 76–82°; analytical sample, mp 82–84° (ether–hexane); λ_{max}^{chf} 5.75 (sh), 5.80 (sh), and 5.89 μ; λ_{max}^{MeOH} 295 mμ (ϵ 4830), 264 (24,200), and 213 (37,200); mass spectrum showed a parent peak at 296 (calcd mol wt 296.1). The mother liquor was rich in **6** (tlc), increasing the yield an additional 15% (63% over-all) by ultraviolet estimation.

Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.08; H, 6.68.

Condensation of 415 mg of acetoxydione **5** with 500 mg of 1-vinyl-1-hydroxy-1,2,3,4-tetrahydro-6-methoxynapthalene (**1**) in 5 ml of *t*-butyl alcohol at 25° for 17 hr gave after chromatography on Florisil 159 mg (18%) of adduct **6**, mp 82–84°. A similar scale experiment in 3 ml of xylene and 1.6 ml of *t*-butyl alcohol (2-hr reflux) led to 46 mg (5%) of **6**.

3-Methoxy-8(14)-secoestra-1,3,5(10),9(11)-tetraene-14,17-dione (3).—A solution of 150 mg (0.5 mmole) of the tricyclic-dione (**6**) and 25 mg of tris(triphenylphosphine)rhodium chloride[7] in 10 ml of dry benzene was stirred under hydrogen at 25° and 1 atm. After approximately 0.5 mmole of hydrogen had been absorbed, the uptake stopped. The clear, orange reaction mixture was taken to dryness under vacuum. The residual brown oil was dissolved in a minimum amount of methylene chloride, placed on a dry column of 850 mg of silica gel H (E. Merck), and eluted with 15 ml of CH_2Cl_2. The highly colored catalyst remained on the column and eluate yielded, after trituration of the residue with hexane containing 5% ether, 89 mg of tricyclic **3**, mp 76–77°; there was no depression in mixture melting point with an authentic sample and the respective infrared and ultraviolet spectra were identical.

3-Methoxyestra-1,3,5(10),8(14),9(11),15-hexaen-17-one (7).—*p*-Toluenesulfonic acid monohydrate (10 mg) was made anhydrous by treatment with benzene and removal of the water as the benzene azeotrope. This material was then treated with 195 mg (0.65 mmole) of the tricyclic dienedione (**6**) in 8 ml of dry benzene, under nitrogen, at 60° for 10 min. The reaction mixture was washed with 5 ml of 5% potassium bicarbonate, 5 ml of saturated salt solution, dried over magnesium sulfate, and taken to dryness under vacuum to yield a light green oil with the following properties: λ_{max}^{MeOH} 377 mμ (ϵ 3712), 313 (12,960), 288 (11,440), 251 (13,470); λ_{max}^{chf} 5.91, 6.21, and 6.71 μ; nmr in $CDCl_3$, C_{11} H, τ 3.52 (quartet), C_{15} H, τ 1.99 (d, J = 5.5 cps), C_{16} H, τ 3.75 (d, J = 5.5 cps), and C_{13} CH_3, τ 8.92 (s).

8-Isoestrone Methyl Ether (8a).—The trisdehydroestrone methyl ether (**7**) obtained in the preceding experiment (*ca.* 180 mg, 0.60 mmole) was dissolved in 5 ml of benzene and added to 100 mg of 10% palladium-on-charcoal catalyst in 3 ml of benzene (prereduced). Hydrogenation was carried out at room temperature and 1 atm. Uptake stopped after a total of 1.71 mmoles of hydrogen had been absorbed. The reaction mixture was filtered through Celite to remove the catalyst, the filter pad was washed thoroughly with benzene, and the combined filtrate and washings were taken to dryness *in vacuo* to yield, after trituration with methanol, a crystalline product. Two recrystallizations from methanol afforded 50 mg of 8-isoestrone methyl ether (**8a**): mp 150–152°; λ_{max}^{MeOH} 286 mμ (ϵ 2160), 279 (2390), 221 (10,210); infrared spectrum identical with 8-isoestrone methyl ether reference spectrum.

