hydroxide were added. The liquid phase was decanted from the precipitated mercury and extracted with ether. The organic extract was washed with sodium chloride solution and dried, and the solvent was removed *in vacuo* to yield 1.80 g of a yellow liquid which showed four spots on tlc. Chromatography on 30 g of silica gel eluting with hexane–ethyl acetate (2:1) gave 0.300 g of a compound which had ir, nmr, mass spectrum, and tlc identical with those of **4**.

Cyclization of 4.—To a solution of 0.40 ml of 75% aqueous sulfuric acid was added 0.10 g of **4**. After stirring for 4 hr at 10°, the mixture was poured onto 2 g of ice and extracted four times with ether. The organic phases were washed with sodium bicarbonate and sodium chloride solutions and dried. The residue, after evaporation of the solvent *in vacuo*, showed by vpc analysis **2** and **3** in the ratio of 81:19 as the only reaction products.

Registry No.—(*E*)-**1**, 27539-94-2; (*Z*)-**1**, 27575-61-7; **2**, 37709-65-2; **3**, 37709-66-3; **4**, 27243-05-6; **5**, 29481-98-9; **6**, 37709-69-6; **7**, 37709-70-9; **8**, 37709-71-0.

Acknowledgment.—We are indebted to Firmenich et Cie., Geneva, for generous financial support.

Synthesis of *C*-Methyl Derivatives of 1-Phenyl-1,3,5-hexanetrione[1]

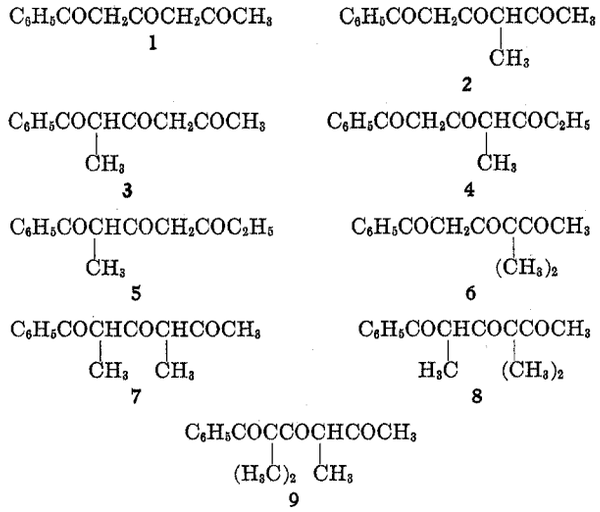
PHILIP J. WITTEK, KEITH B. HINDLEY, AND THOMAS M. HARRIS*

Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37235

Received September 27, 1972

Eight *C*-methyl derivatives of 1-phenyl-1,3,5-hexanetrione (**1**) have been prepared using two basic techniques: acylation of substituted diketones with esters using lithium amide or sodium hydride as the base, and alkylation of triketone **1** with methyl iodide using sodium hydride or potassium carbonate as the base. The lithium amide method compliments the sodium hydride method in the acylation of diketones, since the former gives good yields when aliphatic esters are employed and the latter is convenient for, but limited to, aromatic esters. The reaction of triketone **1** with sodium hydride and methyl iodide gave the 2- and 4-mono- and 2,2- and 4,4-dimethylation products, the 4 position being the preferred site of reaction. Proton transfer reactions played a major role in the formation of the dialkylation products. Under conditions suppressing proton transfer reaction, the disodium salt of triketone **1** reacted with methyl iodide to give the 2,4-dimethyl derivative. The 2,2,4- and 2,4,4-trimethyl derivatives were prepared by treatment of **1** with excess methyl iodide and potassium carbonate in acetone; both of the trimethylation products cyclized spontaneously to give cyclic hemiketals.

The cyclization reactions of 3,5,7-triketo acids have been studied intensively because they are possible models of the pathways by which resorcylic acids, acylphloroglucinols, and related compounds are formed in nature.[2] Often these metabolites are found having methyl or other alkyl groups present at one or more of the unsubstituted positions, and it has been proposed[3] and, in some cases, demonstrated[4] that these substituents can be introduced prior to cyclization of the triketo acids. For this reason we sought to study the cyclization reactions of 2-, 4-, and 6-*C*-methyl derivatives of 7-phenyl-3,5,7-trioxoheptanoic acid, the synthesis of which required the corresponding methyl derivatives of 1-phenyl-1,3,5-hexanetrione (**1**). Numerous triketones have been prepared previously, but most of those required for this study have not. This paper, therefore, describes synthetic approaches to methyl derivatives **2**–**9**, employing either acylation reactions of β diketones or methylation reactions of anions of **1**. Although the alkylation reactions of β-dicarbonyl compounds have been studied extensively,[5] the reactions of β triketones have received only limited attention.[6,7]



Results

Acylation Reactions.—Hauser and coworkers developed several closely related procedures for the preparation of 1,3,5 triketones by acylation of β diketones with esters in the presence of strong bases. The use of sodium amide or potassium amide in liquid ammonia gave satisfactory results with aromatic esters, but aliphatic esters required the use of lithium amide.[8] These reactions involve formation and acylation of 1,3 dianions of the β diketones; the metallic cation effect results from rapid proton abstraction from aliphatic esters by disodio and dipotassio diketones but relatively slow abstraction by the dilithium derivatives. With aromatic esters, an attractive alternative to the amide methods is the use of sodium hy-

(1) We gratefully acknowledge the generous support by the U. S. Public Health Service through Research Grant GM-12848 and Career Development Grant (to T. M. H.) GM-27013.

(2) T. T. Howarth and T. M. Harris, *J. Amer. Chem. Soc.*, **93**, 2506 (1971), and references cited therein.

(3) A. J. Birch, *Proc. Chem. Soc.*, 3 (1962).

