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(30) Both routes are reasonable for the reaction of an α-phenyl substituted system in a low dielectric solvent, but in the absence of kinetic data the nature of the transition state in the ionization is unknown.
(31) While the same products are formed from **3-Br** and **4-Br** in pivalic acid, this cannot be used for deducing the nature of the intermediate, since the **3-Br** $\rightleftharpoons$ **4-Br** isomerization is much faster than the solvolysis reaction.
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Formation of Trianions of 2,4,6-Triketones. Synthesis of 3,5,7-Triketo Acids Using Lithium Diisopropylamide

Thomas M. Harris,* George P. Murphy, and Albert J. Poje

Contribution from the Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37235. *Received June 3, 1976*

Abstract: Ionization of the methyl group of 1-phenyl-1,3-butanedione (**1**) and of 1-phenyl-1,3,5-hexanetrione (**2**) by KNH_2, $NaNH_2$, and $LiNH_2$ in liquid NH_3 has been studied by measurement of deuterium loss from the methyl-deuterated species. KNH_2 and $NaNH_2$ brought about rapid and complete formation of the dianion of **1**; formation of trianion with **2** was slow and failed to go to completion. Reversibility led to loss of >1.0 D/methyl group from **2** after long reaction periods. Using $LiNH_2$, dianion formation was slow with **1**, and **2** failed to form the trianion. Lithium diisopropylamide (LDA) in tetrahydrofuran brought about rapid and complete ionization of the methyl group of **2**, 3 equiv of the base being required. The use of LDA for synthesis of 3,5,7-triketo acids from triketones was found to be a substantial improvement over the alkali amides. An improved yield of triketo acid **9** was obtained using LDA with **2**. Four small aliphatic triketones (**5–8**) also gave satisfactory yields of carboxylation products; alkali amides in liquid NH_3 had previously failed to give useful quantities of trianions with these compounds. Carboxylation of an unsymmetrical triketone, 3-methyl-2,4,6-heptanetrione, did not show regiospecificity; equal amounts of isomeric resorcylic acids (**24** and **25**) were obtained after aldol cyclization of the carboxylation products. The chemistry of the biologically important triketo acid, 3,5,7-trioxooctanoic acid (**13**), was explored. Acid **13** was converted to orsellinic acid (**15a**) by pH 5 acetate buffer, to tetraacetic lactone (**22**) by Ac_2O, to 4-pyrone ester **19** by H_2SO_4/MeOH, and to methyl ester **18** by CH_2N_2. Ester **18** was cyclized to methyl orsellinate (**15b**) by pH 5 acetate buffer and to a mixture of **15a**, **15b**, and 2,4,6-trihydroxyacetophenone (**21**) by aqueous KOH.

The chemistry of 3,5,7-triketo acids has attracted much attention due to the apparent involvement of some of these compounds in the biosynthesis of phenolic natural products.[1] Much of the effort has been concentrated on derivatives of the triketo acids, i.e., pyrones and ketals, because of the inaccessibility and instability of the polycarbonyl compounds themselves, but in this laboratory the emphasis has been on unprotected compounds, following the discovery that triketo

Table I. Loss of Deuterium from Methyl-Deuterated Diketone **1** Treated with Alkali Metal Amides in Liquid NH_3[a]

No.	Metal amide	Reaction time, min	Initial H/methyl	Final H/methyl
1	KNH_2	20	0.06	1.02
2	KNH_2	60	0.31	1.08
3	KNH_2	180	0.06	0.99
4	$NaNH_2$	20	0.06	0.95
5	$NaNH_2$	60	0.31	1.08
6	$NaNH_2$	180	0.06	0.98
7	$LiNH_2$	60	0.31	0.55
8	$LiNH_2$	180	0.31	0.70

[a] Diketone **1**, 1×10^{-2} M; alkali amide, 9×10^{-2} M.

acids could be synthesized from the corresponding triketones.[2] The procedure for this conversion involves treatment of the triketones with 3 or more equiv of alkali amide in liquid NH_3, followed by carboxylation in an ethereal solvent with CO_2. This procedure lacks generality.[3] Sodium amide worked well with 1-phenyl-1,3,5-hexanetrione (**2**) and other aromatic triketones but gave poor results with aliphatic ones. Potassium amide gave satisfactory results with some of the aliphatic triketones but failed with others. In particular, carboxylation of 2,4,6-heptanetrione (**8**) and other small triketones failed under all conditions investigated. The failure with **8** is most unfortunate because the corresponding triketo acid, 3,5,7-trioxooctanoic acid (**13**), in an enzyme-bound form is a putative intermediate in fungal biosynthesis of orsellinic acid (**15a**) and other phenols. Trianions of the triketones are presumed to be the reactive intermediates in the carboxylation reactions, and the low yields and failures with some triketones have been ascribed to incomplete formation of trianions by the amide bases.[3]

$$\mathrm{RCOCH_2COCH_2COCH_3} \xrightarrow[\text{liq } NH_3]{2NH_2^-} \mathrm{RCOCHCOCHCOCH_3}$$

$$\mathrm{RCOCHCOCHCOCH_2} \xrightarrow[NH_3]{NH_2^-} \mathrm{RCOCHCOCHCOCH_2}$$

$$\xrightarrow[2.\ H^+/H_2O]{1.\ CO_2/Et_2O} \mathrm{RCOCH_2COCH_2COCH_2CO_2H}$$

This paper describes experiments demonstrating that alkali amides are, in fact, insufficiently basic to effect complete ionization of triketones. Lithium diisopropylamide (LDA) in tetrahydrofuran (THF) is shown to be a more efficacious base and to be capable of essentially complete conversion of triketones to their trianions. Using this base, good yields of triketo acids can now be obtained with triketones including 2,4,6-heptanetrione.[4]

The shortcomings of alkali amides in liquid ammonia as ionizing bases are most readily understood when the reactions of triketones are compared with those of β-diketones. The synthetic reactions of dianions of diketones have been studied extensively; these reactions include alkylation, arylation, aldol condensation, acylation, and carboxylation.[5] The presence of a dianion intermediate has been established by NMR spectroscopy in the case of 1-phenyl-1,3-butanedione.[6] No evidence has been obtained to indicate whether formation of the dianion is complete in liquid ammonia, although the argument has been made that ionization must be essentally complete since alkylation of dianions of diketones with benzyl chloride gives no detectable concomitant formation of stilbene.[7] If ionization were not complete, amide ion would still be present and would cause self-condensation of benzyl chloride. Potassium, sodium, and lithium amides all react with diketones in liquid ammonia to give dianions, but differences in the reactivities of these anions have been observed.[8] In the present investigation a preliminary study of the ionization of 1-phenyl-1,3-butanedione was made so that it could serve as a frame of reference for triketones.

1-Phenyl-1,3-butanedione (1). The method of choice for examining the extent of ionization of diketone **1** involved hydrogen-deuterium substitution reactions. Diketone **1** was chosen for this study because the dianion of **1** had been the subject of an earlier NMR study,[6] and because the nonexchangeable aromatic protons of **1** would serve as an integration standard in NMR analysis of protium content of the methyl group. Because the investigation was to be carried out in a protic solvent, liquid NH_3, the experiments were limited to studies of deuterium removal from the methyl group. In spite of this limitation, information could still be obtained bearing on the rate, extent, and reversibility of ionization.

Methyl-deuterated diketone **1** was prepared by equilibration of the diketone with D_2O at 140 °C in the presence of pyridine. A typical reaction gave material having 2.69 D/methyl as determined by careful integration of NMR spectra. A second treatment of the diketone raised the deuterium content of the methyl group to 2.94. Deuterium incorporation occurred at the 2 position as well, and, although it would not have interfered with the ionization reaction by amide bases or with subsequent nmr analysis, it could be removed readily by treatment with cold, dilute HCl.