8-Isoestrone (8b).—A mixture of 50 mg (0.175 mmole) of 8-isoestrone-3-methyl ether (**8a**) and 500 mg of pyridine hydrochloride was heated, under a nitrogen atmosphere, at 180–181° for 2.5 hr. The homogeneous reaction mixture was cooled to room temperature, treated with 2.5 ml of 1.5 *N* HCl, and extracted three times with methylene chloride. The combined extracts were washed three times with water and dried over magnesium sulfate; the solvent was evaporated under nitrogen. The crude product was purified by chromatography on silica gel impregnated glass fiber sheets (Gelman ITLC, Type SG) to afford 33.8 mg (71.5%) of crystalline 8-isoestrone (**8b**), mp 248–250°. The infrared spectrum (Nujol mull) was identical with a reference spectrum of authentic **8b**.

2-Methylcyclopentane-1,3-dione Acid Salts 9. A. The Hydrobromide and Hydrochloride Salts 9 (X = Br, Cl).—2-Methylcyclopentane-1,3-dione (**2**) (200 mg, 1.78 mmoles) was dissolved in 7 ml of warm glacial acetic acid and cooled to room temperature. To this stirred solution was added 1 ml of glacial acetic acid saturated with dry H (Cl, Br). A crystalline precipitate formed within 0.5 min. The mixture was chilled in an ice bath; the precipitate was filtered, washed once with cold acetic acid and three times with ether, and air dried to yield (85%) 2-methylcyclopentane-1,3-dione hydrohalide salt **9** (X = Br, Cl). The melting point behavior of both salts was the same; they sublimed to form needles as the volatile hydrohalogen acid escaped at 130–160° and finally melted at 208–210° (melting point of 2-methylcyclopentane-1,3-dione). Both salts showed $\lambda_{max}^{H_2SO_4}$ 263 mμ (ϵ 19,300 and 22,000), respectively. A sample of the hydrobromide salt on titration with base showed two equivalence points (1st $pH_{1/2}$ 3.0, 2nd $pH_{1/2}$ 4.6 (pK_a for 2-methylcyclopentane-1,3-dione is 4.5)); equivalent weight of 190 (calcd 193); λ_{max}^{Nujol} 3.85 (w), 4.05 (m), 4.30 (w), 6.10 (w), 6.40 (w), 6.70 (s), 7.80 μ (s). Nmr of **9** (X = Br) follows: (F_3CCOOH) τ 8.07 (s) $-CH_3$, τ 6.90 (s) $-CH_2CH_2-$; (pyridine-d_5) τ 8.07 (t, J = 1 cps) $-CH_3$, τ 7.54 (t, J = 1 cps)[16] $-CH_2CH_2-$; (FSO_3H) τ ~8.30 (s) $-CH_3$, τ ~7.15 (s) $-CH_2CH_2-$. The band positions in fluorosulfonic acid are slightly uncertain owing to the instability of the tetramethylsilane internal standard in this solvent.

B. Fluorosulfonic Acid Salt 9 (X = FSO_3).—2-Methylcyclopentane-1,3-dione (200 mg) was dissolved in 5 ml of warm glacial acetic acid and cooled to room temperature. To this solution was added 5 drops of fuming fluorosulfonic acid and the resulting light yellow solution kept overnight at room temperature. The reaction mixture was concentrated *in vacuo* to 1.5-ml volume and chilled at 0° until the residue solidified. On warming to room temperature most of the solid remelted to yield 30 mg of solid starting material. The mother liquor was diluted with 4.5 ml of ether and chilled to 0°. Addition of 0.5 ml of ether to the cold solution yielded a yellow oil which was gradually brought back into solution by dropwise addition of glacial acetic acid until crystallization occurred. After aging at 0° for 60 hr, the crystalline product was filtered and washed three times with ether to yield 180 mg of 2-methylcyclopentane-1,3-dione fluorosulfonic acid salt with the following properties: mp 135–145° (with gas evolution); λ_{max}^{Nujol} 3.57–4.35, 6.54, and 8.62 μ.

