Aromatic Carboxylic Acids as Latent Aromatic Ketones. New Regioselective Synthesis of Aromatic Ketones

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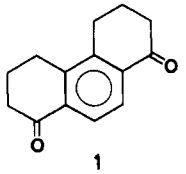
Received June 1, 1987

A new, general synthetic strategy for the regioselective synthesis of aromatic ketones of the 1-tetralone type is described. The synthetic methodology employs fused aromatic carboxylic acids as latent aromatic ketones via a simple reduction–oxidation sequence and is illustrated by the facile, high-yield conversion of 1,8- and 4,5-phenanthrenedicarboxylic acids into the angularly annelated 1,8-diketo-2,3,4,5,6,7- and 4,5-diketo-1,2,3,6,7,8-hexahydrophenanthrene, respectively. Exclusive and complete reduction of the outside rings is done with lithium in ammonia followed by catalytic reduction. Oxidative decarboxylation of the resulting benzylic octahydro diacids with lead tetraacetate, followed by deacetylation and Jones oxidation, completes the functional group transformation. Application of this methodology to 1,5- and 1,8-anthracenedicarboxylic acids affords the isomeric linearly annelated diketones in high yield; these substrates require an additional oxidation step to correct for the reduction of the reactive middle ring in the lithium–ammonia reaction step.

Aromatic ketones play a crucial role in much of the chemistry of fused polycyclic systems where they are often the first and only entry point via the classical Friedel–Crafts acylation.[1] It is well-known from studies on ketones of the 1-tetralone type that such cycloacylation reactions provide only limited control over the regioselectivity of the introduction of the keto group and lead to isomeric products resulting from linear and angular annelation.[1a] Synthetic alternatives to the Friedel–Crafts reaction for the synthesis of fused aromatic ketones are very limited; oxidation of partially hydrogenated aromatic hydrocarbons at benzylic carbon–hydrogen bonds may be used,[2,3] but suffers from a similar lack of regioselectivity. We were confronted with these limitations of the traditional methodologies when we considered their possible use in an antithetic analysis of a deceptively simple series of isomeric ketones **1**–**4**, which were needed for our studies



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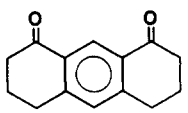

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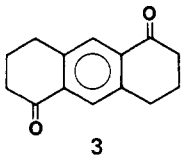

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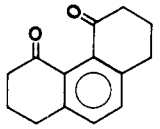

4

on the regioselective annelation of heterocyclic ring systems.[4] For example, attempted double cycloacylations leading to **3** were not successful,[5] chromium trioxide oxidation of *sym*-octahydroanthracene and *sym*-octahydrophenanthrene resulted in random benzylic attack and gave mixtures of isomeric diketones.[2b] We describe herein a new, general strategy for the synthesis of aromatic ketones of the 1-tetralone type and illustrate the facile, regioselective introduction of such keto groups in anthracene and phenanthrene skeletons.

Results and Discussion

We start from readily accessible[6] fused aromatic carboxylic acids and employ the carboxylic acid moiety as a latent ketone functional group via a series of individually simple reduction and oxidation steps, which, when combined, result in a powerful and general method for the regioselective introduction of the keto group in polycyclic systems. The carboxylic acid group was chosen to direct and control the reduction of aromatic fused systems in the carboxylic acid substituted rings via a metal–ammonia reduction step, and then to serve as the future site for the keto group by its facile oxidative removal from the benzylic position created during a second, catalytic reduction step.

Thus, lithium–ammonia reduction of 1,8-phenanthrenedicarboxylic acid[7] (**5**) in the presence of water as added proton donor resulted in the exclusive reduction of the outer carboxylic acid substituted rings of the tricyclic system to give the tetrahydro derivative **6** in nearly quantitative yield[8] (Scheme I). This unusual regiochemistry for the reduction of a phenanthrene derivative was clearly evident from the ^{1}H NMR spectrum of the dimethyl ester, obtained from **6** and diazomethane, which showed only a single absorption in the aromatic region of the spectrum (δ 7.1, s, C-9, C-10) and a complex multiplet for the alkene protons (δ 5.79–6.22) with the proper proton counts; the unsubstituted benzylic protons at C4 and C5 were found at δ 3.26 (m, 4) and the COOH-substituted benzylic protons H1 and H8 at 4.44 (dd, 2), confirming the positions of the two double bonds. The mass spectrum (M^+ at m/e 298) confirmed its tetrahydro oxidation stage. The preferential reduction of **5** in the outer rings instead

(1) (a) Clar, E. *Polycyclic Hydrocarbons*; Academic: New York, 1964; Vol. 1 and 2. (b) For a recent modification of the classical procedure, see: Hulin, B.; Koreeda, M. *J. Org. Chem.* **1984**, *49*, 207.