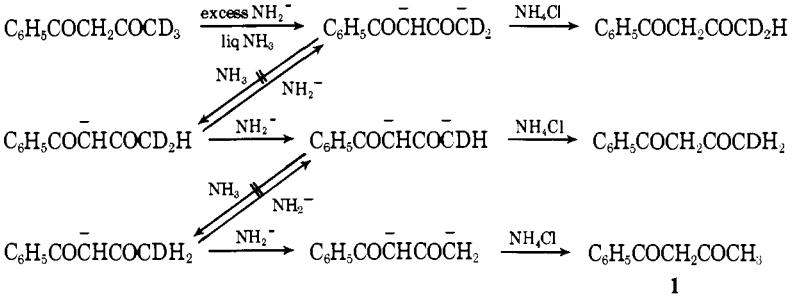
The reaction of diketone **1** with a large excess (9 molar equiv) of KNH_2 in liquid NH_3 for 20 min followed by reprotonation with NH_4Cl increased the protium content of the methyl group from 0.06 to 1.02. Other experiments carried out for 60 and 120 min gave essentially the same result (see Table I). It can be concluded that twofold ionization of the diketone by KNH_2 is rapid and quantitative, being essentially complete in 20 min. Moreover, ionization is effectively irreversible. If protonation of the dianion by NH_3 had occurred to a significant extent, the remaining deuterium atoms in the methyl group would gradually have been lost (see Scheme I), but no diminution in deuterium content was observed with increased reaction times.

The reaction of $NaNH_2$ with methyl-deuterated diketone **1** was also studied. The same ratio of base to diketone was employed, but an essential difference in the reactions was that $NaNH_2$ has only slight solubility in liquid NH_3, whereas KNH_2 was completely soluble at the concentration employed. In spite of this difference, the ionization process was essentially complete within 20 min, and no further loss of deuterium was observed after an additional 100 min.

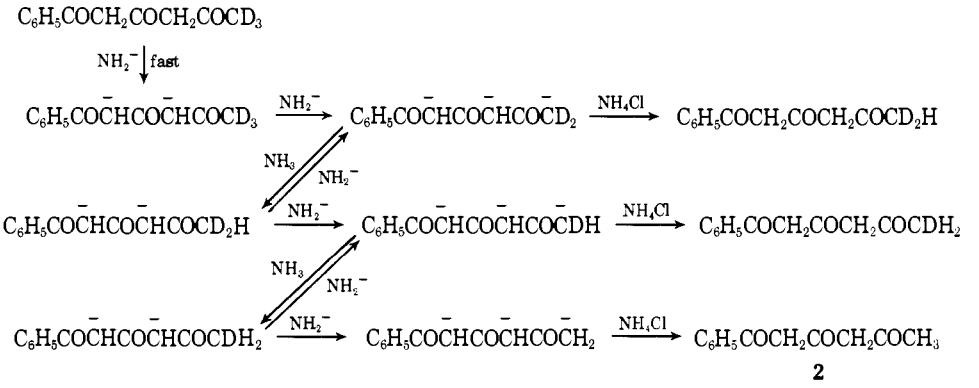
$LiNH_2$ is also only slightly soluble in liquid NH_3; with it a different result was obtained. After 60 min, no more than 0.55 of the diketone had been converted to the dianion; after 180 min, conversion still did not exceed 0.70. Deuterium loss was too slow to establish whether dianion formation would ever reach completion, so it is not known whether the shortcomings of $LiNH_2$ are only kinetic.

1-Phenyl-1,3,5-hexanetrione (2). As with **1**, the nonexchangeable phenyl group of triketone **2** provided a convenient standard for measurement by NMR of deuterium loss from the methyl group. The triketone exists in solution as a mixture of enol-keto forms. The ratios of phenyl and methyl signal areas were measured without considering what mixtures of tautomers were present, but in no case did signals for methylene, vinyl, or hydroxyl groups fall into the areas being integrated. Deuterium was introduced into the methyl group by treatment of **2** with D_2O in the presence of 1.4 equiv of NaOD. The exchange was rapid, being complete within 20 min at room temperature. NMR analysis of a typical sample showed incorporation of 2.85 D/methyl group. The 2 and 4 positions of the tautomers of **2** were deuterated in varying amounts. The isolation of triketone from the alkaline solution involved neutralization by addition to cold, dilute HCl. It should be noted

Scheme I



Scheme II



in passing that no exchange at the methyl position of diketone **1** was observed when it was treated with $NaOD/D_2O$ at room temperature.

The exchange reactions of deuterated **2** were studied by the procedure that had been used with **1**. The triketone was treated with excess alkali amide in liquid NH_3. After acidification with NH_4Cl, the triketone was recovered and assayed by NMR for deuterium content of the methyl group. Using KNH_2 (see Table II), one deuterium atom was lost from the methyl group within 30 min, but in contrast to the experience with diketone **1** longer reaction periods caused further loss of deuterium. After 180 min, only 0.62 D/methyl remained. With $NaNH_2$, the ionization process proceeded more slowly; NMR analysis showed only 0.52 H/methyl after 30 min. Experiments ranging as long as 180 min gave a steady increase in this value; the final figure, 1.29 H/methyl, suggests that the ionization process is similar to but slower than that with KNH_2. $LiNH_2$ was investigated as well, but with this base little or no loss of deuterium from the methyl group of **2** occurred. The 0.05 measured increase in protium content of the methyl group after 180 min does not exceed the uncertainties of the analytical method.

The results obtained with KNH_2 indicate that reprotonation of the methyl position competes with formation of the trianion of **2** (see Scheme II). Thus, the basicity of the terminal anion must be comparable with the basicity of KNH_2. The results with $NaNH_2$ are qualitatively similar but formation and reprotonation of the trianion proceed more slowly. The exchange data do not permit a conclusion to be drawn concerning the relative concentrations of trianion in equilibrium with the two bases; detailed kinetic analysis of the system would be futile on account of the heterogeneous nature of the reaction systems. Carboxylation gives a higher yield of triketo acid with the sodio system, but this result should not be interpreted as higher steady state concentrations of trianion in liquid NH_3. Prior to carboxylation the liquid ammonia solvent must be replaced by an ethereal solvent to avoid reaction between NH_3 and CO_2; reprotonation of the trianion by NH_3 could occur to a greater extent in the presence of one cation than the other during this process. The relative solubilities of the dianion and trianion of triketone **2** in NH_3–ether mixtures play an important part in determining the amount of trianion remaining after NH_3 has been replaced by Et_2O. Reversal of anion formation has been observed during transfer of other strongly basic anions from NH_3 to Et_2O.[9]

Table II. Loss of Deuterium from Methyl-Deuterated Triketone **2** Treated with Alkali Metal Amides in Liquid NH_3[a]

No.	Metal amide	Reaction time, min	Initial H/methyl	Final H/methyl
1	KNH_2	15	0.15	0.91
2	KNH_2	30	0.15	1.18
3	KNH_2	60	0.15	1.55
4	KNH_2	90	0.15	1.89
5	KNH_2	120	0.15	2.06
6	KNH_2	180	0.15	2.38
7	$NaNH_2$	15	0.15	0.24
8	$NaNH_2$	30	0.15	0.52
9	$NaNH_2$	60	0.15	0.67
10	$NaNH_2$	120	0.15	0.92
11	$NaNH_2$	180	0.15	1.29
12	$LiNH_2$	30	0.15	0.18
13	$LiNH_2$	180	0.15	0.20

[a] Triketone **2**, 1×10^{-2} M; KNH_2, 9.1×10^{-2} M; $NaNH_2$, 7.4×10^{-2} M; $LiNH_2$, 9.1×10^{-2} M.