(4) For example, see A. I. Scott, H. Guilford, and E. Lee, *J. Amer. Chem. Soc.*, **93**, 3534 (1971).

(5) See H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, Chapter 9.

(6) K. G. Hampton, T. M. Harris, C. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 4263 (1965).

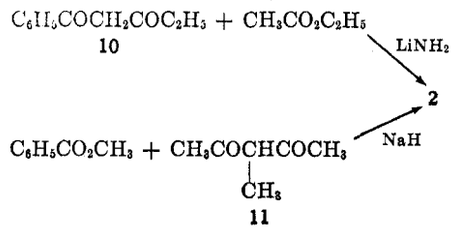
(7) J. Carnduff, J. A. Miller, B. R. Stockdale, J. Larkin, D. C. Nonhebel, and H. C. S. Wood, *J. Chem. Soc., Perkin Trans. 1*, 692 (1972).

(8) C. R. Hauser and T. M. Harris, *J. Amer. Chem. Soc.*, **80**, 6360 (1958); R. J. Light and C. R. Hauser, *J. Org. Chem.*, **25**, 538 (1960); S. D. Work and C. R. Hauser, *ibid.*, **28**, 725 (1963); F. B. Kirby, T. M. Harris, and C. R. Hauser, *ibid.*, **28**, 2266 (1963).

dride in ethereal solvents.[6,9] Here the reaction mechanism is far from clear. Sodium hydride converts diketones into their monoanions but not their dianions; yet the monosodio diketones in the presence of excess sodium hydride react at the terminal position with aromatic esters to give 1,3,5 triketones.

Either the acetylation of diketone **10** or the benzoylation of diketone **11** should be satisfactory for the preparation of diketone **2** (Scheme I). Because of the

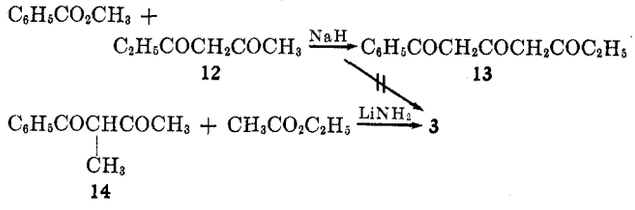
SCHEME I



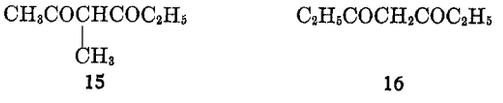
simplicity of the sodium hydride method, the latter was chosen and gave diketone **2** in 43% yield.

For the preparation of **3** the sodium hydride method would not have been satisfactory, since methyl–methylene type unsymmetrical diketones undergo aroylation at the methyl position.[6] Consequently, benzoylation of diketone **12** would have given the isomeric triketone **13**. However, triketone **3** was formed in 46% yield by acetylation of diketone **14** using the lithium amide method (Scheme II).

SCHEME II

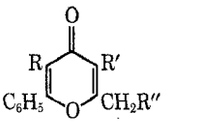


In contrast, the sodium hydride method was the method of choice for the preparation of **4**; benzoylation of unsymmetrical diketone **15** occurred preferentially at the acetyl methyl group to give **4** in 65% yield. Similarly, triketone **5** was prepared in 52% yield by the benzoylation of symmetrical diketone **16**.



The structures of triketones **2–5** were consistent with physical data (see Experimental Section), the mass spectra being of particular value. These showed α cleavage on one and sometimes both sides of each of the carbonyl groups, along with some McLafferty-type cleavages. The structures were confirmed by the conversion of **2–5** into the corresponding 4-pyrones (**17–20**) by treatment with cold, concentrated sulfuric acid. It is noteworthy that **2–5** undergo pyrone formation much more readily than **1**; indeed, pyrone formation was observed during distillation of the compounds and sometimes on storage.

(9) (a) M. L. Miles, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 1007 (1965); (b) D. M. von Schriltz, M. L. Miles, and C. R. Hauser, *ibid.*, **32**, 1774 (1967).

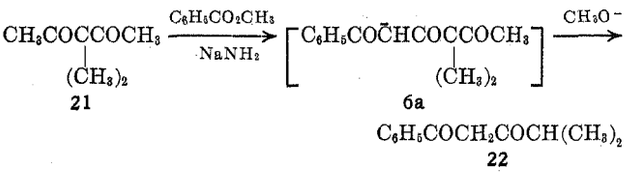


17, R = R'' = H; R' = CH_3
18, R = CH_3; R' = R'' = H
19, R = H; R' = R'' = CH_3
20, R = R'' = CH_3; R' = H

It should be mentioned that the successful benzoylations of diketones **11**, **15**, and **16** provide a useful extension of the sodium hydride method. Previous examples have been limited to aroylations of acetyl methyl groups of diketones, yielding triketones lacking substituents at the central methylene positions.

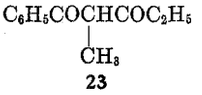
For the preparation of triketone **6**, benzoylation of diketone **21** was investigated, sodium amide being employed as the condensing agent (Scheme III). The

SCHEME III



method was unsatisfactory; the only product isolated was diketone **22**, which presumably arises by cleavage of the triketone. Cleavage occurs at the 4 bond because the uncharged 5-carbonyl group of **6a** is prone to attack by methoxide ion. The same problem exists with the sodium hydride method; in fact, the higher temperatures required for sodium hydride reactions increase the risk of this type of cleavage. The prospects for assembly of **6** by acetylation of **22** are poor; acylation of dianions of isobutyryl-type diketones has never been observed and alkylation occurs only in low yield.[10]

For the preparation of **7**, the best method appeared to be acetylation of the dilithium salt of diketone **23**, but the reaction was unsuccessful and unaltered diketone **23** was recovered. It is not known whether the dianion of **23** failed to form or failed to be acylated, but the successful acetylation of the dilithium salt of **14** suggests the former.