(2) (a) For benzylic oxidation with chromium(VI) reagents, see, for example: Burnham, J. W.; Duncan, W. P.; Eisenbraun, E. J.; Keen, G. W.; Hamming, M. C. *J. Org. Chem.* **1974**, *39*, 1416 and references cited therein. (b) Eisenbraun, E. J.; Premasagar, V.; Holba, A. G.; Keen, G. W. *Prep. Am. Chem. Div. Pet. Chem.* **1980**, *25*, 508.

(3) For benzylic oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone, see: Lee, H.; Harvey R. G. *J. Org. Chem.* **1983**, *48*, 749 and references cited therein.

(4) (a) Majewicz, T. G.; Caluwe, P. *J. Org. Chem.* **1979**, *44*, 531. (b) Caluwe, P. *Tetrahedron* **1980**, *36*, 2359.

(5) (a) Ahmad, M. S.; Baddeley, G. *J. Chem. Soc.* **1961**, 2520. (b) Rahman, A.-U.; Vazquez, A. T.; Khan, A. A. *J. Org. Chem.* **1963**, *28*, 3571.

(6) Many aromatic carboxylic acids are easily obtained. The syntheses of the individual acids used in this paper are indicative of some of the synthetic approaches to such compounds.

(7) Rubin, M. B.; Welner, S. *J. Org. Chem.* **1980**, *45*, 1847.

(8) This product was obtained as a mixture of diastereomers as evidenced by ^{1}H NMR spectroscopy of the crude reaction product. These cis–trans mixtures could not be readily separated, and this was therefore not further pursued. Their separation was not important for our purpose since the carbon atoms involved return to trigonal carbon in the last reaction step of our synthetic sequence.

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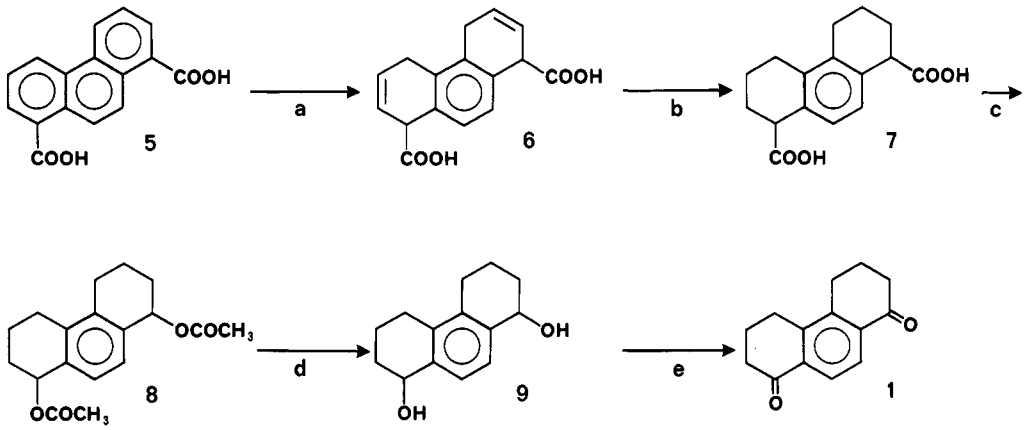
Scheme I[a]



[a] (a) $Li/NH_3/H_2O$; (b) H_2/Pd; (c) $Pb(OCOCH_3)_4$; (d) KOH or $LiAlH_4$; (e) CrO_3.

of the usual reaction at the C9,C10-position of the phenanthrene middle ring[9] shows the strong activating effect of the carboxylic acid group. Similar, although less striking, activation of a COOH-substituted ring occurs in the reduction of naphthoic acids.[10] We note that the central tetrasubstituted ring of **6** is inert to further reduction under our reaction conditions. The choice of water rather than the traditionally used ethyl alcohol as added proton source was made in order to prevent isomerization of the double bonds and was based on a detailed study of its use in the reduction of a large number of benzoic acids.[11] The exceptionally clean reduction of diacid **5**, as well as other polycondensed aromatic carboxylic acids described in this paper, clearly shows the benefits of this synthetic procedure.[12]