The failure with $LiNH_2$ in this case is primarily a kinetic problem, although it is likely that this base is not strong enough to bring about complete trianion formation. This result is consistent with the much slower ionization of diketone **1** by $LiNH_2$ than by $NaNH_2$ or KNH_2.

The conclusion that must be reached with regard to trianions of triketones is that ammonia is too acidic to be used as a solvent for their reactions. It might be possible to use KNH_2 or $NaNH_2$ as the ionizing base in an inert solvent with NH_3 being removed from the reaction mixture as it was formed in the proton abstraction process, but the insolubility of alkali amides and of some enolate anions in organic solvents would probably make the process too slow to be useful. A better approach is to use a base which is soluble in ethereal solvents. Lithium

Table III. Loss of Deuterium from Methyl-Deuterated Triketone **2** Treated with Lithium Diisopropylamide in THF[a]

No.	Base/ triketone	Reaction time, min	Starting H/methyl	Final H/methyl
1	5/1	15	0.15	0.94
2[b]	5/1	30	0.15	1.14
3	5/1	60	0.22	1.08
4	5/1	180	0.22	1.04
5[c]	5/1	1560	0.15	0.92
6	3/1	60	0.15	0.90
7	2/1	60	0.15	0.20

[a] Triketone concentration 2.7×10^{-2} M except run 5 which was 1.9×10^{-2} M. [b] Product also analyzed by mass spectrometry. [c] Diisopropylamine (2.8 M) added.

Table IV. Isotopic Species Present in Methyl-Deuterated Triketone **2** before and after Treatment with LDA in THF[a]

Isotopic species	Before LDA treatment, %	After LDA treatment, %
d_4	3.0	0.4
d_3	82.2	2.3
d_2	13.7	89.0
d_1	1.1	7.9
d_0	0.0	0.4

[a] Run 2 in Table III.

diisopropylamide (LDA) was selected for investigation on the basis of its solubility in THF, strong basicity, and low nucleophilicity.[10] The base is readily prepared by treatment of diisopropylamine with an equivalent amount of *n*-butyllithium.

Treatment of methyl-deuterated **2** with 5 equiv of LDA for 15 min followed by neutralization with dilute HCl caused the protium content of the methyl group to rise from 0.15 to 0.94. In other experiments, longer reaction periods were employed but no significant increase in protium content was observed (see Table III). This result is not surprising because no significant protium reservoir is present in the LDA/THF system, whereas available protium in liquid NH_3 is approximately 180 M. The reversibility of the ionization process in the LDA/THF system was investigated using a THF/diisopropylamine mixture for the solvent (Table III, run 5). In this experiment the concentration of diisopropylamine was 2.8 M while the trianion of **2** was 2.8×10^{-2} M. After an extended reaction period (1560 min) recovered triketone still contained approximately 2 D/methyl group, indicating that ionization at the methyl position was essentially irreversible under the reaction conditions.

NMR analysis does not distinguish between material in which each molecule contains two deuterium atoms in the methyl group and that in which several deuterated species are present with an average deuterium content of 2 D/methyl group. As a further test of completeness and irreversibility of trianion formation in the LDA/THF system, the deuterium distribution in recovered **2** was examined by mass spectroscopy. The presence of some deuterium at the 2 and 4 positions of methyl-deuterated **2** would complicate analysis of mass spectral data, but it was found that most of the deuterium could be removed from these positions by equilibrating a $CHCl_3$ solution of the compound with pyridine and H_2O. NMR analysis of the treated starting material showed an average protium content of the methyl group of 0.15 with very little deuterium remaining at the 2 and 4 positions.

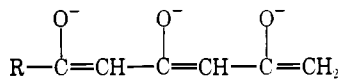
Table V. Preparation of 3,5,7-Triketo Acids from Triketones

Triketone	Triketo acid	Yield with alkali amide in liq NH_3[a]	Yield with LDA in THF
2	**9**	46% ($NaNH_2$)	82%
5	**10**	16 (KNH_2)	44
6	**11**	<5 (KNH_2)	28
7	**12**	Not previously prepared	42
8	**13**	<5 (KNH_2)	47

[a] Reference 3.

Mass spectral analysis was carried out at 12 eV to minimize fragmentation of the molecular ion; whereas in the 70 eV spectrum of undeuterated **2** the P − 1 ion (*m/e* 203) was 4% of the parent ion (*m/e* 204), at 12 eV the P − 1 ion was undetectable. The methyl-deuterated triketone after removal of deuterium from the 2 and 4 positions was found to be 82.2% d_3 and 13.7% d_2; only 3% of the material was d_4. Material recovered from a 30-min treatment with LDA (Table III, run 2) contained 1.14 H/methyl group by NMR analysis. Mass spectral analysis (Table IV) showed 2.3% was d_3, 89% d_2, and 7.9% d_1. These results support the contention that ionization is complete and irreversible. It should be noted that the product recovered from the ionization reaction had a narrower spread of isotopic species than the starting material. Whereas **2**-d_3 is converted exclusively to d_2, **2**-d_2 yields a mixture of d_1 and d_2 species. If removal of a D or an H from the methyl group of **2**-d_2 were strictly statistical, the d_1 fraction after LDA treatment would have been 9.7%.

In the above studies it has been tacitly assumed that the intermediates in reactions of 2,4,6-triketones at their 1 positions are trisenolate anions (**3**) resulting from removal of



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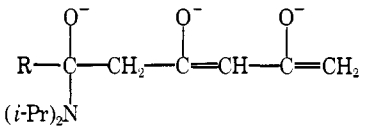
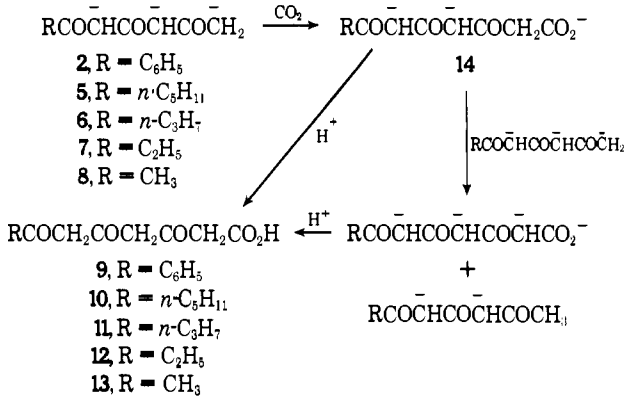


4

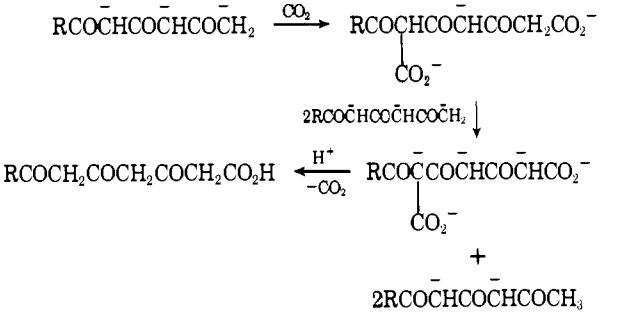
protons from the 1, 3, and 5 positions. The main basis for this assumption is the analogy with formation of dianions of 2,4-diketones. Using methyl-deuterated triketone **2**, it has now been possible to demonstrate the stoichiometric requirement for 3 equiv of the ionizing base to form the reactive intermediate. Whereas negligible loss of deuterium occurred when the triketone was treated with 2 equiv of LDA, triketone recovered from treatment with 3 equiv of LDA had had the protium content of the methyl group increased from 0.15 to 0.90. This result provides strong support for the trisenolate formulation. It does not, however, exclude the possibility that a diisopropylamide anion has added to a carbonyl group, as in **4**, but the high basicity and low nucleophilicity of LDA makes this alternative appear less likely.

