Acknowledgments.—The authors are indebted to Dr. Robert Lundin for the nmr spectra and to Dr. H. M. Gaskins, Officer-in-Charge, and Mr. N. Almeyda of the Federal Experiment Station for the fruit collections.

An Efficient Synthesis of Symmetrical 1,3-Diglycerides[1]

P. H. BENTLEY[2] AND W. MCCRAE

Institute of Organic Chemistry, Syntex Research, Palo Alto, California 94304

Received November 26, 1969

The symmetrical 1,3-diglycerides have been obtained by a variety of procedures, most of which involve protecting groups requiring chemical or catalytic cleavage.[3] Syntheses of the unsymmetrical 1,2-diglycerides also require the use of protective groupings which must be removed under very mild conditions in order to prevent acyl migration from the C-2 to the terminal positions. Hydrogenolysis overcomes this problem but limits the route to the synthesis of saturated diglycerides.

Recently, Windholz and coworkers[4] described the use of β,β,β-trichloroethoxycarbonyl chloride as a generally applicable protecting group for hydroxyl and amino functions. The carbonates and urethans formed are stable under a variety of oxidation and reduction conditions but are easily removed by treatment with zinc dust in acetic acid or methanol.

This reagent has been utilized by Pfeiffer[5] in the synthesis of 1,2-diglycerides thus avoiding many of the drawbacks of the earlier methods. There is as yet, however, no satisfactory synthetic approach to the synthesis of the symmetrical 1,3-diglycerides, particularly those with unsaturated side chains.

Rearrangement of the 1-iodo-2,3-diglyceride by refluxing with silver nitrite in 80% aqueous alcohol,[6] a convenient procedure for the synthesis of saturated 1,3-diglycerides, proved unsatisfactory in our hands for the corresponding unsaturated compounds owing to silver catalyzed isomerization of the olefinic center. The catalytic part played by the silver in this rearrangement was established by treating pure oleic acid with silver nitrite under the prescribed experimental conditions, *viz.*, reflux in 80% aqueous alcohol for 2–3 hr—this produced a mixture containing 32% elaidic acid.

Use of dihydroxyacetone as a starting material has been examined by Barry and Craig,[7] but the synthetic sequence used was elaborate, requiring the protection of the carbonyl group as a mercaptal, and no further work has appeared in the literature since that time. We have found that dihydroxyacetone is an ideal starting material for the synthesis of long-chain 1,3-diglycerides, *i.e.*, glycerol 1,3-dipalmitate and -dioleate since it is readily acylated with a fatty acid chloride in the presence of pyridine in high yield and the central keto group rapidly reduced by borohydride in tetrahydrofuran solution at 5° to give the 1,3-diglyceride without detectable amounts, by thin layer chromatography, of the 1,2-diglycerides. Synthesis of short-chain diglycerides is also possible by this method, but results are less satisfactory. In a typical experiment glycerol 1,3-diacetate was obtained in over 80% yield but when examined by nmr was shown to contain approximately 10% 1,2 isomer.

Experimental Section[8]

1,3-Dihydroxypropan-2-one 1,3-Diacetate.—Dihydroxy acetone (15.0 g) was dissolved in pyridine (50 ml) and acetic anhydride (50 ml). After 1 hr at 20°, the solvents were removed as completely as possible by vacuum distillation. The residue, dissolved in ethyl acetate, was washed with water, 3% aqueous hydrochloric acid, and water and dried. Evaporation and crystallization from benzene–hexane gave the diacetate (22.9 g, 81%) as long colorless needles, mp 46–47° (lit.[9] mp 46–47°).

1,2,3-Trihydroxypropane 1,3-Diacetate.—The above diacetate (10.0 g) was dissolved in tetrahydrofuran (150 ml), and water (10 ml) and treated portionwise at 5° with neutral sodium borohydride (2 g).[10] After 30 min excess borohydride was destroyed by dropwise additon of glacial acetic acid (1 ml), and the solution was diluted with chloroform, washed with water, aqueous sodium bicarbonate, and water, and dried over magnesium sulfate. Evaporation gave the diacetate as a colorless oil (9.10 g), bp 150° (12 mm) [lit.[11] bp 149° (12 mm)]. The nmr, however, showed a peak at δ 3.75 ($CDCl_3$ solution, unesterified $-CH_2OH$) indicating the presence of up to 10% 1,2 isomer.