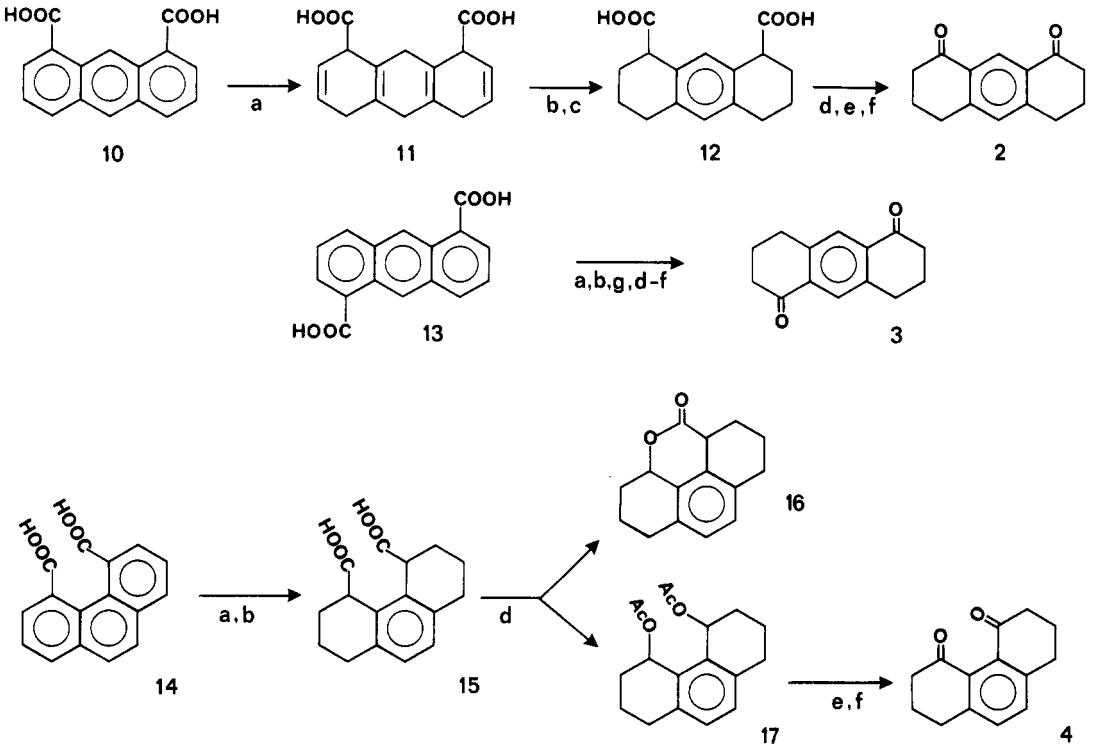
Completion of the reductive part of our synthetic sequence was carried out by catalytic hydrogenation of the double bonds in **6** with palladium on carbon to give octahydro diacid **7** (95% yield).[8] This facile reduction of the double bonds of **6** further confirms the regiochemistry of the initial metal–ammonia reduction step. To minimize undesirable dehydrogenation, this reduction was best done on crude **6** immediately after its isolation and with catalyst pretreated with hydrogen.

The stage was now set for the oxidative removal of the carboxylic acid moieties from their benzylic positions. For this we chose lead tetraacetate since its use for the oxidative decarboxylation from activated positions is well documented.[13] Thus, treatment of **7** with lead tetraacetate under standard conditions (benzene–acetic acid–potassium acetate–catalytic amount of cupric acetate, reflux for 2 h) resulted in clean decarboxylation of **7** to give the diacetate **8**[8] (93% yield), easily identified by the benzylic ester protons centered at δ 5.97 and the acetate protons at δ 2.09 in its ^1H NMR spectrum. This cis–trans mixture of diacetates was used for the deacetylation step. Standard hydrolysis (KOH in methanol) or lithium aluminum hydride[14] reduction of the acetate groups gave diol **9**[8] (90% yield), which was oxidized, without further purification, with Jones reagent to the ketone **1** (mp 167–168 °C), obtained in 82% yield after recrystallization from diethyl ether. Its structure was confirmed by the ^1H NMR spectrum, which showed a single, sharp absorption in the aromatic portion of the spectrum (δ 8.0, s, 2); the aliphatic protons displayed the characteristic pattern for fused six-membered-ring ketones and were found at δ 2.94 (t, 4), 2.69 (t, 4), and 2.22 (m, 4). The proton-decoupled ^{13}C NMR spectrum showed the expected seven-line spectrum with the CO resonance at 197.7 ppm (lit.[2b] 198.6 ppm); its mass spectrum gave a molecular ion at m/e 214.