Synthesis of 3,5,7-Triketo Acids. The syntheses of triketo acids **9-13** from triketones **2** and **5-8** were chosen to evaluate the use of LDA as the ionizing base; the preparation of all but **12** had been investigated previously with alkali amides in liquid NH_3 (see Table V). The new procedure involved treatment of the triketone with 4-5 equiv of LDA in THF at 0 °C, followed by a rapid addition of gaseous CO_2. After evaporation of the solvent, the mixture was neutralized with cold, dilute HCl and

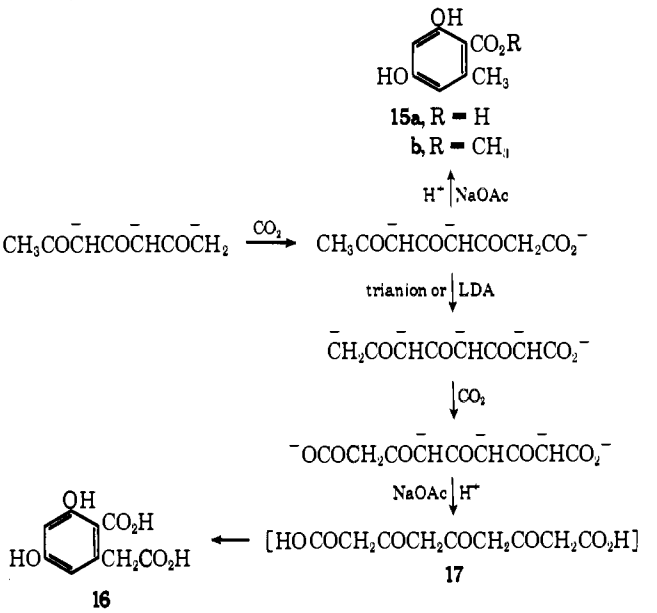
Scheme III



Scheme IV



Scheme V



extracted with Et_2O. Chromatography of the extract on silica gel gave essentially pure triketo acids which could be purified further by recrystallization. The yields shown in Table V are calculated on the assumption that trianion carboxylation has 1:1 stoichiometry, but this may not actually be the case. Little is known about the details of carboxylation of the trianions of triketones (or of the dianions of diketones). Terminal carboxylation of the triketone trianion gives salt **14** having a new, acidic methylene group; proton transfer from this methylene group to a second trianion would result in 2:1 stoichiometry for trianion and CO_2 (Scheme III).

A further complication is that one or both of the other negative centers in the triketone trianion could become carboxylated, but this would not be apparent because the additional carboxyl groups would be lost again during isolation of the product. After each additional carboxylation, reionization of the resulting methine could occur. For example, if trianion reacted at both the 1 and 5 positions with CO_2, each position could undergo reionization by reaction with trianion (Scheme IV).

The reaction of diisopropylamine with CO_2 could also consume trianion, but this reaction is probably of lesser importance on account of the steric hindrance around the nitrogen atom. The extent to which all of these reactions occur is difficult to assess or control. Their rates and relative importance will depend upon the rate of introduction of CO_2, the quantity used, solubility of the anions, agitation, etc. Use of excess LDA to reionize carboxylation products might improve the yields of triketo acids but only if CO_2 reacted more rapidly with trianions than it did with LDA. In each case shown in Table V one extra equivalent of LDA was employed, i.e., 4 equiv total.

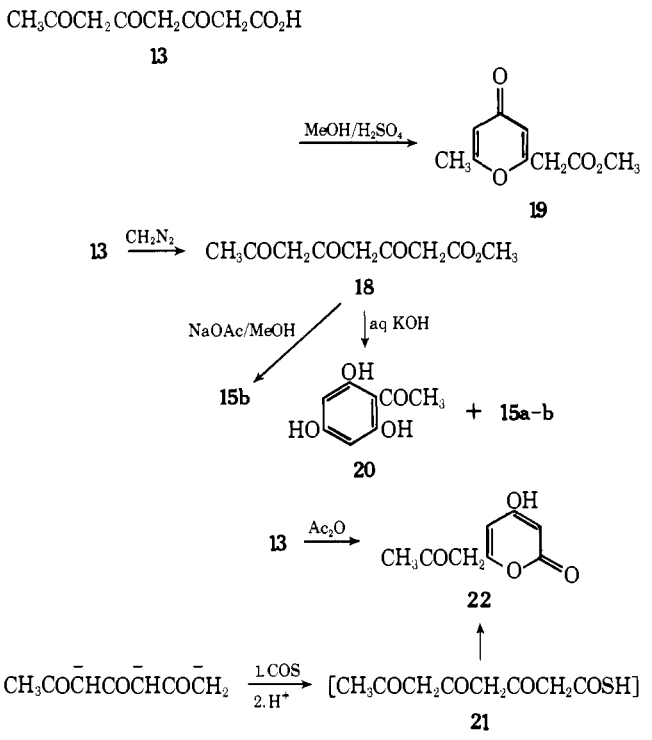
As can be seen in Table V, the synthesis of triketo acid **9** from triketone **2** was much improved (82%) using LDA; the earlier yield[3] with $NaNH_2$ had been 46%. It had been observed previously that triketones of this type undergo preferential anion formation and subsequent reactions at the methyl terminus rather than the methylene.[3] The preparation of triketo acid **13** is of particular interest because of the importance of **13** in biosynthesis.[1] This acid was substantially less stable than any that had been prepared previously, undergoing rapid cyclization in the presence of acidic or basic contaminants.[11] Very fast chromatography was required to purify **13** before it underwent cyclization. After chromatography **13** was sufficiently stable to permit recrystallization from ether at −20 °C.

The cyclization of **13** is a convenient preparation of orsellinic acid (**15a**) (see Scheme V). Isolation of the triketo acid was not required; treatment of unchromatographed **13** with pH 5 buffer converted it efficiently to **15a**. Orsellinic acid can be prepared from triketone **8** in an overall yield of 35%. Chromatographic purification of **15a** revealed the presence of a by-product, dicarboxylic acid **16**.[12] Although the yield of **16** was low (~5%), the compound is of interest because it presumably arose from triketo diacid **17**. Diacid **17** may have been formed by a twofold carboxylation of the 1,3,7-trianion or 1,3,5,7-tetraanion of **8**, but at present no evidence bearing on these possibilities is available. Alternatively, **17** might arise from **13**. During carboxylation of **8**, the initially formed trianion (**14**) of triketo acid **13** could become ionized further by trianion of **8** or by the excess LDA to give the pentaanion, carboxylation of which would give **17** and ultimately **16**. This last possibility was supported by the finding that triketo acid **13** when treated with excess LDA followed by CO_2 gave diacid **16** after cyclizative workup. Dicarboxylation products were not observed with triketones **5–7**, although small quantities could have been overlooked. Ionization at a terminal methylene position is less likely than at a terminal methyl position.

Because of the importance of triketo acid **13**, its chemistry was explored (see Scheme VI). The methyl ester (**18**)[13] was prepared by treatment of **13** with a molar equivalent of CH_2N_2, but it could not be formed by simple esterification. Treatment of **13** with methanolic H_2SO_4 gave pyrone ester **19**. Ester **18** cyclized readily. In methanolic NaOAc, it gave methyl orsellinate (**15b**); in aqueous KOH, it gave a mixture of 2,4,6-trihydroxyacetophenone (**20**), **15a**, and **15b**. The lactone **22**[14] was prepared from **13** by treatment with Ac_2O. It was also prepared by treatment of the trianion of **8** with COS; the reaction gave an unstable triketo thiolacid (**21**) which cyclized spontaneously to **22**.[15]

The final phase of the synthetic study was an investigation of the carboxylation of 3-methyl-2,4,6-heptanetrione (**23**) to see whether anion formation and subsequent condensation occurred preferentially at either of the methyl termini. The carboxylation products were cyclized without prior separation;

Scheme VI



subsequent chromatography gave equal quantities of resorcylic acids **24** and **25** (12% each) and a smaller amount (5%) of diacid **26** (see Scheme VII). Although **24** and **25** are well-known compounds,[16,17] neither melting points nor spectra provided a basis for assigning their structures. Esterification by treatment with CH_2N_2 gave the corresponding esters for which the melting points had diagnostic value.[16-18] In addition, the ester of **24** was compared with an authentic sample.[19] Confirmation of the structure assignments came from decarboxylations of **24** and **25**; equivalence of the aromatic protons in the first case and nonequivalence in the second provided definitive evidence. The structure of diacid **26** was established by the NMR spectrum of the monodecarboxylation product and by an independent synthesis of the diester. It is concluded that triketone **23** shows little selectivity in trianion formation.

Experimental Section

All melting points were taken with a Thomas-Hoover apparatus using open capillaries. In most cases triketo acids and resorcylic acids underwent decomposition at their melting points. As a consequence these melting points were somewhat variable depending on rate of heating and presence of catalytic impurities. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. NMR spectra were obtained with a Varian A-60 spectrometer employing tetramethylsilane as an internal standard. Only the chemical shifts of protons bound to carbon are reported; in many cases OH signals were too broad to be identified with certainty. Mass spectra were obtained by direct insertion with an LKB 9000 spectrometer at 70 eV except as noted. The parent ion, if any, and three-five of the most intense ions are listed. A fluorescent silicic acid adsorbant was used for TLC; the plates were examined under uv light. Column chromatography was carried out using Mallinckrodt CC-4 or similar acid-washed silica gel having a low iron content.

Methyl-Deuterated Diketone 1. 1-Phenyl-1,3-butanedione (**1**, 3.5 g), D_2O (23 g), and pyridine (15 ml) were heated in a sealed Carius tube for 1 h at 125 °C. The product was washed with dilute HCl and sublimed [50 °C (0.3 mm)]. The initial fraction of sublimate contained a substantial amount of benzoic acid and was discarded. The procedure gave 3.1 g of diketone which contained 2.69 D/methyl group by NMR analysis. Retreatment of this material with D_2O–pyridine gave 2.2 g of diketone, mp 58–60 °C, having a deuterium content of 2.94 D/methyl group (98% exchange). The residual protium content of the methyl group of **1** was determined by integration of NMR spectra with the five aromatic protons being used as an internal integration standard. The reproducibility of the method was generally better than ±0.1 H/CH_3.

Methyl-Deuterated Triketone 2. 1-Phenyl-1,3,5-hexanetrione[20] (**2**, 6.0 g, 30 mmol) was treated for 30 min at 25 °C with 46 ml of D_2O containing 44 mmol of NaOD. The solution was poured into cold 6 M HCl. The mixture was extracted with Et_2O; the extract was dried ($MgSO_4$) and evaporated in vacuo. The residue was sublimed [85 °C (0.3 mm)] and recrystallized from heptane to give 3.8 g of triketone, mp 104–106 °C, having a residual protium content of 0.15 H/methyl group. Triketone **2** exists in solution as a mixture of several enol forms; protium content of the methyl groups of these tautomers was determined by comparing the total integral for the methyl region of the NMR spectrum with that of the aromatic region. Analysis of protium content of the 2 and 4 positions of the tautomers was less accurate but indicated that the HCl workup had failed to remove all the deuterium from these positions.

The sample (2.0 g) of methyl-deuterated **2** that was to be used in the experiment in which deuterium content was measured by mass spectral analysis was dissolved in 50 ml of $CHCl_3$ and treated with H_2O (25 ml) and pyridine (0.5 ml) for 3 h at 50 °C. After sublimation and recrystallization, NMR analysis of recovered triketone showed removal of deuterium from the 2 and 4 positions but no loss from the methyl group. The mass spectral analysis of this material is shown in Table IV; the procedures employed for the acquisition of suitable spectra and for analysis of the spectra have been described by Biemann.[21]

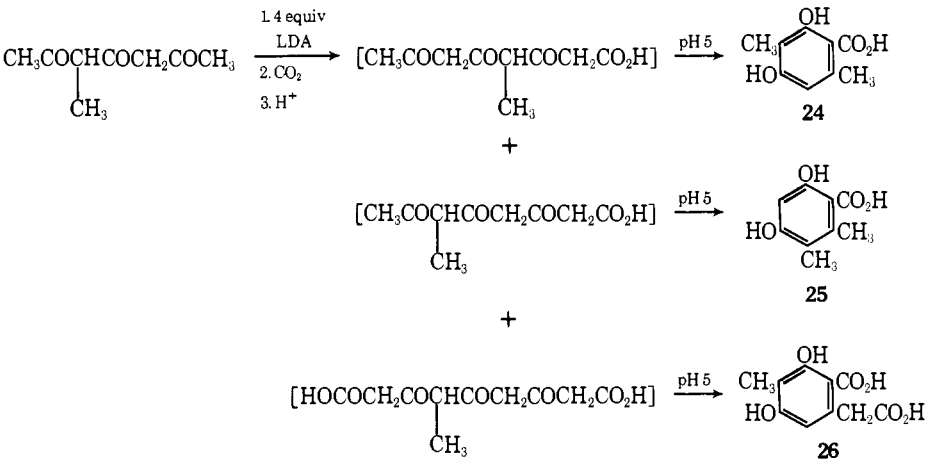
Exchange Reactions of Methyl-Deuterated 1 and 2 with Alkali Amides in Liquid NH_3 (Tables I and II). Into a 250-ml round-bottom flask equipped with a dry ice condenser and containing 90 ml of anhydrous, liquid NH_3 were placed the alkali metal and a small amount of $Fe(NO_3)_3$. The mixture was stirred magnetically by means of a polyethylene-covered stirring bar. $NaNH_2$ and $LiNH_2$ formed grey precipitates but KNH_2 remained in solution. After formation of alkali amide was complete, as indicated by disappearance of the blue color characteristic of dissolved alkali metals, a weighed pellet of methyl-deuterated **1** or **2** (approximately 1.1 mmol) was added. At the end of the specified reaction period, 1.0 g of NH_4Cl was added to neutralize the solution. After evaporation of the NH_3, dilute HCl was added, and the aqueous suspension was extracted with Et_2O. The ethereal solution was washed with H_2O and with 2% KH_2PO_4, dried ($MgSO_4$), and evaporated. The residue was sublimed. With **1**, sublimation [50 °C (0.3 mm)] gave material of adequate purity for NMR analysis, but with **2**, recrystallization from Et_2O–hexane was often required after sublimation [85 °C (0.3 mm)]. Much of the effort devoted to purification, particularly with **2**, was to remove traces of Fe compounds or other paramagnetic species prior to NMR analysis.

Exchange Reactions of Methyl-Deuterated 2 Using Lithium Diisopropylamide (LDA) (Table III). For the preparation of LDA[10] (approximately 10 mmol) the appropriate quantity of *n*-butyllithium (22% in hexane) was added slowly by syringe to a flask containing a stoichiometric quantity of diisopropylamine and 50 ml of anhydrous THF. The solution was maintained at 0 °C under a N_2 blanket. Triketone **2** dissolved in THF was introduced by syringe. After the specified reaction period, the reaction mixture was poured into cold, dilute HCl. The mixture was extracted with Et_2O, and the ethereal extract was dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography and/or sublimation, followed by recrystallization from heptane. Deuterium content of the product was assayed by NMR spectroscopy.