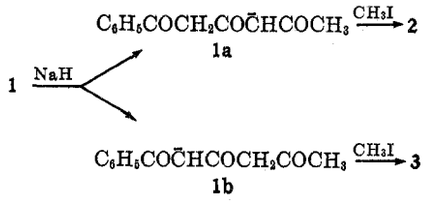
In view of these failures, the synthesis of **8** and **9** by anionic acylation procedures appeared unlikely and alkylation methods were next investigated as possible routes to the 2- and 4-di- and -trimethylated triketones **6–9**.

Methylation Reactions.—Triketone **1** reacts with 1 equiv of sodium hydride to form monoanions **1a** and **1b**. By monitoring the evolution of hydrogen, ionization was found to be essentially complete after 1–2 min. Treatment of the mixture of **1a** and **1b** with 1 equiv of methyl iodide gave a product mixture composed mainly of **1**, **2**, and **3** in the ratios 56:26:18

(10) K. G. Hampton, T. M. Harris, and C. R. Hauser, *ibid.*, **31**, 1035 (1966).

(Scheme IV). The analysis was made by comparison of the nmr spectrum of the unfractionated product

SCHEME IV



mixture with spectra of authentic samples of **1**–**3**. We would expect the acidities of **1a** and **1b** to be similar since the pK_a values (determined in hydroxylic solvents) of acetylacetone and benzolacetone are, respectively, 9.01 and 8.73.[11] The 4-methylation to 2-methylation ratio of 1.4 suggests that **1a** might be slightly more nucleophilic than **1b**.

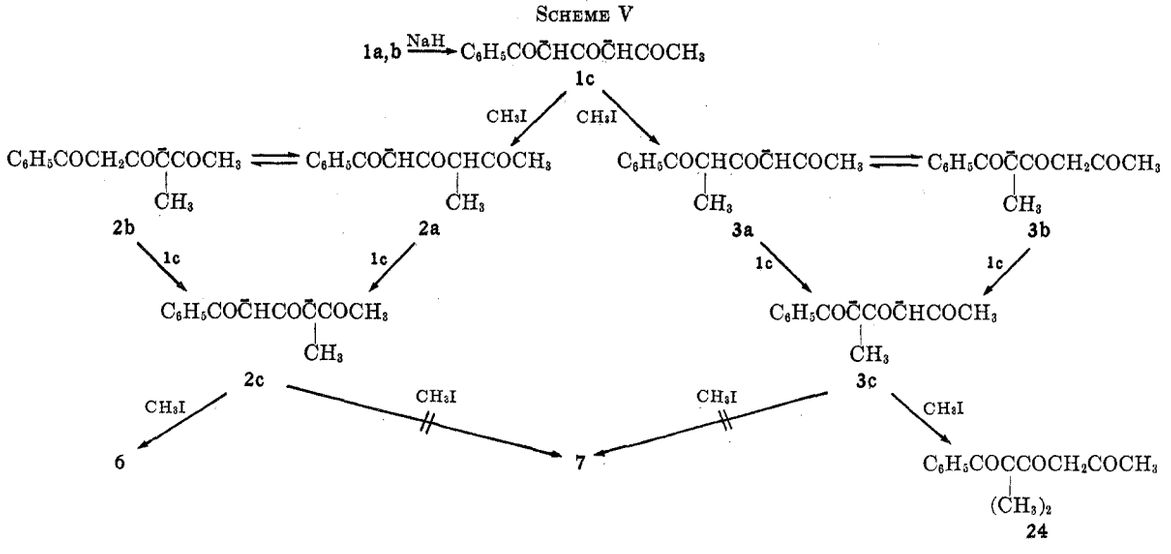
An additional equivalent of hydrogen was evolved when the mixture of **1a** and **1b** was treated with excess sodium hydride, the ionization process to form dianion **1c** requiring as much as 2 hr to go to completion. No significant additional amount of hydrogen was evolved during a subsequent 24-hr period. A crude comparison of alkylation rates showed **1c** to be at least ten times more reactive than **1a,b**. When **1c** was treated with 1 equiv of methyl iodide, nmr analysis of the product mixture indicated **1**, **2**, **3**, and **6** to be present in the approximate ratios 18:46:24:12 (Scheme V).

In view of the lower reactivity of monoanions **1a,b** compared with **1c**, it seems likely that **6** arose primarily from **2c**, which was formed by reionization of **2a,b** by **1c**. This hypothesis for formation of **6** requires that **2c** not be appreciably more basic than **1c** and that **2c** show high selectivity for methylation at the 4 position. The pK_a of diketone **11**, measured in an aqueous medium, has been reported to be 10.88,[13] which by comparison with that for benzoylacetone[11] suggests that **2c** should be about 100 times more basic than **1c**. However, recent studies of the acidities of aliphatic monoketones by House and coworkers have shown that with lithium salts in an ethereal solvent alkyl branching at the α position tends to stabilize enolate anions.[14] A similar effect in the present case would diminish the difference in the basicities of **1c** and **2c** and would facilitate formation of **2c**.

The selectivity of **2c** for methylation at the 4 position was demonstrated by forming **2c** from **2** and treating it with 1 equiv of methyl iodide. The reaction afforded 43% of triketone **6**; most of the remainder of the product mixture was starting triketone **2** and the related pyrone **18**. Less than 3% of triketone **7** was present, emphasizing the greater nucleophilicity of the 4 position of **2c** compared to the 2 position.