The successful conversion of **5** to **1** suggested a similar strategy for the synthesis of linearly annelated ketones starting from 1,5- and 1,8-anthracenedicarboxylic acids.[15] Reduction of the latter as described above resulted in the reduction of the middle ring as well to give the hexahydro diacid **11**[8] in 85% yield (Scheme II). The extent of reduction was evident from the mass spectrum (molecular ion at m/e 272) and from the ^1H NMR spectrum, which showed no absorptions for aromatic protons and displayed the characteristic multiplet for the alkene protons, identical with the one observed earlier for **6**; the allylic methine and methylene protons were observed, with the correct proton count, as unresolved peaks centered at δ 3.45 and 2.52, respectively. The reduction of the middle ring together with the outside rings of diacid **10** was not unexpected, since the high reactivity of the anthracene middle ring in dissolving metal reductions is well documented.[9] Catalytic reduction was carried out as before on the crude diacid **11** and resulted in the clean selective reduction of the disubstituted double bonds to the symmetrical decahydro diacid in 95% yield. Its ^1H NMR spectrum showed only broad absorptions in the aliphatic part of the spectrum; they were readily assigned to the allylic and cycloaliphatic protons. Rearomatization of the middle ring was conveniently accomplished by catalytic dehydrogenation with Pd–C in refluxing xylene to give **12**[8] in 70% yield after recrystallization from toluene (mp 211–224 °C). Its structure was consistent with the ^1H NMR spectra of the individual separated diastereomeric esters,[16] which each showed two singlets of correct proton count in the aromatic part of the spectrum at δ 6.92, 6.85 and at δ 7.03, 6.85, assigned to the respective H9 and H10 protons. Oxidative

(9) Harvey, R. G. *Synthesis* **1970**, 161 and references cited therein.
(10) Rabideau, P. W.; Burkholder, E. G.; Yates, M. J. *Synth. Commun.* **1980**, *10*, 627.
(11) van Bekkum, H.; van den Bosch, C. B.; van Minnen-Pathuis, G.; de Mos, J. C.; van Wijk, A. M. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 137.
(12) The use of water in the sodium–ammonia reduction of carboxylic acid esters has also been reported: Rabideau, P. W.; Wetzel, D. M.; Young, D. M. *J. Org. Chem.* **1984**, *49*, 1544.
(13) For a review of the oxidative decarboxylation of carboxylic acids by lead tetraacetate, see: Sheldon, R. A.; Kochi, J. K. *Org. React. (N.Y.)* **1972**, *19*, 279.
(14) Deacetylation by lithium aluminum hydride reduction gave a diol of somewhat higher purity than the product obtained from KOH hydrolysis.
(15) The 1,5- and 1,8-anthracenedicarboxylic acids were obtained from the corresponding dichloro-9,10-anthraquinones; see, for example: Golden, R.; Stock, L. M. *J. Am. Chem. Soc.* **1972**, *94*, 3080.
(16) The cis–trans mixture of isomeric methyl esters could be separated into the individual isomers by repeated analytical HPLC chromatography (silica gel/hexane–ethyl acetate).

Scheme II[a]



[a] $Li/NH_3/H_2O$; (b) H_2/Pd; (c) Pd/C, xylene; (d) $Pb(OAc)_4$; (e) KOH; (f) CrO_3; (g) DDQ.

removal of the carboxylic acid moieties of **12** with lead tetraacetate gave the expected diacetate[8] (95% yield). Deacetylation followed by Jones oxidation of the resulting diols[8] gave ketone **2** in 81% yield (mp 175–176 °C) after recrystallization from diethyl ether. Its structure is consistent with the ^1H NMR spectrum, which showed two widely separated singlets with the proper proton count at δ 8.68 and 7.15, assigned to H9 and H10, respectively; the aliphatic protons showed a pattern nearly identical with that of **1** with absorptions at δ 2.98 (t, 4), 2.67 (t, 4), and 2.16 (m, 4). The ^{13}C proton-decoupled NMR spectrum displayed the expected eight-line spectrum with the carbonyl resonance at 196.8 ppm (lit.[2b] 196.6 ppm). The mass spectrum gave a molecular ion at *m/e* 214.

Application of our synthetic strategy to the highly insoluble 1,5-anthracenedicarboxylic acid (**13**) very easily produced diketone **3** by a nearly identical procedure (Scheme II). The dehydrogenation step with Pd–C in xylene was unsatisfactory and was carried out instead with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in hot dioxane to give the symmetrical 1,2,3,4,5,6,7,8-octahydroanthracene-1,5-dicarboxylic acid[8] in 80% yield after recrystallization from acetone. Oxidative decarboxylation gave the expected diacetate (88%), which was converted into the desired diketone **3** in 84% yield after recrystallization from ethyl acetate (mp 160 °C). Its structure was confirmed by the ^1H NMR spectrum, which gave a single peak for the aromatic protons at δ 7.93 and displayed the characteristic pattern for the cycloaliphatic protons, nearly identical with the ones observed for ketones **1** and **2**, at δ 3.00 (t, 4), 2.70 (t, 4), and 2.17 (m, 4). The proton-decoupled ^{13}C NMR spectrum showed the anticipated seven-line spectrum, with the CO resonance at 197.9 ppm (lit.[2b] 197.7 ppm); mass spectrum M^+ at *m/e* 214.