1,3-Dihydroxypropan-2-one 1,3-Dioleate.—Dihydroxyacetone (3.0 g) was stirred under nitrogen in chloroform (150 ml). To this heterogeneous mixture was added oleoyl chloride (20 ml) in chloroform (150 ml) followed by anhydrous pyridine (10 ml). After 30-min stirring at room temperature the reaction mixture became homogeneous and 1 hr later no trace of acid chloride could be detected. The bulk of the solvent was removed under vacuum. The residue was shaken with water and ethyl acetate and the organic layer separated. The aqueous layer was again shaken with ethyl acetate and the combined extracts were washed with water, dried over sodium sulfate, and evaporated. The resulting final oil was recrystallized from methanol to give 1,3-dihydroxypropan-2-one 1,3-dioleate (15.8 g, 76%) as small plates, mp 43–44°.

Anal. Calcd for $C_{39}H_{70}O_5$: C, 75.80; H, 11.4. Found: C, 75.85; H, 11.04.

1,2,3-Trihydroxypropane 1,3-Dioleate.—The dioleate (10 g) was dissolved in tetrahydrofuran (150 ml) and water (10 ml). The heterogeneous solution was chilled to 5° and sodium borohydride[10] (1.0 g) added in small portions. After reaction and work-up as described above, an oil (9.0 g, 89%) was obtained which partially crystallized to give 1,2,3-trihydroxypropane 1,3-dioleate as needles, mp 20–22° (lit.[3] mp 25°). No trace of the 1,2 isomer was detected by thin layer chromatography [tlc system hexane–ethyl acetate (6:1)].

1,3-Dihydroxypropan-2-one 1,3-Dipalmitate.—Dihydroxyacetone (7.0 g) was stirred in chloroform (300 ml) under nitrogen at room temperature. To this was added palymitoyl chloride (44 g) followed by anhydrous pyridine (15 ml). The heterogeneous mixture was stirred for 3 hr and diluted with water and the chloroform layer separated. The aqueous layer was extracted

(1) Contribution No. 371 from the Institute of Organic Chemistry, Syntex Research. For No. 370, see H. Carpio, P. Crabbé, and W. Rooks, *J. Med. Chem.*, in press.

(2) Syntex Postdoctoral Fellow, 1967–1968.

(3) L. Hartman, *Chem. Rev.*, **58**, 845 (1958).

(4) T. B. Windholz and D. B. R. Johnston, *Tetrahedron Lett.*, 2555 (1967).

(5) (a) F. R. Pfeiffer *et al.*, *ibid.*, 3549 (1968); (b) F. R. Pfeiffer *et al.*, *J. Org. Chem.*, **34**, 2795 (1969).

(6) F. L. Jackson, Ph.D. Thesis, Pittsburgh University, Pittsburgh, Pa., 1943.

(7) P. J. Barry and B. M. Craig, *Can. J. Chem.*, **33**, 716 (1955).

(8) Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Boiling points are uncorrected. Microanalyses were performed in the Microanalytical Laboratory of Dr. A. Bernhardt, Max Planck Institute, West Germany.

(9) "Heilbron's Dictionary of Organic Compounds," Vol. 2, Oxford University Press, Oxford, England, 1965, p 1046.

(10) The sodium borohydride used was first stirred in ethyl acetate overnight, washed with ether, and dried. Thanks are due to Dr. Ian Harrison for suggesting this procedure.

(11) See ref 9, p 845.

with two 50-ml portions of chloroform and the chloroform solutions were combined and washed once with water. Concentration of the chloroform to small volume resulted in the precipitation of a crystalline solid which was recrystallized from methylene chloride–ether to give 1,3-dihydroxypropan-2-one 1,3-dipalmitate (37 g, 84%) as small plates, mp 81–82°.

Anal. Calcd for $C_{35}H_{66}O_5$: C, 74.0; H, 11.7. Found: C, 73.6; H, 11.5.

1,2,3-Trihydroxypropane 1,3-Dipalmitate.—1,3-Dihydroxypropan-2-one 1,3-dipalmitate (10.0 g) was dissolved in a mixture of tetrahydrofuran (250 ml) and benzene (50 ml). Water (15 ml) was slowly added to this solution with stirring and the temperature of the mixture reduced to approximately 5° by external cooling in an ice bath; a milky-white suspension resulted. Sodium borohydride[10] (1.0 g) was added to this heterogeneous mixture; after a further 30 min, the reaction mixture was worked up as described above to give 1,2,3-trihydroxypropane 1,3-dipalmitate (10 g, 99%) as a waxy white solid, mp 67–68°, which was recrystallized from chloroform to give mp 72–73° (lit.[12] mp 72–74°). Thin layer chromatography showed no trace of the 1,2 isomer [tlc system hexane–ethyl acetate (6:1)].