In the alkylation of **1c**, the failure of product **3** to undergo further methylation under the reaction conditions would appear to stem from failure of **3a,b** to be reionized by **1c**. Steric inhibition of resonance in **3c**, resulting from interaction between the phenyl and

SCHEME V



Complete interpretation of the nmr spectrum was not possible until after the synthesis of **6** and **7** had been achieved and a sample of **24** had been prepared by the method of Pinder and Robinson.[12] Little evidence was found for the presence of triketones **7** and **24**, indicating that, if present, they made up less than 3% of the product mixture. Combining the yields of **2** and **6** to obtain the total amount of initial attack at the 4 position, the ratio of 4- to 2-methylation was 2.1, reflecting again a preference for the initial attack to occur at the 4 position.

the 2-methyl groups, makes **3c** substantially more basic than **1c**.

From the above considerations, it is clear that, for the synthesis of **6**, the use of 3 equiv of sodium hydride (as well as 2 equiv of methyl iodide) would be advantageous. The third equivalent would replace **1c** in the ionization of **2a,b** to form **2c** (see Scheme V). Another way to view this is that, irrespective of the mechanism of formation of **6**, as much as 3 equiv of base will be consumed in the formation of **6**, since the com-

(11) L. Laloi and P. Rumpf, *Bull. Soc. Chim. Fr.*, 2461 (1964).
(12) A. R. Pinder and R. Robinson, *J. Chem. Soc.*, 3341 (1955).
(13) L. Laloi and P. Rumpf, *Bull. Soc. Chim. Fr.*, 1645 (1961).
(14) H. O. House and V. Kramer, *J. Org. Chem.*, **28**, 3362 (1963); H. O. House and B. M. Trost, *ibid.*, **30**, 1341 (1965).

pound will probably be present in the final reaction mixture as its monoanion. These expectations were borne out when a reaction employing 3 equiv of sodium hydride and 2 of methyl iodide produced triketones **2**, **3**, **6**, and **24** in the ratios 1:12:81:6. Triketone **6** was isolated from the mixture by column chromatography in 52% yield. The course of this reaction was followed by taking aliquots from the reaction mixture periodically and estimating their composition by nmr. The results are shown in Table I.

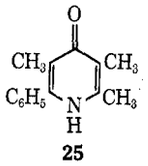
TABLE I

ALKYLATION OF TRIKETONE 1 EMPLOYING 3 EQUIV OF SODIUM HYDRIDE AND 2 EQUIV OF METHYL IODIDE IN TETRAHYDROFURAN

Reaction period, hr	Triketones, %					
	1	2	3	6	7	24
0.1	80	12	6	2	0	0
0.5	52	24	11	10	0	3
3	3	4	12	75	0	6
18	0	5	7	80	0	8
21	0	1	12	81	0	6

Initially, the main products were monomethylated triketones **2** and **3**, with the former predominating, the concentration of **2** peaking after 0.5 hr and then falling as further alkylation occurred to give **6**. This second alkylation was rapid and **6** made up 75% of the mixture after 3 hr, the reaction being essentially complete at that point. The presence of **24** in the reaction mixture reflects the fact that sodium hydride, in contrast to **1c**, is able to convert **3a,b** to **3c** (see Scheme V). It is interesting that **3c**, like **2c**, methylates at the site of initial methylation. Thus, **24**, not **7**, was the product formed.

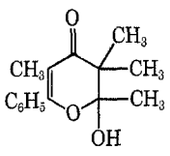
In order to prepare triketone **7** from **1**, conditions were required under which the alkylation of both of the anions of **1c** would proceed faster than proton transfer reactions. This would avoid the formation of **6** and **24** and was achieved using methyl iodide as the solvent, following a procedure for the monoalkylation of a benzoylacetone by Hindley.[15] The disodium salt of **1c** was formed in tetrahydrofuran, isolated, and resuspended in methyl iodide. After refluxing for 3 hr, **7** was isolated in 24% yield by column chromatography. Longer reaction periods gave higher yields of **7** but the isolation was complicated by the presence of additional products. The structure of **7** was confirmed spectroscopically and by transformation into pyridone **25**. Triketone **7** might also have been prepared by use



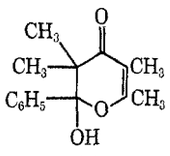
25

of the thallium salt of **1c**.[16] However, the present method avoids the toxicity hazards associated with the handling of thallium compounds.

Triketones **8** and **9** were prepared by treatment of **1** with excess methyl iodide and potassium carbonate in refluxing acetone. The reaction yielded 20% of a mixture of the two trimethylated compounds with **8** predominating and no indication of the tetramethylation product. Triketones **8** and **9** exist as cyclic hemiketals **26** and **27** with dissymmetry of the molecules



26



27

evident in the nmr spectra, the geminal methyl groups being nonequivalent in both cases. The hemiketals were distinguished from each other by their ultraviolet spectra, the more highly conjugated **26** exhibiting λ_{max} at 296 nm compared with 243 nm for **27**. Similar structures could not be detected in the tautomer mixtures of **1**–**6**, although it is likely that they are intermediates in the formation of 4-pyrones from triketones lacking geminal substituents. Triketone **7** possibly has small amounts of hemiketal epimers in equilibrium with the acyclic tautomers. A more useful preparative synthesis of **26** is treatment of triketone **6** with methyl iodide and potassium carbonate in refluxing acetone. Cyclic hemiketal **26**, identical in all respects with the sample prepared above, was isolated in 57% yield.

Experimental Section

Silicar CC-4 (100–200 mesh) silicic acid, obtained from Mallinckrodt Chemical Works, was used for column chromatography. The products were eluted with hexane containing increasing amounts of ether. Melting points were taken in open capillaries and are corrected. Infrared spectra were obtained using either liquid films or potassium bromide discs with a Beckman IR-10 spectrophotometer. Ultraviolet spectra were recorded with a Beckman DB spectrophotometer. Nuclear magnetic resonance spectra were recorded on either a Varian A-60 or an XL-100 spectrometer with tetramethylsilane as the internal standard. With triketones, which can exist as a mixture of several keto–enol tautomers, data are given for the dominant form. Mass spectra were recorded using the direct inlet of an LKB-9000 gas chromatograph–mass spectrometer at 70 eV. Only molecular ions and important α-cleavage and McLafferty-type fragments are reported. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

4-Methyl-1-phenyl-1,3,5-hexanetrione (**2**).—A solution of 3-methyl-2,4-pentanedione[17] (**11**, 19.4 g, 0.17 mol) in 20 ml of tetrahydrofuran (THF) was added to a cooled (ice bath) suspension of sodium hydride (16.8 g, 0.7 mol, from a sodium hydride suspension in oil) in THF (600 ml). When hydrogen evolution from the mixture had ceased, methyl benzoate (46 g, 0.34 mol) in THF (50 ml) was added dropwise over 2 hr. After an additional 7 hr at reflux, the solvent was removed *in vacuo*, ether (250 ml) was added to the cooled residue, and excess base was destroyed with the cautious addition of ice. The mixture was extracted with water and the extract was acidified with dilute hydrochloric acid and extracted with ether. The ethereal extract was washed with 5% sodium bicarbonate and with water, dried with magnesium sulfate, and evaporated *in vacuo* to leave a brown oil. Distillation afforded **2** (14.0 g, 38%) as a pale yellow oil: bp 115–120° (0.2 mm); ir (neat oil) 1720, 1601, 1450 cm^{-1}; uv (EtOH) 310 nm (ϵ 15,700), 247 (5400), 222 (6200); nmr (CCl_4) δ (2-enol tautomer), 1.39 (3, d, J = 7 Hz, 4-$CHCH_3$), 2.23 (3, s, 6-CH_3), 3.57 (1, q, J = 7 Hz, 4-$CHCH_3$), 6.24 (1, s, 2-CH=), 7.25–8.00 (5, m, 1-C_6H_5), 12.0–13.5 ppm (1, s, enol); mass spectrum m/e (rel intensity) 218 ($M^{\cdot+}$, 21), 176 (46), 147 (100), 120 (4), 105 (87), 99 (5), 43 (52).

(15) K. B. Hindley, Ph.D. Thesis, Liverpool University, England, 1970, p 30.

(16) E. C. Taylor, G H. Hawks, and A. McKillop, *J. Amer. Chem. Soc.*, **90**, 2421 (1968).

(17) A. W. Johnson, E. Markham, R. Price, and K. B. Shaw, *J. Chem. Soc.*, 4254 (1958).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.57; H, 6.52.

2-Methyl-1-phenyl-1,3,5-hexanetrione (**3**).—To a suspension of 0.5 mol of lithium amide (prepared from 3.5 g of lithium) in anhydrous, liquid ammonia (750 ml) was added 2-methyl-1-phenyl-1,3-butanedione[18] (**14**, 16.3 g, 0.0925 mol) in ether (15 ml). After 2 hr, 35.2 g (0.4 mol) of ethyl acetate was added and, after an additional 10 hr, the ammonia was evaporated. Ether (300 ml), ice, and then dilute hydrochloric acid were added; the ethereal layer was separated, washed with water and with 5% sodium bicarbonate, dried over magnesium sulfate, and evaporated *in vacuo* to leave a dark red-brown oil. Chromatography afforded **3** (9.0 g, 45%) as a pale yellow oil which solidified below 0°: bp 115–118° (0.2 mm); mp 25–30°; ir (neat) 1690, 1600, 1455 cm^{-1}; uv (EtOH) 281 nm (ϵ 11,500), 249 (11,900); nmr (CCl_4) δ (4-enol tautomer) 1.41 (3, d, J = 7 Hz, 2-$CHCH_3$), 1.93 (3, s, 6-CH_3), 4.25 (1, q, J = 7 Hz, 2-$CHCH_3$), 5.43 (1, s, 4-CH=), 7.3–8.1 (5, m, 1-C_6H_5), 15–17 ppm (1, s, enol); mass spectrum *m/e* (rel intensity) 218 ($M\cdot^+$, 3), 134 (3), 105 (100), 85 (5), 43 (16).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.80; H, 6.60.

4-Methyl-1-phenyl-1,3,5-heptanetrione (**4**).—Following the general procedure outlined for triketone **2**, the reaction of 3-methyl-2,4-hexanedione[19] (**15**, 12.8 g, 0.1 mol), methyl benzoate (34 g, 0.25 mol), and sodium hydride (7.2 g, 0.3 mol) afforded **4** (15 g, 65%) as a pale yellow oil: bp 118–125° (0.18 mm); ir (neat) 1720, 1605, 1455 cm^{-1}; uv (EtOH) 314 nm (ϵ 15,300), 248 (5550), 222 (5700); nmr (CCl_4) δ (2-enol tautomer) 1.02 (3, t, J = 7 Hz, 7-CH_3), 1.35 (3, d, J = 7 Hz, 4-$CHCH_3$), 2.46 (2, q, J = 7 Hz, 6-CH_2), 3.52 (1, q, J = 7 Hz, 4-$CHCH_3$), 6.20 (1, s, 2-CH=), 7.25–8.00 (5, m, 1-C_6H_5), 13.7–15.5 ppm (1, s, enol); mass spectrum *m/e* (rel intensity) 232 ($M\cdot^+$, 9), 203 (5), 176 (57), 147 (71), 105 (100), 57 (52).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.26; H, 6.95.

2-Methyl-1-phenyl-1,3,5-heptanetrione (**5**).—Following the general procedure outlined for triketone **2**, the reaction of dipropionylmethane[19] (**16**, 12.8 g, 0.1 mol), methyl benzoate (27.2 g, 0.2 mol), and sodium hydride (7.2 g, 0.3 mol) afforded **5** (12.0 g, 52%) as a pale yellow oil: bp 110–113° (0.08 mm); ir (neat) 1685, 1600, 1452 cm^{-1}; uv (EtOH) 282 nm (ϵ 11,000), 249 (11,300); nmr (CCl_4) δ (4-enol tautomer) 1.05 (3, t, J = 7 Hz, 7-CH_3), 1.42 (3, d, J = 7 Hz, 2-$CHCH_3$), 2.22 (2, q, J = 7 Hz, 6-CH_2), 4.27 (1, q, J = 7 Hz, 2-$CHCH_3$), 5.47 (1, s, 4-CH=), 7.25–8.10 (5, m, 1-C_6H_5), 12.6–14.0 ppm (1, s, enol); mass spectrum *m/e* (rel intensity) 232 ($M\cdot^+$, 3), 176 (4), 134 (5), 105 (100), 99 (5), 57 (8).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.49; H, 6.96.

4,4-Dimethyl-1-phenyl-1,3,5-hexanetrione (**6**).—This compound was synthesized by two routes.

(1) A solution of 1-phenyl-1,3,5-hexanetrione[9a] (1, 10.2 g, 0.08 mol) in THF (100 ml) was added with stirring to an ice–salt cooled suspension of sodium hydride (6.0 g, 0.25 mol) in THF (100 ml). The mixture was stirred at −20° for 2 hr and then methyl iodide (15 g, 0.17 mol) was added in one batch. The mixture was stirred for 6 hr at −20° and 20 hr at room temperature. The solvent was removed *in vacuo*, the excess base was destroyed by cautious addition of ice, and the mixture was acidified with dilute hydrochloric acid and extracted with ether. The extract was washed with water, dried over magnesium sulfate, and evaporated *in vacuo* to give a red-brown oil. Chromatography on silicic acid afforded **6** (6.05 g, 52%) as a pale yellow oil: ir (neat) 1710, 1600, 1565, 1455, and 1350 cm^{-1}; uv (EtOH) 306 nm (ϵ 15,900), 244 (5500), 229 (sh, 6400), 223 (7100); nmr ($CDCl_3$) δ (2-enol tautomer) 1.35 [6, s, 4-$C(CH_3)_2$], 2.08 (3, s, 6-CH_3), 6.11 (1, s, 2-CH=), 7.25–7.94 (5, m, 1-C_6H_5), 13.7–15.7 ppm (1, s, enol); mass spectrum *m/e* (rel intensity) 232 ($M\cdot^+$, 11), 190 (60), 147 (100), 105 (80), 86 (31), 43 (47).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.60; H, 7.04.

(2) Triketone **2** was added to a suspension of sodium hydride (0.286 g, 0.012 mol) in THF (100 ml). After the evolution of hydrogen had slowed, the mixture was warmed at 40° until evolution ceased. The mixture was cooled and methyl iodide (1.5 g, 0.011 mol) was added. After 0.5 hr at room temperature and 1 hr at 45°, the solvent was removed *in vacuo* and the excess base was destroyed with the cautious addition of ice. The mixture was acidified with dilute hydrochloric acid and extracted with ether. The extract was washed with water, dried with magnesium sulfate, and evaporated *in vacuo* to yield a brown oil. Chromatography afforded **6** (1.0 g, 43%) as a pale yellow oil, identical in all respects with the sample prepared above.

2,4-Dimethyl-1-phenyl-1,3,5-hexanetrione (**7**).—Triketone **1** (25.5 g, 0.125 mol) in THF (120 ml) was added to a slurry of sodium hydride (6.0 g, 0.25 mol) in THF (500 ml) over 1 hr. The mixture was stirred at room temperature for 18 hr, concentrated to 200 ml *in vacuo*, and cooled in an ice bath. The precipitate was collected by filtration and recrystallized from THF (100 ml) to yield fine crystals of disodium salt **1c** (9.8 g, 39%).

A mixture of disodium salt **1c** (2.00 g, 0.0115 mol) and methyl iodide (80 ml) was refluxed for 3 hr, cooled to room temperature, and filtered. The filtrate was evaporated *in vacuo* to yield a yellow oil which was taken up in ether. The solution was washed with water, dried with magnesium sulfate, and evaporated *in vacuo*. Chromatography of the residue furnished **7** (0.445 g, 24%) as a pale yellow oil: ir (neat) 1692, 1600, 1454 cm^{-1}; uv (EtOH) 290 nm (ϵ 9620), 220 (8030); nmr ($CDCl_3$) δ (triketo tautomer) 1.15–1.55 (2- and 4-$CHCH_3$ not resolved from signals of enol tautomers), 2.1 (3, s, 6-CH_3), 3.83 (1, q, J = 7 Hz, 4-$CHCH_3$), 4.8 (1, q, J = 7 Hz, 2-$CHCH_3$), 7.25–8.1 ppm (m, 1-C_6H_5); mass spectrum (rel intensity) 232 (1.1, $M\cdot^+$), 190 (6.1), 161 (9.1), 134 (10), 105 (100), 43 (25). The material, although substantially free of impurities, was not analytically pure; purification was hampered by decomposition that occurred during chromatography and other manipulation. A satisfactory analysis was obtained on the pyridone derivative **25** described below.

2,3-Dihydro-2-hydroxy-2,3,3,5-tetramethyl-6-phenyl-4*H*-pyran-4-one (**26**) **and 5,6-Dihydro-6-hydroxy-2,3,5,5-tetramethyl-6-phenyl-4*H*-pyran-4-one** (**27**) **by Methylation of 1.**—A mixture of triketone **1** (10.2 g, 0.05 mol), methyl iodide (18.2 g, 0.128 mol), anhydrous potassium carbonate (17.0 g, 0.123 mol), and acetone (150 ml) was refluxed for 7 hr, cooled, and filtered. The filtrate was evaporated *in vacuo;* recrystallization of the residue from chloroform–hexane gave **26** (3.0 g, 20%), containing a small amount of **27**. Chromatography gave **26** as colorless crystals: mp 120–140° after recrystallization from chloroform–hexane; ir (KBr pellet) 1640, 1600, 1455, 1375 cm^{-1}; uv (EtOH) 296 nm (ϵ 13,800), 227 (6700); nmr ($CDCl_3$) δ 1.20 (3, s, 3-CH_3), 1.26 (3, s, 3-CH_3), 1.62 (3, s, 2- or 5-CH_3), 1.83 (3, s, 5- or 2-CH_3), 3.61 (1, s, 2-OH, exchangeable with D_2O), 7.1–7.8 ppm (5, m, 6-C_6H_5); mass spectrum *m/e* (rel intensity) 246 ($M\cdot^+$, 10), 204 (14), 161 (100), 134 (6), 105 (97), 86 (20), 43 (37).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.17; H, 7.48.

A later fraction from the column was recrystallized from chloroform–hexane to give **27**: mp 136–148°; ir (KBr pellet) 1600, 1440, 1385, 1342 cm^{-1}; uv (EtOH) 273 nm (ϵ 10,300); nmr ($CDCl_3$) δ 0.93 (3, s, 5-CH_3), 1.11 (3, s, 5-CH_3), 1.80 (3, s, 2- or 3-CH_3), 2.08 (3, s, 3- or 2-CH_3), 3.1 (1, s, 6-OH, exchangeable with D_2O), 7.1–7.8 ppm (5, m, 6-C_6H_5); mass spectrum *m/e* (rel intensity) 46 ($M\cdot^+$, 6), 204 (3), 148 (21), 105 (100), 99 (6), 43 (21).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15, H, 7.37. Found: C, 73.33; H, 7.53.

Pyran 26 by Methylation of 6.—A mixture of triketone **6** (1.0 g, 0.0043 mol), methyl iodide (1.4 g, 0.0106 mol), anhydrous potassium carbonate (3.0 g, 0.0217 mol), and acetone (60 ml) was refluxed for 5 hr, cooled, and filtered. The filtrate was evaporated *in vacuo*, the residue was dissolved in ether, and the ethereal solution was washed with water, dried with magnesium sulfate, and evaporated *in vacuo*. Recrystallization of the residue from chloroform–hexane gave **26** (0.6 g, 57%) as colorless cubes, mp 120–140°, identical in all respects with the specimen prepared above.

General Procedure for Preparation of Pyran-4-ones 17–21.—Approximately 1.5 g of the appropriate triketone was combined with sulfuric acid (20 ml) at 0°. After 2 hr, the mixture was neutralized by the addition of ice and solid sodium bicarbonate and was extracted with ether. The extract was washed with 2 *M* sodium hydroxide and with water, dried with magnesium sulfate, and evaporated *in vacuo*. Solid products were re-

(18) Diketone **14**, bp 90° (0.2 mm), was prepared in 88% yield by the procedure described by Johnson, *et al.*, for the preparation of **11**.[17]

(19) F. W. Swamer and C. R. Hauser, *J. Amer. Chem. Soc.*, **72**, 1352 (1950).

crystallized from chloroform–hexane; liquids were purified by column chromatography. Yields and physical data are given for each compound.

2,3-Dimethyl-6-phenyl-4*H*-pyran-4-one (**17**) was obtained (62%) as tan needles: mp 103–105°; ir (KBr pellet) 1650, 1605, 1445, 1415, 1370 cm^{-1}; nmr ($CDCl_3$) δ 2.00 (3, s, 3-CH_3), 2.39 (3, s, 2-CH_3), 6.70 (1, s, 5-CH=), 7.3–7.9 ppm (5, m, 6-C_6H_5).

Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 78.17; H, 6.18.

2,5-Dimethyl-6-phenyl-4*H*-pyran-4-one (**18**) was obtained (87%) as a pale yellow oil: ir (neat) 1660, 1620, 1445, 1405 cm^{-1}; nmr ($CDCl_3$) δ 2.00 (3, s, 2-CH_3), 2.22 (3, s, 5-CH_3), 6.15 (1, s, 3-CH=), 7.3–7.7 ppm (5, m, 6-C_6H_5).

Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.75; H, 6.02.

2-Ethyl-3-methyl-6-phenyl-4*H*-pyran-4-one (**19**) was obtained (98%) as tan needles: mp 62–63°; ir (KBr pellet) 1640, 1600, 1450, 1410, 1370 cm^{-1}; nmr ($CDCl_3$) δ 1.34 (3, t, J = 7 Hz, 2-CH_3), 2.01 (3, s, 3-CH_3), 2.74 (2, q, J = 7 Hz, 2-CH_2), 6.70 (1, s, 5-CH=), 7.3–7.9 ppm (5, m, 6-C_6H_5).

Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.45; H, 6.58.

2-Ethyl-5-methyl-6-phenyl-4*H*-pyran-4-one (**20**) was obtained (98%) as a pale yellow liquid: ir (neat) 1660, 1650, 1620, 1445, 1405, 1370 cm^{-1}; nmr ($CDCl_3$) δ 1.25 (3, t, J = 7 Hz, 2-CH_3), 2.06 (3, s, 5-CH_3), 2.57 (2, q, J = 7 Hz, 2-CH_2), 6.20 (1, s, 3-CH=), 7.51 ppm (5, s, 6-C_6H_5).

Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.26; H, 6.69.

2,3,5-Trimethyl-6-phenyl-4-(1*H*)-pyridone (**25**).—Liquid ammonia (10 ml) was added to a solution of triketone **7** (1.0 g, 0.0045 mol) in absolute ethanol (300 ml) and the mixture was warmed gently for 10 min and then boiled to dryness on the steam bath. The remaining oil was triturated with acetone to form crude **25** (0.83 g, 86%) as a pale yellow solid. Recrystallization from acetone–absolute ethanol and then from chloroform gave colorless needles: mp 270°; ir (KBr pellet) 1614, 1598, 1490, 1371 cm^{-1}; nmr ($CDCl_3$) δ 2.33 (3, s, 2-CH_3), 2.45 (3, s, 5-CH_3), 2.75 (3, s, 3-CH_3), 7.3–7.7 (5, m, 6-C_6H_5), the 2- and 3-CH_3 signals are broadened by long-range coupling.

Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.73; H, 6.99; N, 6.45.

Registry No.— **1**, 1469-95-0; **1c**, 37676-25-8; **2**, 37676-26-9; **3**, 37676-27-0; **4**, 37676-28-1; **5**, 37676-29-2; **6**, 37676-30-5; **7**, 37676-31-6; **11**, 815-57-6; **14**, 6668-24-2; **15**, 4220-52-4; **16**, 7424-54-6; **17**, 37676-33-8; **18**, 37676-34-9; **19**, 37735-76-5; **20**, 37676-35-0; **25**, 37676-36-1; **26**, 37676-37-2; **27**, 37735-77-6; methyl benzoate, 93-58-3; ethyl acetate, 141-78-6.

Synthesis of 1,4 and 1,5 Diketones from *N,N,N′,N′*-Tetramethyldiamides and Organolithium Reagents

DENNIS C. OWSLEY,* JANICE M. NELKE, AND JORDAN J. BLOOMFIELD

Corporate Research Department, Monsanto Company, St. Louis, Missouri 63166

Received September 20, 1972

A new, one-step synthesis of 1,4 and 1,5 diketones from a variety of organolithium compounds and *N,N,N′,N′*-tetramethylsuccinamide and *N,N,N′,N′*-tetramethylglutaramide is described. Yields vary from 4 to 76%. Yields of 1,5 diketones are generally higher than those of 1,4 diketones. *N,N,N′,N′*-Tetraethylsuccinamide did not give 1,4 diketones with phenyllithium, 2-pyridyllithium, or 6-bromo-2-pyridyllithium.

During the course of some studies on the synthesis and properties of a number of heterocyclic systems, we needed a series of 1,4 and 1,5 diketones as intermediates. In the case of a bis-2-pyridyl diketone, no ready one-step synthesis of these compounds was available. The pyridine substitution pattern dictated the use of a 2-pyridyl Grignard reagent or 2-pyridyllithium compound.

Both aldehydes and ketones have been prepared from *N,N*-dialkylamides and either Grignard reagents[1] or organolithium compounds.[2] Furthermore, it has been reported that diketones are produced in low yield by the reaction of 2 equiv of a Grignard reagent with an *N,N,N′,N′*-tetraalkyldiamide.[3] Repeated failures to prepare any ketone from the Grignard reagent of 2,6-dibromopyridine led us to investigate the organolithium compound.[4] Owing to our initial success, we decided to study the scope of the reaction. To our knowledge, no reaction of 2 equiv of an organolithium compound with *N,N,N′,N′*-tetraalkyldiamides has been reported.

(1) (a) L. Bouveault, *Bull. Soc. Chim. Fr.*, **31**, 1322 (1904); (b) G. Gilbert and B. F. Aycock, *J. Org. Chem.*, **22**, 1013 (1957).

(2) (a) J. Sicé, *J. Amer. Chem. Soc.*, **75**, 3697 (1953); (b) J. Sicé, *J. Org. Chem.*, **19**, 70 (1954); (c) E. A. Evans, *J. Chem. Soc.*, 4691 (1956); (d) E. A. Braude and E. A. Evans, *ibid.*, 3334 (1955); (e) E. Jones and I. M. Moodie, *J. Chem. Soc. C*, 1195 (1967).

(3) (a) E. E. Blaise, *C. R. Acad. Sci.*, **173**, 313 (1921); (b) E. E. Blaise and M. Montague, *ibid.*, **180**, 1345 (1925).

(4) J. E. Parks, B. E. Wagner, and R. H. Holm, *Inorg. Chem.*, **10**, 2477 (1971).

Results and Discussion

The results of our study of the reaction of a variety of organolithium reagents with either *N,N,N′,N′*-tetramethylsuccinamide or *N,N,N′,N′*-tetramethylglutaramide are summarized in Table I. With the exception of 2-thienyllithium, no attempts were made to optimize yields. Butyllithium gave a very complex mixture with *N,N,N′,N′*-tetramethylsuccinamide. In general, the yields of 1,5 diketones were higher than those of the 1,4 diketones.

TABLE I

YIELDS OF PRODUCTS FROM THE REACTION

$$2RLi + Me_2NCO(CH_2)_nCONMe_2 \xrightarrow{-78^\circ} RCO(CH_2)_nCOR$$

R	n	Yield,[a] %	Solvent	Reaction time, hr
Phenyl	2	4	Ether	24
6-Bromo-2-pyridyl	2	71	Ether	3
2-Pyridyl	2	20	Ether	3–4
2-Thienyl[b]	2	33	THF	24
Phenyl	3	50	Ether	24
6-Bromo-2-pyridyl	3	76	Ether	3
2-Pyridyl	3	20	Ether	3–4
2-Thienyl[b]	3	24	THF	24
n-Butyl	3	19	Ether	2

[a] Yields based on purified product. [b] Run with 4 equiv of 2-thienyllithium.