4,4-Dibromo-2-methylcyclopentane-1,3-dione (10).—A solution of 1.0 g (8.91 mmoles) of 2-methylcyclopentane-1,3-dione (**2**) in 25 ml of glacial acetic acid was treated at room temperature with 1.43 g (8.91 mmoles) of bromine in 10 ml of glacial acetic acid, added at a rate such that the reaction mixture did not retain a yellow color. After 2 ml of the bromine solution had been added, a crystalline precipitate formed and after one-half the bromine solution had been added the reaction mixture remained yellow. The addition was completed in 25 min and the mixture stirred at room temperature for 2 hr, the yellow color being finally discharged after 1 hr. The crystalline solid was filtered, washed with acetic acid, and dried to yield 530 mg of 2-methylcyclopentane-1,3-dione hydrobromide salt **9** (X = Br). An additional 165 mg was obtained from the mother liquor by concentration and trituration with ether. The ethereal mother liquor solidified on standing for 1 week. This solid mass was dissolved in ether and filtered to remove a very small amount of ether-insoluble material. The mixture was concentrated to an oil, in which a few crystals formed. Treatment of this material with benzene yielded 290 mg of crystalline material formulated as 4,4-dibromo-2-methylcyclopentane-1,3-dione (**10**): mp 128–

(16) *Cf.* C. M. Cimarusti and J. Wolinsky, *J. Org. Chem.*, **31**, 4118 (1966).

133°; λ_{max}^{MeOH} 266 mμ (ε 11,750); λ_{max}^{chf} br, bonded absorption 3.0–4.5, 5.92, 6.2–6.3 (br), 7.2, and 7.4 μ; nmr in deuterioacetone τ 5.04 (s) $-CH_2$, τ 8.28 (s) $-CH_3$; positive ferric chloride test.

Anal. Calcd for $C_6H_6O_2Br_2$: C, 26.69; H, 2.24; Br, 59.21. Found: C, 27.45; H, 2.55; Br, 58.79.

Registry No.—**3**, 899-79-6; **5**, 13865-85-5; **6**, 13865-86-6; **7**, 13765-87-7; **8**, 13865-88-8; **8a**, 517-06-6; **9** (X = Br), 13865-90-2; **9** (X = Cl), 13865-91-3; **9** (X = FSO_3), 13865-92-4; **10**, 13865-93-5.

Nuclear Magnetic Resonance Studies on Acetylated 1-Thioaldopyranose Derivatives[1,2]

CHARLES V. HOLLAND, DEREK HORTON,[3] MARTHA J. MILLER,[4]

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

AND NORMAN S. BHACCA

Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803

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The nmr spectra of the fully acetylated 1-thioaldopyranoses having the configurations β-D-*xylo* (**1**), α-L-*arabino* (**2**), β-D-*ribo* (**4**), β-D-*gluco* (**5**), and β-D-*galacto* (**6**) were determined in chloroform-*d*, acetone-d_6, and benzene-d_6. The H-1 signal in these derivatives appears ~0.35 ppm to higher field than its position in the 1-oxygenated analogs. The relative chemical shifts of the various ring protons were sufficiently different in the three solvents to permit useful conformational and configurational information to be derived by partial first-order analysis of spectra measured at 60 MHz. Spectral measurements at 100 MHz were required for first-order analysis of the spectra of the hexose derivatives **5** and **6**. First-order analysis of the signals of the methine protons, in the α-L-*arabino* derivative **2** (or its D enantiomorph, **3**), was not possible at 100 MHz with any of the three solvents; complete first-order analysis was, however, possible when the spectrum was measured at 220 MHz in chloroform-*d*. Comparative spectral data are recorded for a series of *S*-substituted analogs (**7**–**10**) of substance **6**, and 4,6-di-*O*-acetyl-1-*S*-acetyl-2,3-dideoxy-1-thio-α-D-*erythro*-hex-2-enopyranose (**11**) is shown to adopt the *H1* conformation.

Investigations in this laboratory on the reactions of thio sugar derivatives with halogens have shown[2] that the progress of the reactions can be followed conveniently by nmr spectroscopy. Acetylated 1-thioaldose derivatives react with bromine to give acetylated glycosylsulfenyl bromides,[2b,5] acetylated glycosyl bromides, and other products, according to the conditions. The nmr spectra of a range of acetylated aldopyranosyl bromides have been analyzed[6] in terms of configurational and conformational factors, and it has been shown[2] that these products are readily detected in the mixtures of substances formed when 1-thioaldose derivatives are treated with bromine under various conditions.

The present report describes a comparative analysis of the nmr spectra of a series of acetylated 1-thioaldopyranoses and some related derivatives, at 60, 100, and, in some cases, at 220 MHz. The results illustrate the use of solvent effects as an aid in spectral analysis, for reducing the signals of methine and methylene protons to patterns that are amenable to first-order interpretation. Such interpretation is particularly facile for a proton (or protons) attached to C-5 of the pyranoid ring, and the derived coupling constants are especially useful for providing information on conformation and configuration.

Materials

1-Thio-β-D-glucopyranose pentaacetate (**5**) was prepared from tetra-*O*-acetyl-α-D-glucopyranosyl bromide and potassium thiolacetate.[7,8] 1-Thio-β-D-galactopyranose pentaacetate (**6**), 1-thio-β-D-xylopyranose tetraacetate[9] (**1**), 1-thio-α-L-arabinopyranose tetraacetate (**2**), and the α-D analog (**3**) of **2** were prepared similarly. Low yields of product were obtained when this procedure was used to prepare 1-thio-β-D-ribopyranose tetraacetate (**4**) from tri-*O*-acetyl-β-D-ribopyranosyl bromide, and it was difficult to remove an accompanying side product. Condensation of tri-*O*-acetyl-β-D-ribopyranosyl bromide with thiourea, to give 2-(2,3,4-tri-*O*-acetyl-β-D-ribopyranosyl)-2-thiopseudourea hydrobromide, followed by cleavage of the *S*-amidino group by the general procedure of Černý, Vrkoč, and Staněk,[10] with subsequent reacetylation, gave pure **4**. The same route was also used to prepare **2** (an **3**[10]) by way of 2-(2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl)-2-thiopseudourea (and its D enantiomorph[10]). The enantiomorphs **2** and **3** had the anticipated opposite signs of rotation, and were each obtained in two dimorphous forms, one melting at 39° and the other at 81.5–82°. Melting points of 79°[9] and 80–81°[10] have been reported for substance **3**. The anomeric configurations assigned to the products are those anticipated to result from attack by the sulfur nucleophile on an intermediate, 1,2 cyclic acetoxonium ion during the condensation step. Nmr and optical rotatory data provide firm support for the anomeric assignments. Each of the products **1**–**6** showed absorption at 5.85–5.90 μm in its infrared spectrum, characteristic[8] of the

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(2) Preliminary reports of parts of this work have been given: (a) C. V. Holland, D. Horton, M. J. Miller, and W. N. Turner, Abstracts, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, p 1D; (b) D. Horton and M. J. Miller, *Carbohydrate Res.*, **1**, 335 (1965).

(3) To whom inquiries should be addressed.

(4) Undergraduate Research Participant, 1964–1965.

(5) R. H. Bell, D. Horton, and M. J. Miller, to be published.

(6) D. Horton and W. N. Turner, *J. Org. Chem.*, **30**, 3387 (1965).

(7) J. F. Danielli, M. Danielli, J. B. Fraser, P. D. Mitchell, L. N. Owen, and G. Shaw, *Biochem. J.*, **41**, 325 (1947).

(8) D. Horton and M. L. Wolfrom, *J. Org. Chem.*, **27**, 1794 (1962).

(9) M. Gehrke and W. Kohler, *Ber.*, **64**, 2696 (1931).

(10) M. Černý, J. Vrkoč, and J. Staněk, *Collection Czech. Chem. Commun.*, **24**, 64 (1959).