7-Phenyl-3,5,7-trioxoheptanoic Acid (9). To a stirred solution of 122 mmol of LDA (prepared as above from stoichiometric amounts of diisopropylamine and *n*-butyllithium) in freshly distilled THF (150 ml) under N_2 and at 0 °C was added 5 g (24.5 mmol) of triketone **2**. After 30 min, CO_2 was bubbled vigorously through the solution for 5 min. The solvent was then evaporated in vacuo, and the residue was filtered and washed with anhydrous Et_2O. The resulting solid was suspended in cold Et_2O to which cold, dilute HCl was added. The ethereal layer and additional extracts of the aqueous solution were combined, dried ($MgSO_4$), and evaporated. After chromatography of the residue on silica gel (Et_2O–hexane elution), the resulting yellow solid was crystallized from CH_2Cl_2 to give 5.0 g (82%) of **9**, mp 92–96 °C (lit.[2] mp 98–99 °C). The NMR spectrum was identical with that of an authentic sample.[3]

3,5,7-Trioxododecanoic Acid (10). By the same procedure, triketone **5**[3] (1.0 g, 5 mmol) was treated with 4 equiv of LDA, followed by CO_2.

Scheme VII



Isolation by chromatography followed by one recrystallization from $CHCl_3$–hexane gave 0.547 g (44%) of **10**, mp 74–78 °C (lit.[3] mp 80–81 °C). The material was spectroscopically identical with previously prepared material[3] with no evidence of isomeric acids.

3,5,7-Trioxodecanoic Acid (11). By the same procedure, triketone **6**[3] (1.0 g, 5.9 mmol) was treated with 4 equiv of LDA, followed by CO_2. Isolation by chromatography gave 0.352 g (28%) of **11**, mp 63–67 °C and, after three recrystallizations from $CHCl_3$–hexane, 70.5–71.5 °C: ir (KBr) 1715, 1635–1620 (broad), 1615 (sh) cm^{-1}; NMR ($CDCl_3$) showed a mixture of enol–keto forms; MS *m/e* (intensity) 214 (0.3, parent), 170 (21), 127 (42), 113 (38), 85 (100), 71 (67).

Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.39; H, 6.62.

3,5,7-Trioxononanoic Acid (12). 2,4,6-Octanetrione (**7**) was prepared by acylation of acetylacetone with ethyl propionate. 2,4-Pentanedione (20 g, 0.2 mol) was converted to the dilithium salt by addition to 0.6 mol of $LiNH_2$ (prepared from 4.2 g of Li metal) in 800 ml of anhydrous, liquid NH_3. After 2 h, 40.8 g (0.4 mol) of ethyl propionate was added in Et_2O. After an additional 2 h, the NH_3 was evaporated with simultaneous addition of Et_2O. The mixture was poured into cold, dilute HCl. The ethereal solution was dried ($MgSO_4$), evaporated, and distilled to give 10.4 g (34%) of triketone **7**: bp 55–57 °C (0.15–0.10 mm); ir (film) 1720, 1595 cm^{-1}; NMR ($CDCl_3$) showed a mixture of tautomers; MS *m/e* (intensity) 156 (6, parent), 85 (59), 57 (61), 43 (100).

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.29; H, 7.71.

By the procedure used for preparation of **9–11**, triketone **7** (3.0 g, 19 mmol) was treated with 4 equiv of LDA, followed by CO_2. Isolation by rapid chromatography on silica gel (column jacketed with ice-water) gave 1.6 g (42%) of **12**, mp 46–49 °C. The mp was raised to 53–54 °C by several recrystallizations from Et_2O–hexane and $CHCl_3$–hexane; the recrystallizations were carried out by dissolving **12** in the solvent mixture at room temperature and cooling to −20 °C; ir (KBr) 1715, 1625 cm^{-1}; NMR ($CDCl_3$) showed a mixture of tautomers; MS *m/e* (intensity) 200 (not visible, parent), 127 (30), 85 (33), 57 (78), 44 (61), 43 (100).

Anal. Calcd for $C_9H_{12}O_5$: C, 54.00; H, 6.00. Found: C, 54.19; H, 5.97.

Treatment of the crude carboxylation product with pH 5 acetate buffer followed by chromatography gave 2,4-dihydroxy-6-ethylbenzoic acid (32% yield based on triketone **7**), mp 176–182 °C (lit.[22] mp 168–169 °C).

Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.21; H, 5.41.

Traces of the 4-pyrone derived from **7** and the 4-pyrone acid derived from **12** were present, but there was no indication of the products that would have been derived from carboxylating the 7 position or the 1 and 7 positions of **7**.

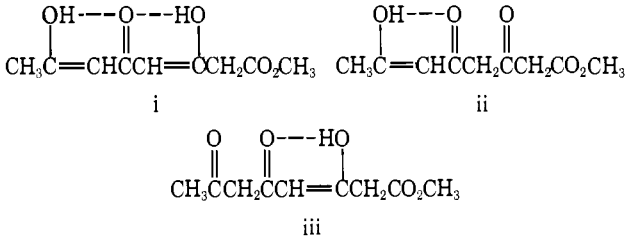
3,5,7-Trioxooctanoic Acid (13). By the same procedure, triketone **8**[23] (2.0 g, 14 mmol) was treated with 4 equiv of LDA, followed by CO_2. The instability of **12** required that the isolation be done as rapidly and cold as possible. Chromatography on silica gel gave 1.2 g (47%) of **12**, mp 67–71 °C. Recrystallization by dissolving in Et_2O at room temperature and cooling to −20 °C raised the melting point to 74.5–75.5 °C; ir ($CHCl_3$) 1695–1729 cm^{-1}; NMR ($CDCl_3$) showed a mixture of tautomers;[4] MS *m/e* (intensity) 186 (0.2, parent), 142 (16), 100 (25), 85 (56), 44 (53), 43 (100).

Anal. Calcd for $C_8H_{11}O_5$: C, 51.61; H, 5.41. Found: C, 51.74; H, 5.30.

TLC of analytically pure material showed two spots, one apparently being orsellinic acid (**15a**) which had formed on the TLC plate. In another experiment the crude product from carboxylation of 5.0 g (35.2 mmol) of **8** was dissolved in EtOH and treated with pH 5 acetate buffer for 15 h at 5 °C. After acidification with HCl, extraction into Et_2O, and chromatography on silica gel (Et_2O–hexane elution) gave 2.3 g (35%) of **15a**, mp 173–174 °C (lit.[24] mp 176 °C for monohydrate). After recrystallization from EtOH–H_2O and drying in vacuo over P_2O_5 (48 h, 56 °C), the melting point rose to 193–196 °C (lit.[25] mp 197–198 °C for anhydrous **15a**). Further elution of the silica gel gave 0.38 g (5%) of diacid **16**, mp 186–187 °C after several recrystallizations from acetone–hexane (lit.[26] mp 197–198 °C for monohydrate); ir (KBr) 1685, 1640 cm^{-1}; NMR (Me_2SO-d_6) 3.8 (s, 2, CH_2) and 6.29 (s, 2, aromatic); MS *m/e* (intensity) 212 (8, parent), 168 (83), 166 (42), 123 (99), 44 (100), 43 (78).

Anal. Calcd for $C_9H_8O_6$: C, 50.95; H, 3.80. Found: C, 50.84; H, 3.80.

Methyl 3,5,7-Trioxooctanoate (18). Acid **13** (1.65 g, 8.9 mmol) was treated with 1 equiv of CH_2N_2 in ether to give 1.7 g (91%) of ester **18** as a waxy solid; mp 16–19 °C. Recrystallization from ether at −60 °C gave analytically pure material, mp 24.5–26.5 °C; ir ($CHCl_3$) 1715–1740, 1590 cm^{-1}; uv (EtOH) 265 (ε 9650) and 318 nm (sh, 4200); MS *m/e* (intensity) 200 (7, parent), 127 (38), 85 (74), 43 (100). The NMR spectrum ($CDCl_3$) showed the presence of three tautomers (i–iii): i, δ 2.00 (s, CH_3), 3.25 (s, CH_2), 3.75 (s, OCH_3), 5.22 and 5.29



(s, vinyls); ii and iii, δ 2.08 and 2.25 (s, CH_3's), 3.38, 3.43, 3.57, and 3.60 (s, CH_2's), 3.75 (s, OCH_3's), 5.59 and 5.70 (s, vinyls).

Anal. Calcd for $C_9H_{12}O_5$: C, 54.00; H, 6.04. Found: C, 53.93; H, 6.22.

Cyclization of 18 in Methanolic NaOAc. Ester **18** (0.10 g, 0.5 mmol) was treated with 1 g of NaOAc in 25 ml of MeOH for 1.5 h at 25 °C to give 0.046 g (50%) of **15b**, mp 137–138.5 °C after recrystallization from EtOH–H_2O (lit.[27] mp 138 °C).

Cyclization of 18 in Aqueous KOH. Ester **18** (0.20 g, 1 mmol) was treated with 5 ml of 0.5 M aqueous KOH for 1 h at 0 °C to give after acidification, extraction, and chromatography on silica gel 0.049 g (27%) of **15b**, mp 136–138 °C, 0.022 g (13%) of **15a**, mp 186–189 °C, and 0.065 g (39%) of 2,4,6-trihydroxyacetophenone (**20**), mp 215–218

°C (lit.[28] mp 218–219 °C). The NMR spectra were consistent with the structure assignments.

Methyl 6-Methyl-4-pyrone-2-acetate (19). Acid **13** (0.50 g, 2.7 mmol) was treated with 5% methanolic H_2SO_4 for 19 h at 5 °C to give after neutralization with $NaHCO_3$, extraction into EtOAc, chromatography on silica gel (Et_2O–MeOH elution), and crystallization from Et_2O 0.248 g (50%) of **19**, mp 64.5–65.5 °C after recrystallization from Et_2O; ir (KBr) 1740, 1665, 1610 cm^{-1}; uv (EtOH) 248 nm (ε 12 280); NMR ($CDCl_3$) δ 2.26 (s, broad, 3, CH_3), 3.53 (s, 2, CH_2), 3.76 (s, 3, OCH_3), 6.09 (unresolved multiplet, 1, 5-CH=), and 6.19 (d, 1, J = 2.5 Hz, 3-CH=); MS *m/e* (intensity) 182 (57, parent), 95 (100), 69 (22), 59 (22), 43 (36).

Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.19; H, 5.57.

6-Acetonyl-4-hydroxy-2-pyrone (22). Treatment of 0.5 g (2.7 mmol) of **13** with 10 ml of Ac_2O for 40 h at 5 °C gave a solid residue after evaporation of the solvent in vacuo. After washing with Et_2O and recrystallization from EtOAc–hexane, 0.298 g (66%) of pyrone **22**, mp 124–127 °C, was obtained. A second recrystallization gave analytically pure, nonhydrated material, mp 126–127 °C, the NMR and mass spectra of which were identical with those reported by Bentley and Zwitkowits.[29]

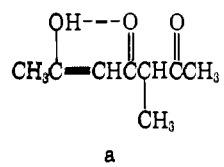
Anal. Calcd for $C_8H_8O_4$: C, 57.14; H, 4.80. Found: C, 56.91; H, 4.82.

Lactone **22** was also prepared by treating triketone **8** (1.0 g, 7 mmol) with 4 equiv of LDA, followed by excess COS.[15] The solvent was evaporated in vacuo. The residue was partitioned between cold, dilute HCl and EtOAc. The organic phase was dried ($MgSO_4$) and evaporated in vacuo. Chromatography of the residue on silica gel (acetone–Et_2O elution) gave 0.20 g (15%) of **22**, identical with the material prepared previously.

6-(Carboxymethyl)-β-resorcylic Acid (16) and the Dimethyl Ester. Triketone **8** (5.0 g, 35 mmol) was treated with 4 equiv of LDA and carboxylated as described previously except that CO_2 was introduced very slowly. The system was flushed with N_2 to remove excess CO_2 after which 2 additional equiv of LDA were introduced. After 15 min at 0 °C, CO_2 was introduced again. The usual workup followed by treatment with pH 5 acetate buffer for 15 h at 5 °C and chromatography on silica gel gave 1.2 g (18%) of orsellinic acid (**15a**) and 1.8 g (24%) of diacid **16**, mp 185–187 °C after recrystallization from acetone–hexane. Brief treatment of **16** with ethereal CH_2N_2 gave methyl 9-(carbomethoxymethyl)-β-resorcylate, mp 143.5–144.5 °C (lit.[30] mp 148–150 °C); ir (KBr) 1710, 1650, 1625 cm^{-1}; NMR ($CDCl_3$–d_6-acetone) δ 3.71 (s, 3, OCH_3), 3.83 (s, 2, CH_2), 3.87 (s, 3, OCH_3), 6.30 (d, 1, J = 2.5 Hz, aromatic), and 6.42 (d, 1, J = 2.5 Hz, aromatic); MS *m/e* (intensity) 240 (39, parent), 208 (52), 180 (100), 165 (93).

Anal. Calcd for $C_{11}H_{12}O_6$: C, 55.00; H, 5.04. Found: C, 54.98; H, 5.00.

3-Methyl-2,4,6-heptanetrione (23). 3-Methyl-2,4-pentanedione (22.8 g, 0.2 mol) was added to 0.6 mol of $LiNH_2$ (prepared from 4.2 g of Li metal) in 800 ml of anhydrous, liquid NH_3 contained in a flask equipped with a glass stirrer and a dry ice condenser. After 5 h, 35.2 g (0.40 mol) of EtOAc diluted with 100 ml of Et_2O was added over 3 h by means of a dropping funnel. The NH_3 was then evaporated with simultaneous addition of Et_2O. The mixture was poured into cold, dilute HCl. The ethereal solution was separated, dried ($MgSO_4$), and evaporated. Chromatography on silica gel (Et_2O–hexane elution) gave 31% of **23**, bp 65 °C (0.3 mm). The analytical sample was prepared by further chromatography; ir (film) 1730–1710, 1625–1595 cm^{-1}; NMR ($CDCl_3$), mainly one tautomer (a) δ 1.27 (d, CH–CH_3), 2.08



a

(s, =C(OH)CH_3), 2.19 (s, —C(=O)CH_3), 3.51 (m, C$H$$CH_3$), and 5.65 (s, =CH); MS *m/e* (intensity) 156 (3, parent), 114 (37), 85 (58), 43 (100).

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.63; H, 7.87.

Carboxylation of 23 and Cyclization of the Resulting Acids. Triketone **23** (3.0 g, 0.19 mmol) was treated with 4 equiv of LDA, followed by CO_2. After the usual workup, the resulting dark oil, diluted with EtOH, was treated with 150 ml of pH 5 acetate buffer for 48 h at 5 °C. Workup by acidification, extraction into Et_2O, and chromatography on silica gel (Et_2O–hexane elution, followed by MeOH–Et_2O) gave three major products in sufficient quantities for identification along with several minor components. The first product to be eluted was 3-methylorsellinic acid (**24**, 0.419 g, 12%), mp 199–202 °C after dissolving in $NaHCO_3$ and reprecipitating with HCl, followed by careful drying (lit.[17] mp 185 °C); ir (KBr) 1655 (sh), 1640, 1630–1615, 1600 cm^{-1}; uv (EtOH) 302 (ε 3665), 266 nm (12,350); NMR (acetone-d_6) δ 2.07 (s, 3, CH_3), 2.50 (s, 3, CH_3), and 6.37 (s, 2, aromatic); MS *m/e* (intensity) 182 (42, parent), 164 (64), 136 (100), 107 (22), 79 (22), 77 (20).

Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.48; H, 5.59.

The second product eluted was 5-methylorsellinic acid (**25**, 0.44 g, 13%), mp 196–198 °C after dissolving in $NaHCO_3$ solution and reprecipitating with HCl, followed by recrystallization from H_2O and drying (lit.[16] mp 163 °C); ir (KBr) 1635–1615 cm^{-1}; uv (EtOH) 307 (ε 5040), 262 nm (10,240); NMR (acetone-d_6) δ 2.11 (s, 3, CH_3), 2.52 (s, 3, CH_3), 6.36 (s, 2, aromatic); MS *m/e* (intensity) 182 (46), 164 (100), 138 (36), 137 (24), 136 (52), 123 (34).

Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.54; H, 5.64.

The third product was identified as 6-(carboxymethyl)-3-methyl-β-resorcylic acid (**26**, 0.283 g, 6%), mp 203–209 °C after recrystallization from acetone–hexane; ir (KBr) 1710 (sh), 1695, 1635, 1610 cm^{-1}; NMR (Me_2SO-d_6) δ 2.0 (s, 3, CH_3), 3.79 (s, 2, CH_2), and 6.33 (s, 1, aromatic); MS *m/e* (intensity) 226 (2, parent), 208 (90), 182 (60), 180 (80), 162 (100), 137 (92), 44 (56).

Anal. Calcd for $C_{10}H_{10}O_6$: C, 53.10; H, 4.46. Found: C, 53.18; H, 4.53.

Two other components were tentatively assigned as 4-pyrone derivatives but were not fully identified. 6-(Carboxymethyl)-5-methyl-β-resorcylic acid was not detected.

Esterification of 24–26. Acids **24**, **25**, and **26** were individually treated for 1 min with CH_2N_2 in Et_2O; the resulting esters were purified by chromatography on silica gel, followed by recrystallization: methyl 3-methylorsellinate, mp 140–142 °C after recrystallization from $CHCl_3$–hexane (lit.[17,18] mp 141, 145 °C; the material was spectroscopically identical with an authentic sample provided by Huneck[19]); methyl 5-methylorsellinate, mp 125–126 °C after recrystallization from $CHCl_3$–hexane (lit.[16b] mp 126 °C); methyl 6-(carbomethoxymethyl)-3-methyl-β-resorcylate, mp 188.5–189.5 °C after recrystallization from $CHCl_3$–acetone; ir (KBr) 1710, 1650, 1620–1600 cm^{-1}; uv (EtOH) 304 (ε 4920), 269 nm (13,700); NMR (acetone-d_6) δ 2.08 (s, 3, CH_3), 3.66 (s, 3, OCH_3), 3.82 (s, 2, CH_2), 3.87 (s, 3, OCH_3), and 6.43 (s, 1, aromatic); MS *m/e* (intensity) 254 (38, parent), 222 (61), 195 (37), 194 (65), 162 (100). The ester was identical (NMR and mmp) with material prepared below by an independent route.

Anal. Calcd for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.51; H, 5.47.

***Independent* Synthesis of Methyl 6-(Carbomethoxymethyl)-3-methyl-β-resorcylate.** Anhydrous $AlCl_3$ (0.834 g, 6.2 mmol) in Et_2O (10 ml) was added slowly to a solution of methyl 6-(carbomethoxymethyl)-β-resorcylate (0.5 g, 2.1 mmol) and $Zn(CN)_2$ (0.67 g, 6.2 mmol) in 12 ml of Et_2O at 0 °C. The solution was saturated with HCl gas and allowed to stand for 65 h at 20 °C. Water was added; the mixture was heated for 20 min then extracted with EtOAc and $CHCl_3$. Evaporation and chromatography of the extract on silica gel (Et_2O–hexane elution) gave 0.344 g (62%) of methyl 6-(carbomethoxymethyl)-3-formyl-β-resorcylate, mp 105.5–106.5 °C after recrystallization from $CHCl_3$–hexane; ir (KBr) 1730, 1655 (sh), 1650, 1625 cm^{-1}; uv (EtOH) 338 (ε 4080), 261 (16 720), and 238 nm (19 000); NMR ($CDCl_3$) δ 3.81 (s, 3, OCH_3), 3.87 (s, 2, CH_2), 3.91 (s, 3, OCH_3), 6.34 (s, 1, aromatic), and 10.42 (s, 1, CHO); MS *m/e* (intensity) 268 (41, parent), 208 (100), 205 (24), 180 (61), 120 (25).

Anal. Calcd for $C_{12}H_{12}O_7$: C, 53.74; H, 4.51. Found: C, 53.64; H, 4.45.

The formylation reaction gave a low yield (5%) of another component, mp 116–119 °C after recrystallization from Et_2O–hexane, tentatively assigned as the 5-formyl isomer on the basis of spectra.

Treatment of methyl 6-(carbomethoxymethyl)-3-formyl-β-resorcylate (0.2 g, 0.75 mmol) with Zn amalgam (1 g) and concentrated HCl (4 ml) in 8 ml of MeOH and 2 ml of H_2O for 45 min at reflux gave 0.062 g (32%) of methyl 6-(carbomethoxymethyl)-3-methyl-

β-resorcylate, mp 187–189 °C after recrystallization from $CHCl_3$–acetone.

Decarboxylation of Acids 24–26. Treatment of the acids with aqueous KOH for 2 h at 100 °C under nitrogen followed by acidification, extraction, and chromatography on silica gel gave the corresponding resorcinols in good yields. Acid **24** gave (81%) 2,5-dimethylresorcinol, mp 158–160 °C after recrystallization from benzene (lit.[18,31] mp 158–159 °C); NMR (Me_2SO-d_6) δ 1.92 (s, 3, CH_3), 2.10 (s, 3, CH_3), 6.15 (s, 2, aromatic). The compound was identical with an authentic sample.[19] Acid **25** gave (52%) 4,5-dimethylresorcinol, mp 135–136 °C after recrystallization from benzene (lit.[16a,32] mp 134–136 °C); NMR (Me_2SO-d_6) δ 1.95 (s, 3, CH_3), 2.10 (s, 3, CH_3), 6.09 (d, 1, J = 2.5 Hz, aromatic), 6.19 (d, 1, J = 2.5 Hz, aromatic). The compound was identical with an authentic sample.[16a,32] Acid **26** gave (81%) 3,5-dihydroxy-4-methylphenylacetic acid, mp 158.5–159.5 °C after recrystallization from Et_2O–$CHCl_3$; ir (KBr) 1690, 1625, 1595 cm^{-1}; uv (EtOH) 281 (ε 997), 274 nm (1005); NMR (Me_2SO-d_6) δ 1.92 (s, 3, CH_3), 3.30 (s, 2, CH_2), 6.23 (s, 2, aromatic); MS *m/e* (intensity) 182 (59, parent), 138 (17), 137 (100), 91 (12).

Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.18; H, 5.52.

Brief treatment of 3,5-dihydroxy-4-methylphenylacetic acid with CH_2N_2 gave the methyl ester, mp 142.5–143.5 °C after recrystallization from Et_2O–$CHCl_3$; ir (KBr) 1705, 1620, 1590 cm^{-1}; uv (EtOH) 282 (ε 1030) and 274 nm (1030); NMR (Me_2SO-d_6) 1.92 (s, 3, CH_3), 3.41 (s, 2, CH_2), 3.60 (s, 3, OCH_3), 6.22 (s, 2, aromatic); MS *m/e* (intensity) 196 (50, parent), 138 (14), 137 (100).

Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.03; H, 6.06.

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