Registry No.—1,3-Dihydroxypropan-2-one 1,3-dioleate, 24472-44-4; 1,3-dihydroxypropan-2-one 1,3-dipalmitate, 24472-45-5.

(12) See ref 9, Vol. 3, p 1267.

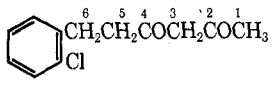
Cyclization at the Less Nucleophilic Center of a β-Diketone Dicarbanion through a Dicarbanion–Benzyne Intermediate[1]

CHARLES F. BEAM, ROBERT L. BISSELL, AND CHARLES R. HAUSER

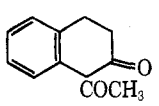
Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

Received September 22, 1969

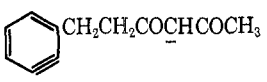
Bunnett and Skorcz[2] have shown that addition of 6-(*o*-chlorophenyl)-2,4-hexanedione (**1**) to excess potassium amide in liquid ammonia affords 1-acetyl-2-tetralone (**2**). A study of the possible intermediates in this cyclization promised to be of particular interest since, although monocarbanion–benzyne **3** appeared to be the intermediate that cyclizes, dicarbanion–benzyne **4** may be the intermediate that cyclizes to give **2**. If so, this would be the first example where the less nucleophilic 3-carbanionic center of a β-diketone dicarbanion reacts preferentially to the much more nucleophilic terminal 1-carbanionic center of such a β-diketone dicarbanion with an electrophilic group.[3]



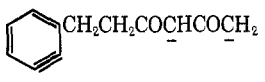
1



2

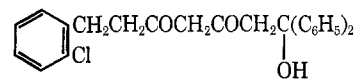


3

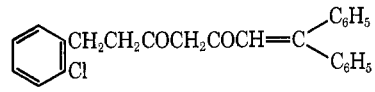


4

We have obtained evidence that dicarbanion–benzyne **4** is indeed the principal intermediate that cyclizes to give **2**, and that the monocarbanion and dicarbanion are formed at a faster rate than an appreciable amount of benzyne, the electrophilic center for cyclization to **2**. Thus, not only could chloro β-diketone **1** be recovered after conversion to its monocarbanion or dicarbanion salts by direct or inverse addition of 1 or 2 mol equiv of potassium amide in liquid ammonia, but the dicarbanion was also condensed at its terminal position with benzophenone to give carbinol–β-diketone **5**. This mode of intermolecular condensation is characteristic of such 1,3 dicarbanions.[3] The yield of **5** was 41%, which is approximately the same as that reported (42%) earlier for cyclic β-diketone **2**.[2]



5



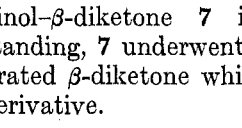
6

The structure of **5** was supported, not only by analysis and absorption spectra, but also by dehydration with acid to give β-diketo olefin **6** in 30% yield. The structure of **6** was also supported by analysis and absorption spectra.

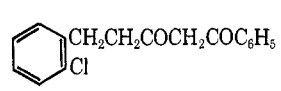
The conversion of chloro β-diketone **1** to its monocarbanion was accompanied by slight coloration which was probably due to a trace amount of benzyne formation. The related β-diketone, 6-phenyl-2,4-hexanedione, which has no chlorine failed to produce coloration under similar conditions. In both cases the β-diketone was recovered quantitatively upon acidification.

The conversion of chloro β-diketone **1** to its dicarbanion was accompanied by distinct coloration, but only **1** was recovered after neutralization; none of **2** was found.

Cyclic β-diketone **2** was converted to its dipotassio salt and condensed with benzophenone to form carbinol–β-diketone **7** in 73% yield; on prolonged standing, **7** underwent dehydration to give the unsaturated β-diketone which was isolated as the pyrazole derivative.



7



8

In contrast to chloro β-diketone **1**, chloro β-diketone **8** failed to afford an isolable product when treated with 2 molar equiv of potassium amide in liquid ammonia followed by 1 molar equiv of benzyl chloride or benzophenone, and, when **8** was treated with excess potassium amide in liquid ammonia, a polymeric material was obtained. The isolation of polymeric material suggests that an intermolecular condensation may have taken precedence over an intramolecular cyclization.

The starting chloro β-diketones **1** and **8** were readily prepared from *o*-chlorobenzyl chloride and the dicarbanions of acetylacetone and benzoylacetone, respectively. Chloro β-diketone **1** can now be made in a

(1) Supported by the National Science Foundation.

(2) J. F. Bunnett and J. Skorcz, *J. Org. Chem.*, **27**, 3836 (1962).

(3) C. R. Hauser and T. M. Harris, *J. