Aldrich Chemical Co.) was added with magnetic stirring. After 30 min, a freshly prepared 3% solution of cyanogen bromide (Eastman Organic Chemicals) in water was slowly added (10 min) to the stirred deep orange solution, until the color was completely discharged; 27 ml was thus consumed (110% of the theoretical). After decreasing the pH to 5 by the dropwise addition of glacial HOAc, excess cyanide was removed by bubbling a stream of nitrogen through the soution for 12 hr. Upon acidification to pH 2.3 with 6 *N* HCl a white solid crystallized out. After ice cooling the mixture, the solid was filtered, washed with cold water, and air-dried, yield 3.42 g (94%) of chromatographically and electrophoretically pure product, mp 248°. Recrystallization from ethanol gave 2.95 g (81% overall) of pale yellow plates, mp 249°. The product proved to be the half potassium salt of **2**.

Anal. Calcd for $KH(C_8H_3N_2O_4S)_2$: C, 39.50; H, 1.45; N, 11.52; S, 13.80; K, 8.04. Found: C, 40.10; H, 1.46; N, 11.39; S, 13.57; K, 7.50.

Titration with 0.1 *N* $HClO_4$ in HOAc using methyl violet as indicator gave a neutral equivalent of 484 (theory 486).

The free acid was prepared by following an analogous procedure but using NaCN in 0.5 *M* Tris acetate[9] buffer of pH 8.2 instead of KCN in $KHCO_3$ solution. The free acid crystallized out upon acidifying the final solution, yield 3.10 g (92%) of chromatographically and electrophoretically pure product, mp 160–161°. Recrystallization from ethyl acetate–petroleum ether gave 2.66 g (79%) of pale yellow prisms, mp 162–163°. Free **2** was also obtained from its half salt by suspending the latter in dilute HCl, followed by extraction with ethyl acetate, evaporation, and recrystallization from ethyl acetate–petroleum ether.

Anal. Calcd for $C_8H_4N_2O_4S$: C, 42.87; H, 1.80; N, 12.50; S, 14.28. Found: C, 42.95; H, 1.75; N, 12.45; S, 14.06.

Attempts to determine the neutral equivalent of the acid by visual titration with NaOMe in benzene–methanol were unsuccessful because the basic titrant decomposed the thiocyanate group, forming **3**.

Both **2** and its half salt showed an identical single uv-absorbing spot on paper electrophoresis (60 V/cm, 90 min, 30 cm from the origin toward the anode) and paper chromatography (R_f 0.83), which turned yellow (forming **3**) on spraying with an aqueous methanolic solution of Na_2S. **1** behaves similarily, but its electrophoretic mobility is 1.17 of that of **2** and its R_f is 0.92, in the above systems, respectively. Both **2** and its half salt showed the following spectral features: identical uv spectra, λ_{max} (0.1 *M* phosphate buffer pH 7.3) 293 mμ (ε 8000); ir (KBr) sharp SCN band 2170 cm^{-1}; mass spectra (70 eV) heaviest peak at *m/e* 224, corresponding to the molecular ion of the free acid.

Upon treatment of 10^{-4} *N* solutions of either **2** or its half salt in 0.1 *M* phosphate buffer pH 7.3 with excess β-mercaptoethanol, **3** was formed instantaneously in 99 and 102% yields, respectively, as determined by its characteristic absorption.[4,5]

5-Mercapto-2-nitrobenzoic Acid (3).—To a solution of 1.00 g (2.5 mmol) of **1** in 50 ml of 0.5 *M* Tris hydrochloride buffer pH 8.0, 5 ml (71 mmol) of β-mercaptoethanol was added. After 5 min the solution was acidified to pH 1.5 by the addition of 6 *N* HCl. By ice cooling the solution for 24 hr, orange crystals were formed which were filtered, washed with diluted HCl, and vacuum-dried over P_2O_5: yield 0.57 g (57%); mp 137–138°; uv λ_{max} (0.1 *M* phosphate buffer containing 0.005 *M* EDTA) 412 mμ (ε 13,660) (lit.[4,5] 13,600); the absorbancy of the solution remained unchanged after addition of either **1** or β-mercaptoethanol, showing that the product was free of traces of either β-mercaptoethanol or **1**, respectively; molecular weight mass spectrum (70 eV) showed the molecular ion peak at *m/e* 199; iodometric titration (in 50% aqueous HOAc) gave a value of 200.1.

Anal. Calcd for $C_7H_5NO_4S$: C, 42.22; H, 2.53; N, 7.03; S, 16.08. Found: C, 42.34; H, 2.45; N, 7.16; S, 15.96.

Reaction of 5-Mercapto-2-nitrobenzoic Acid (3) with Cyanogen Bromide.—To a solution of 40 mg (0.2 mmol) of **3** in 4.5 ml of Tris hydrochloride buffer pH 8.0, 1.0 ml of 3% aqueous solution of CNBr (0.28 mmol) was added dropwise, the initial deep orange color of the thiolate thereby changing to a pale yellow color of the formed disulfide. Ten-μl samples of the mixture were subjected to paper electrophoresis under the above conditions. Two uv-absorbing spots, corresponding to **1** and **2**, were detected. Each spot was cut into thin strips and eluted for 45 min in 5.0 ml of 0.4 *M* β-mercaptoethanol in 0.1 *M* phosphate buffer pH 7.3, thereby forming yellow **3**. The latter was subsequently determined by its absorption at 412 mμ. (By this procedure, the recovery of **3** from chromatographed control samples of pure **1** and **2** was 98–100%.) The results showed that the yields of **1** and **2** obtained by the CNBr reaction were 42 and 58%, respectively.

(9) Tris(hydroxymethyl)aminomethane.

Registry No.—**2**, 30211-77-9; **2** half K salt, 30344-83-3; **3**, 15139-21-6.

Acknowledgment.—The work was supported by Grant No. AM-5098 from the U. S. Public Health Service.

The Stereochemistry of the 2,2′-Methylenedicycloalkanones

GEORGE R. NEWKOME,* R. C. MONTELARO, AND C. J. ADAMS

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

Received January 28, 1971

We recently have been studying potential synthetic routes to C_{20}–C_{26} macrocycles with emphasis on the inclusion of polyketonic functionality. During this initial investigation, we prepared 2,2′-methylenedicyclopentanone (**1**) and -dicyclohexanone (**2**), both of which exist as two separable diastereomers, whose configurations have been tentatively assigned either on the lack of a dipole moment for **1**[1] or a tedious reduction–resolution sequence for **2**.[2] We herein describe a simple procedure for the configurational assignment of these and related δ diketones.

The base-catalyzed condensation of paraformaldehyde with cyclopentanone or cyclohexanone gave *dl*-**1** and *meso*-**1** or *dl*-**2** and *meso*-**2**, respectively.[3] The isomer stability had been previously established, since thermal epimerization of each isomer is negligible at 120°,[2] and each can be easily derivatized without loss of stereochemical integrity.[1]

Upon repetitious recrystallization of **1**, a single pure isomer (mp 71°) can be isolated, along with a lower melting (mp 38°) component. Each isomer was treated with perbenzoic acid in CH_2Cl_2 in the presence of sodium bicarbonate generating (90%) the corresponding lactones. Since this reaction is known to proceed stereospecifically with retention of configuration, the identical stereochemistry of the resultant lactones is thus established.[4]

Without purification, the crude lactones were converted (>80%) to the 2,2-dimethyldioxane dimethyl esters. The 71° melting isomer of **1** was transformed stereospecifically to a *single* substituted dioxane (*dl*-**5**), while the 38° melting component of **1** was shown by glc analysis to be a mixture which was comprised of 39% of *dl*-**5** and 61% of the isomeric dioxane (*meso*-**5**).

(1) J. Colonge, J. Dreux, and H. Delplace, *Bull. Soc. Chim. Fr.*, 1635 (1956).

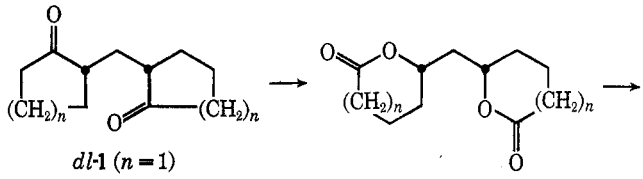
(2) A. Palsky, J. Huet, and J. Dreux, *C. R. Acad. Sci., Ser. C*, **262**, 1543 (1966).

(3) L. Birkofer, S. M. Kim, and H. D. Engles [*Chem. Ber.*, **95**, 1495 (1962)] prepared these diketones *via* the condensation of cyclic ketone-derived morpholine enamines with formaldehyde.

(4) Reveiws: J. B. Lee and B. C. Uff, *Quart. Rev., Chem. Soc.*, **21**, 449 (1967); H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, pp 123–129; P. A. S. Smith in "Molecular Rearrangements," Part 1, P. de Mayo, Ed., Wiley–Interscience, New York, N. Y., 1963, pp 568–591; and C. H. Hassall, *Org. React.*, **9**, 73 (1957).

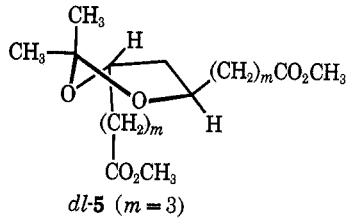
From the 71° melting isomer, the intermediary 5,5′-methylenebis(5-hydroxypentanoic acid lactone) (*dl*-**3**) can be isolated.

Continual recrystallization of **2** also afforded both a single constant melting isomer (mp 60°), which was subjected to the above sequence yielding a *sole* dioxane (*dl*-**6**), as well as an oil, which presumably consisted of a mixture of predominately *meso*-**6** contaminated with

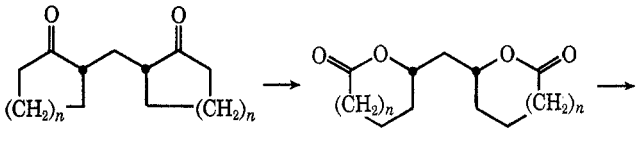


dl-**1** ($n=1$)
dl-**2** ($n=2$)

dl-**3** ($n=1$)
dl-**4** ($n=2$)

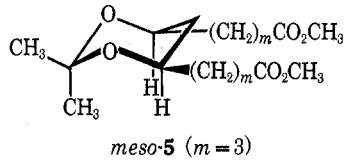


dl-**5** ($m=3$)
dl-**6** ($m=4$)



meso-**1** ($n=1$)
meso-**2** ($n=2$)

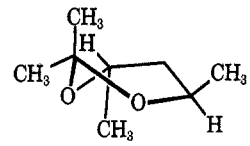
meso-**3** ($n=1$)
meso-**4** ($n=2$)



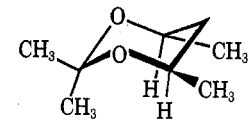
meso-**5** ($m=3$)
meso-**6** ($m=4$)

dl-**6**. The intermediary 6,6′-methylenebis(6-hydroxyhexanoic acid lactone)[5] can be easily isolated from this 60° melting isomer of **2**; thus, its previously unassigned stereochemistry is now established.

The nmr spectra of 2,2-*trans*-4,6-tetramethyldioxane[6,7] (**7**), as well as *dl*-**5** or *dl*-**6**, clearly show the preference for the skew-boat conformation due to the strong 1,3-diaxial compression between the 2- and 4-alkyl groups. The methyl chemical shifts of *dl*-**5** or *dl*-**6** (75 Hz) in CCl_4 are in excellent agreement with the averaged methyl signal of **7** (75.1[6] or 74.1 Hz[7]) in CCl_4. The spectra of *dl*-**5** and *dl*-**6** at −100° also evidenced no appreciable peak broadening of the signals, which is consistent with the presence of pseudorotation of a twist conformation. The nmr spectra of 2,2-*cis*-4,6-tetramethyldioxane (**8**) and *meso*-**5** show that the equilibrium between equatorial and axial 4,6-dialkyl groups lies nearly exclusively in the equatorial conformation; therefore, the 2-methyl groups have distinct chemical shifts [**8**, nmr (CCl_4) 80.6 (axial 2-methyl), 75.6 Hz



7



8

(equatorial 2-methyl);[6] *meso*-**5**, nmr (CCl_4) 81 (axial 2-methyl), 76 Hz (equatorial 2-methyl)].

These nmr data allow us to unequivocally assign the stereochemistry of *dl*-**1** to the 71° melting isomer of **1** and *dl*-**2** to the 60° melting isomer of **2**. Recently, this scheme has been applied to the configurational assignment of compounds found in avocado seeds.[8]

Experimental Section[9]

2,2′-Methylenedicyclopentanones (**1**).—These compounds were prepared according to a previous method.[1] The crude product was distilled [bp 140–150° (3 mm)] affording a semisolid, which was continually recrystallized from petroleum ether (bp 30–60°) giving isomerically pure **1**: mp 71° (lit.[1,3] mp 71°); ir (KBr) 1730 cm^{-1}; nmr (CCl_4) 2.4–1.4 ppm (m). *Anal.* Calcd for $C_{11}H_{16}O_2$: C, 73.29; H, 8.95. Found: C, 73.10; H, 8.92.

The mother liquor from the initial crystallization was concentrated, and upon prolonged standing at −20° the lower melting component was isolated. Several recrystallizations from petroleum ether raised the melting point to 38° (lit.[1,10] mp 38°): ir (KBr) 1740 cm^{-1}; nmr (CCl_4) 2.4–1.4 ppm (m). *Anal.* Calcd for $C_{11}H_{16}O_2$: C, 73.29; H, 8.95. Found: C, 73.07; H, 8.99.

2,2′-Methylenedicyclohexanone. 60° Melting Isomer 2.—The same procedure as above produced isomerically pure **2**: mp 60° (lit. mp 58°,[10,11] 60.5°[12]); ir (KBr) 1712 cm^{-1}. *Anal.* Calcd for $C_{13}H_{20}O_2$: C, 74.95; H, 9.68. Found: C, 74.92; H, 9.50.

Conversion of the 71° Melting Isomer of 1 to *dl*-5.—A solution of 2,2′-methylenedicyclopentanone (**1**, mp 71°, 18 g, 0.1 mol) in dichloromethane (50 ml) was added dropwise to a cold stirred suspension of freshly prepared[13] perbenzoic acid (30.4 g, 0.22 mol) and anhydrous sodium bicarbonate (10 g) in dichloromethane (350 ml). After 20 hr, the solid was filtered and the crude dilactone along with some benzoic acid was obtained upon *in vacuo* concentration.

This mixture was dissolved in 2,2-dimethoxypropane (100 ml) and then saturated with HCl gas. After refluxing for 12 hr, the reaction mixture was added to cold 1% aqueous sodium carbonate (600 ml) and extracted with ether. The organic layer was washed with water and dried over anhydrous calcium sulfate. Removal of the ether gave (>80%) the single[14] dioxane *dl*-**5**: bp 123–127° (0.3 mm); ir (neat) 1725 cm^{-1}; nmr (CCl_4) 1.27 (s, 6 H, $\begin{matrix}O\\O\end{matrix}>C(CH_3)_2$), 3.62 (s, 6 H, CO_2CH_3), 2.28 (dd, J = 6 Hz each, 4 H, $CH_2CO_2CH_3$), and 3.5–3.9 ppm (m, 2 H, CHO); mol wt (mass spectrum), calcd 301.1651 (found 301.166).

A portion (0.3 g) of the crude dilactone was chromatographed on silica gel by elution with 20% ethyl acetate–petroleum ether. The first fraction contained benzoic acid (0.05 g, mp 122°) and subsequent fractions afforded pure 5,5′-methylenebis(5-hydroxy-

(5) P. S. Starcher, S. W. Tinsley, and B. Phillips, U. S. Patent 3,072,680 (1962); *Chem. Abstr.*, **58**, 12427*e* (1963).

(6) K. Pihlaja and P. Äyräs, *Acta Chem. Scand.*, **24**, 531 (1970), and references cited therein.

(7) E. L. Eliel and M. C. Knoebner, *J. Amer. Chem. Soc.*, **90**, 3444 (1968).

(8) Y. Kashman, I. Neeman, and A. Lifshitz, *Tetrahedron*, **26**, 1943 (1970).

(9) Melting points are uncorrected. Elemental analyses were carried out by Mr. R. Seab at Louisiana State University. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrometer. Nmr spectra were obtained on a Varian A-60A spectrometer and measured in parts per million from TMS as the internal reference. Mass spectra were recorded on the Varian M-66 mass spectrometer by Mrs. G. White at Louisiana State University.

(10) J. Colonge, *Bull. Soc. Chim. Fr.*, 250 (1955).

(11) M. N. Tilichenko and V. I. Vysotskii, *Uch. Zap. Yakutsk. Gas. Univ.*, **8**, 27 (1960); *Chem. Abstr.*, **57**, 9678*i* (1962).

(12) M. N. Tilichenko, *Uch. Zap. Saratov. Gos. Univ.*, **75**, 60 (1962); *Chem. Abstr.*, **60**, 4195 (1964).

(13) C. E. Braun, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1947, p 431.

(14) Analytical gas–liquid partition chromatography was performed on a Perkin-Elmer Model 900 instrument equipped with a flame ionization detector and a stainless steel column (12 ft × 0.125 in., 15% AP-L on 80–100 mesh Chromosorb W). Preparative chromatography was carried out on a Perkin-Elmer Model F-21 instrument equipped with a flame ionization detector and a copper column (20 ft × 0.5 in., 15% Carbowax on 60–80 mesh Chromosorb W).

pentanoic acid lactone). Recrystallization from carbon tetrachloride gave analytically pure *dl*-**3**: 0.21 g; mp 95–96°; ir ($CHCl_3$) 1735 cm^{-1}; nmr ($CDCl_3$) 4.90–4.31 (m, methine H) and 2.72–1.5 ppm (m). *Anal.* Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.25; H, 7.62.

Conversion of the 60° Melting Isomer of 2 to *dl*-6.—The crude dilactone was prepared from the 60° melting isomer of **2**, and without subsequent purification it was converted (>80%) *via* the above sequence to a single[14] dioxane *dl*-**6**: bp 129–134° (0.3 mm); ir (neat) 1725 cm^{-1}; nmr (CCl_4) 1.27 (s, 6 H, $\overset{O}{\underset{O}{>}}CMe_2$), 3.65 (s, 6 H, CO_2CH_3), 2.28 (dd, J = 6 Hz each, 4 H, $CH_2CO_2CH_3$), and 3.5–3.9 ppm (m, 2 H, CHO); mol wt (mass spectrum), calcd 329.196 (found 329.194).

The crude intermediary dilactone can be easily purified by chromatography on silica gel by eluting with 25% ethyl acetate–petroleum ether. After the solution of traces of benzoic acid, the 6,6′-methylenebis(6-hydroxyhexanoic acid lactone) was isolated. Recrystallization from petroleum ether gave pure *dl*-**4**, mp 107° (lit.[5] mp 108–109.5°).

Analysis of the 38° Melting Isomer of 1.—The conversion of this 38° melting component of **1** to the dilactone and then to the substituted dioxane **5** followed the above sequence. The glc analysis[14] indicated a mixture of 39% of *dl*-**5** and 61% of the isomeric dioxane *meso*-**5**: ir (neat) 1725 cm^{-1}; nmr (CCl_4) 1.29 (s, 3 H, $\overset{O}{\underset{O}{>}}CCH_{3\ equatorial}$), 1.38 (s, 3 H, $\overset{O}{\underset{O}{>}}CCH_{3\ axial}$), 3.61 (s, 6 H, CO_2CH_3), 2.25 (dd, J = 6 Hz each, 4 H, $CH_2CO_2CH_3$), 3.5–4.0 ppm (m, 2 H, CHO); mol wt (mass spectrum), calcd 301.1651 (found 301.165).

Registry No.—*dl*-**1**, 30469-91-1; *meso*-**1**, 30469-92-2; *dl*-**2**, 30469-93-3; *dl*-**3**, 30469-94-4; *dl*-**5**, 30469-95-5; *meso*-**5**, 30469-96-6; *dl*-**6**, 30469-97-7.

Acknowledgment.—We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research, the Research Corporation, and the National Science Foundation for the Science Faculty Fellowship (1969–1970) for research (C. J. A.).

Stereospecific Reduction of Steroidal 4-Ene-3β-ols with Hydrazine

YUSUF J. ABUL-HAJJ

College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455

Received March 9, 1971

In connection with a related problem under investigation in our laboratory, it became desirable to prepare 5α-androstane-3β,17β-diol labeled stereospecifically with isotopic hydrogen in the 4α position. We now wish to report a convenient method for the reduction of the 4,5 double bond to the 5α isomer.

The reduction of olefins with hydrazine has been shown to occur by a stereospecific cis addition of hydrogen.[1] Thus, reduction of androst-4-ene-3β,17β-diol with hydrazine gave 5α-androstane-3β,17β-diol in yields ranging from 85 to 95% with no detectable amounts of the 5β isomer.

Heretofore, heterogeneous catalytic hydrogenation of 4-ene-3β-ol using various catalysts and conditions[2] has been the preferred method for the reduction of the 4,5 double bond. This method not only results in a mixture of the 5α and 5β isomers but also involves isotope exchange at an allylic position when deuterium or tritium gas is employed.[3–5]

The use of hydrazine has the distinct advantage of convenience and speed in the preparation of the 5α isomer and offers a useful alternative to the catalytic hydrogenation that gives a mixture of the 5α and 5β isomers which often is tedious and time consuming to separate. The reaction gives also exclusively the 5α isomer when cholest-4-ene-3β-ol and pregn-4-ene-3β,20β-diol are used.

Experimental Section

To a solution of androst-4-ene-3β,17β-diol (612 mg)[6] in methanol (15 ml) was added hydrazine hydrate (7 g)[7] and cupric acetate (1.9 mg). The reaction mixture was stirred at room temperature for 7 hr[8] in an atmosphere of dry air, poured into dilute HCl solution, and extracted with ether. The combined ether extracts were washed with water, allowed to stand for 10 min over sodium sulfate, filtered, and evaporated to dryness. The crystalline residue weighed 550 mg (90%), mp 160–163°. Recrystallization from ethanol gave 5α-androstane-3β,17β-diol melting at 163–164° (mixture melting point, ir).

Registry No.—Hydrazine, 302-01-2; androst-4-ene-3β,17β-diol, 1156-92-9.

(1) E. J. Corey, D. J. Pasto, and W. L. Mock, *J. Amer. Chem. Soc.*, **83**, 2957 (1961).
(2) C. W. Shoppee, B. D. Agashae, and G. H. R. Summers, *J. Chem. Soc.*, 3107 (1957).
(3) D. K. Fukushima and T. F. Gallagher, *J. Amer. Chem. Soc.*, **77**, 139 (1955).
(4) H. J. Brodie, S. Baba, M. Gut, and M. Hyano, *Steroids*, **6**, 569 (1965).
(5) Y. J. Abul-Hajj, *J. Label Compounds*, **7**, 33 (1971).
(6) Prepared by sodium borohydride reduction of testosterone in isopropyl alcohol.
(7) Supplier: K & K Laboratories, Inc., Plainview, N. Y.
(8) In more recent experiments the stirring time was reduced to 3 hr with equally good results.