A more demanding situation is at hand in the application of our procedure to the synthesis of the angularly annelated ketone **4** since the oxidative part of our reduction–oxidation sequence needs to be carried out on the highly crowded "bay" side of the phenanthrene skeleton, where the very strong, well-documented[17] tendency for intramolecular reactions could prevent the correct functionalization of the 4,5-bay carbon atoms.

Lithium–ammonia reduction of 4,5-phenanthrenedicarboxylic acid (**14**), readily accessible from pyrene by ozonolysis,[18] followed by catalytic reduction (Pd–C) gave the desired octahydro diacid **15**[8] in 90% yield after recrystallization from ethanol (Scheme II). The regiochemistry of the reduction steps is evident from the single sharp peak in the aromatic part of the ^1H NMR spectrum at δ 7.00 (s, 2); the COOH-substituted benzylic protons were found centered at δ 3.91 (m, 2) and the unsubstituted benzylic protons at δ 2.80 (m, 4). This finding is identical with the results obtained earlier in the reduction of 1,8-phenanthrenedicarboxylic acid and confirms the higher reactivity of the COOH-substituted outside rings toward lithium–ammonia reductions. Oxidative decarboxylation of **15** under reaction conditions similar[19] to those employed earlier for the decarboxylation of **7** resulted in the formation of a 1:1 mixture of the diastereomeric acetates **17** and lactone **16**. The structure of **16** was consistent with spectroscopic and chemical data (see below). Its ^1H NMR spectrum showed the two methine protons, H4 and H5, as widely separated triplets with the proper proton counts at δ 3.52 and 5.31, respectively; the benzyl protons were found at δ 2.75 (m, 4) and the aromatic protons H9 and H10 as a distorted doublet of doublets at δ 7.03; the spectrum did not display any peaks attributable to acetate groups. The mass spectrum gave a pronounced molecular ion at *m/e* 228. Formation of lactone **16** is not unexpected

(17) See, for example: Barton, D. H. R.; Sammes, P. G.; Weingarten, G. G. *J. Chem. Soc.* C **1971**, 729.
(18) Medenwald, H. *Chem. Ber.* **1953**, *86*, 287.
(19) Lead tetraacetate should be added to an ice-cold solution of the other reactants and then allowed to come to room temperature. The reaction mixture was then refluxed for 2 h. For reasons that are not clearly understood, the ratio of acetates:lactone changes in favor of intramolecular lactone formation when lead tetraacetate is added to a warm solution of the other reactants.

and can be seen as the result of intramolecular capture of the carbocation, formed during the decarboxylation step of the first carboxylic acid moiety, by the remaining carboxylate unit across the bay region of the phenanthrene nucleus. The diacetates **17**, easily recognized in the ^1H NMR spectrum (acetate protons at δ 2.09 and 2.02; benzylic methines at δ 6.11 and 5.89), could not be separated completely from lactone **16**, and the crude reaction mixture was therefore directly hydrolyzed (KOH in aqueous methanol) to the desired diol[8] and the ring-opened lactone, which were easily separated by base extraction. Oxidation of the diol with Jones reagent gave diketone **4** (mp 130 °C (lit.[5a,20] mp 132–133 °C) in 90% yield after recrystallization from hexane. Its structure is consistent with its ^1H NMR spectrum (C_6D_6), which showed a sharp singlet with the correct proton count for the aromatic protons at δ 6.67; the aliphatic protons displayed the characteristic absorptions for such ketones at δ 2.50 (t, 4), 2.21 (t, 4), and 1.55 (m, 4) in a pattern very similar to that observed for the isomeric ketones discussed above. The proton-decoupled ^{13}C NMR spectrum displayed the anticipated seven-line spectrum with the carbonyl absorption at 198.9 ppm; the mass spectrum gave the molecular ion at m/e 214.

Conclusion

The transformation of fused aromatic carboxylic acids into aromatic ketones described in this paper for the synthesis of diketones **1–4** documents a new and valuable synthetic strategy for the regioselective incorporation of the carbonyl group in angular as well as linear polycyclic systems. Our synthetic methodology provides a stereoselective alternative to the classical Friedel–Crafts cycloacylation and outlines a unique solution for the selective functionalization of polycyclic systems. The successful conversion of the highly insoluble 1,5-anthracenedicarboxylic acid into ketone **3** shows that low solubility, a problem often encountered in polycyclic systems, does not interfere with the functional group transformations. The correct functionalization of the bay side of the phenanthrene nucleus in **4** demonstrates its successful application even in a sterically unusually demanding environment. In practice, our synthetic sequence of reduction and oxidation steps is easily carried out, and the process may be scaled up readily.

The use of fused aromatic carboxylic acids as latent 1-tetralone moieties described here is in some respects reminiscent of the use of alkoxy-substituted aromatic compounds as latent cyclohexenone units.[21] We note that 1-alkoxy-substituted aromatic systems require drastic metal–ammonia reduction conditions and very easily lose the alkoxy group upon dissolving metal reductions,[21,22] and hence are not very suitable for a general synthesis of aromatic ketones analogous to 1-tetralone.

Experimental Section

General. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian XL-100 instrument in $CDCl_3$ solutions unless indicated otherwise. NMR spectra of the various carboxylic acids were obtained on their methyl esters, made from the acids and diazomethane. Chemical shifts are reported in parts per million relative to internal Me_4Si. Mass spectra were obtained at 70 eV on a Finnegan Model 4000. Uncorrected melting points were determined on a Laboratory Device Mel-Temp apparatus.

Lithium–Ammonia Reduction of Aromatic Carboxylic Acids. General Procedure. Reductions were carried out under a nitrogen atmosphere. Lithium wire (120 mg, 17 mmol) was added in one piece to a vigorously stirred suspension of the aromatic carboxylic acid (1.8 mmol) in 50 mL of distilled liquid ammonia and 2 mL of water. The lithium metal was consumed within about 10 min. The ammonia was left to evaporate overnight under a nitrogen atmosphere. The residue was dissolved in a minimum amount of distilled water, filtered if necessary, cooled in ice, and acidified very cautiously with ice-cold 1 N HCl. The resulting precipitate was collected by filtration. Attempted purification by crystallization invariably led to products that by NMR analysis were less pure than the crude reduction products. Reported yields are therefore based on the examination of the ^1H NMR spectra of the methyl esters obtained from the reduced carboxylic acids and diazomethane. The crude reaction product was best used without purification and without delay in the next catalytic hydrogenation step. A 10-fold scale-up of the metal–ammonia reduction reaction gave identical results.

Catalytic Hydrogenation of Partially Reduced Aromatic Carboxylic Acids. General Procedure. The crude product obtained from the above reduction was hydrogenated at atmospheric pressure in the presence of 0.1 g of 5% Pd–C, pretreated with hydrogen, in 95% ethyl alcohol. The catalyst was filtered off, and the residue obtained after removal of ethyl alcohol was recrystallized from an appropriate solvent.

Oxidative Decarboxylation of Partially Reduced Aromatic Carboxylic Acids with Lead Tetraacetate. General Procedure. To a stirred mixture of the octahydro aromatic dicarboxylic acid (2 g, 7 mmol), anhydrous potassium acetate (8 g), and cupric acetate (0.05 g) in 200 mL of anhydrous benzene and 200 mL of glacial acetic acid was added lead tetraacetate (7 g, 16 mmol). (See footnote 19 for the decarboxylation of octahydrophenanthrene-4,5-dicarboxylic acid (**15**).) The mixture was then refluxed for 2 h under a nitrogen atmosphere. The excess lead tetraacetate was destroyed by the addition of a few drops of ethylene glycol. The solvents were removed on a rotary evaporator, and water was added to the residue and the mixture extracted with methylene chloride. The methylene chloride extracts were washed with sodium bicarbonate and water and then dried ($MgSO_4$). The solvent was removed on a rotary evaporator to give the products from decarboxylation.

Deacetylation of Diacetates with Lithium Aluminum Hydride. General Procedure. The benzylic diacetate (2.0 g, 6.6 mmol) was added with stirring to a suspension of lithium aluminum hydride (0.364 g, 9.6 mmol) in anhydrous diethyl ether (200 mL). The mixture was stirred at room temperature for 3 h and then quenched by successive additions of water (0.4 mL), 15% sodium hydroxide (0.4 mL), and water (1.2 mL). The mixture was filtered and the precipitate extracted with tetrahydrofuran. The combined solvents were evaporated on a rotary evaporator to give the diol, which was used as received in the next oxidation step.

Deacetylation of Diacetates with Potassium Hydroxide. General Procedure. The diacetate was refluxed for 2 h in 5% methanolic potassium hydroxide. The mixture was poured into 200 mL of water and extracted with methylene chloride; the extracts were dried (sodium sulfate) and evaporated on a rotary evaporator to give the diol, which was used as received in the next oxidation step.

Oxidation of Benzylic Diols to Aromatic Diketones. General Procedure. Jones reagent (2.3 mL) was added to a solution of the diol (1.25 g) in acetone (100 mL). The reaction mixture was stirred at room temperature for 1 h and filtered and the precipitate extracted with acetone. The combined extracts were dried, and the solvent was removed on a rotary evaporator to give the ketone, recrystallized from an appropriate solvent (see text).

1,2,3,4,5,6,7,8-Octahydroanthracene-1,8-dicarboxylic Acid (12). A mixture of 1,2,3,4,5,6,7,8,9,10-decahydroanthracene-1,8-dicarboxylic acid (1.0 g) and 5% palladium on carbon (0.3 g) in 200 mL of xylene was refluxed vigorously for 5 h while nitrogen was passed through the reaction mixture. The hot mixture was filtered, concentrated on a rotary evaporator, and allowed to

(20) The diketone of mp 132–133 °C obtained in very low yield from successive cycloacylations on *p*-phenylenedibutyric acid[5a] is thus the expected angularly annelated diketone **4** rather than the linearly annelated **3** (mp 160 °C).

(21) (a) Lednicer, D. *Adv. Org. Chem.* **1972**, *8*, 179. (b) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: Menlo Park, 1972; Chapter 3.

(22) Caluwe, P.; Shyamasundar, N. *Tetrahedron Lett.* **1980**, *21*, 4799.

crystallize to give a mixture of diastereomeric **12** (mp 211–224 °C dec) in 75% yield.

1,2,3,4,5,6,7,8-Octahydroanthracene-1,5-dicarboxylic Acid. To a solution of 1,2,3,4,5,6,7,8,9,10-decahydroanthracene-1,5-dicarboxylic acid (1.0 g, 3.6 mmol) in anhydrous dioxane (200 mL) was added 2,3-dichloro-5,6-dicyanobenzoquinone (0.9 g, 3.9 mmol). The mixture was refluxed for 2 h, cooled, and filtered. The filtrate was rotary evaporated to give the diastereomeric symmetrical octahydro diacids (mp 220–230 °C dec) in 80% yield after recrystallization from acetone.

Acknowledgment. We thank Marc Rosoff for his help on the "bay side" of phenanthrene.

Registry No. **1**, 82817-89-8; **2**, 82817-90-1; **3**, 82817-91-2; **4**, 110028-98-3; **5**, 59795-49-2; **6**, 113162-64-4; *cis*-**7**, 113162-50-8; *trans*-**7**, 113162-51-9; *cis*-**8**, 113162-65-5; *trans*-**8**, 113162-66-6; *cis*-**9**, 113162-58-6; *trans*-**9**, 113162-59-7; **10**, 38378-77-7; *cis*-**11**, 113162-67-7; *trans*-**11**, 113162-68-8; *cis*-**12**, 113162-52-0; *trans*-**12**, 113162-53-1; **13**, 41694-83-1; **14**, 5462-82-8; *cis*-**15**, 113162-54-2; *trans*-**15**, 113162-55-3; **16**, 113162-69-9; *cis*-**17**, 113162-70-2; *trans*-**17**, 113162-71-3; 1,4,4a,5,8,8a,9,9a,10,10a-decahydro-1,8-anthracenedicarboxylic acid, 113162-72-4; *cis*-1,2,3,4,5,6,7,8-octahydro-1,8-bis[(1-oxoethyl)oxy]anthracene, 113162-73-5; *trans*-1,2,3,4,5,6,7,8-octahydro-1,8-bis[(1-oxoethyl)oxy]anthracene, 113162-74-6; *cis*-1,2,3,4,5,6,7,8-octahydro-1,8-anthracenediol, 113162-60-0; *trans*-1,2,3,4,5,6,7,8-octahydro-1,8-anthracenediol, 113162-61-1; 1,2,3,4,5,6,7,8,9,10-decahydroanthracene-1,5-dicarboxylic acid, 113162-75-7; *cis*-1,2,3,4,5,6,7,8-octahydroanthracene-1,5-dicarboxylic acid, 113162-56-4; *trans*-1,2,3,4,5,6,7,8-octahydroanthracene-1,5-dicarboxylic acid, 113162-57-5; 1,2,3,4,5,6,7,8-octahydro-1,5-bis[(1-oxoethyl)oxy]-anthracene, 113162-76-8; *cis*-1,2,3,4,5,6,7,8-octahydro-4,5-phenanthrenediol, 113162-62-2; *trans*-1,2,3,4,5,6,7,8-octahydro-4,5-phenanthrenediol, 113162-63-3; 5-hydroxy-1,2,3,4,5,6,7,8-octahydro-4-phenanthrenecarboxylic acid, 113162-77-9.

Potential Inhibitors of Vitamin D Metabolism: An Oxa Analogue of Vitamin D[1]

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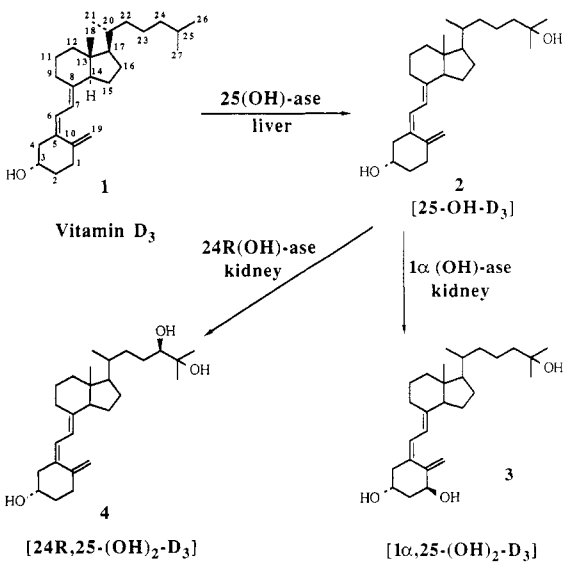
Received November 29, 1987

Inhibitors of the enzyme which is responsible for hydroxylation of 25-hydroxyvitamin D_3 (**2**) to the biologically active form 1α,25-dihydroxyvitamin D_3 (**3**) would serve as useful biochemical research tools. The syntheses of 25-hydroxy-3-deoxy-2-oxavitamin D_3 (**5**), a potential inhibitor of 25-hydroxyvitamin D_3 1α-hydroxylase, and the novel seco-A ring vitamin 2-nor-1,3-seco-1,25-dihydroxyvitamin D_3 (**8**) are described. The CD ring ketone **12**, readily prepared via an improved synthetic sequence, was converted to the enol triflate **10**. Coupling of **10** with enyne lactone **27** afforded dienyne lactone **26**. Hydrogenation of **26** produced tetraene **35**, which was oxymercurated–demercurated and then reduced with diisobutylaluminum hydride (DIBAL) to give the novel seco-vitamin **8**. Alternatively, treatment of **35** with DIBAL afforded diol **37**. Cyclodehydration of **37** was achieved by treatment with *n*-BuLi and tosyl chloride to afford **40** and **41**, which after oxymercuration–demercuration gave the desired target molecule **5** and its previtamin form **42**. Vitamin **40** and previtamin **41** (as well as **5** and **42**) are readily interconverted at room temperature via a remarkably facile [1,7]-sigmatropic hydrogen shift. The ratio of vitamin to previtamin for the oxavitamins was determined to be 56 to 44. This is in marked contrast to the behavior of the parent vitamin D_3 system, which exists primarily in the vitamin D rather than the previtamin D form.

Introduction

The principal pathway of vitamin D metabolism (Scheme I) entails three hydroxylations of primary significance.[2,3] The first step involves hydroxylation at the C_{25} position of vitamin D_3 (**1**, D_3) in the liver[4] and the second involves competitive hydroxylation at C_1 and C_{24} of 25-hydroxyvitamin D_3 (**2**, 25-OH-D_3) in the kidney[5] to

Scheme I



(1) This is Paper 34 in the series, Studies of Vitamin D (Calciferol) and Its Analogues. For Paper 33, see: Okamura, W. H.; Hoeger, C. A.; Miller, K. J.; Reischl, W. *J. Am. Chem. Soc.* **1988**, *110*, 973. This article was taken in part from the Ph.D. thesis submitted to the University of California, Riverside, by S. A. Barrack, 1987.

(2) For reviews of the chemistry and biochemistry of Vitamin D, see: (a) Norman, A. W. *Vitamin D the Calcium Homeostatic Hormone*; Academic: New York, 1979. (b) DeLuca, H. F.; Paaren, H. E.; Schnoes, H. K. *Top. Curr. Chem.* **1979**, *83*, 1. (c) Georghiou, P. E. *Chem. Soc. Rev.* **1977**, *6*, 83. (d) Fieser, L. F.; Fieser, M. *Steroids*; Reinhold: New York, 1959. (e) Pardo, R.; Santelli, M. *Bull. Chim. Soc. Fr.* **1985**, 98.

(3) For previous studies of inhibitors of vitamin D_3 25-hydroxylase, see: (a) Johnson, R. L.; Okamura, W. H.; Norman, A. W. *Biochem. Biophys. Res. Commun.* **1975**, *67*, 797. (b) Norman, A. W.; Johnson, R. L.; Okamura, W. H. *J. Biol. Chem.* **1979**, *254*, 11450. (c) Onisko, B. L.; Schnoes, H. K.; DeLuca, H. F. *Tetrahedron Lett.* **1977**, 1107. (d) Onisko, B. L.; Schnoes, H. K.; DeLuca, H. F. *Vitamin D, Basic Research and Its Clinical Application*; Norman, A. W., Shafer, K., Herrath, D. v., Grigolet, H.-G., Coburn, J. W., DeLuca, H. F., Mawer, E. B., Suda, T., Eds.; Walter de Gruyter: Berlin, 1979; p 77. Inhibitors of the 25-OH-D_3-1α-hydroxylase are unknown.

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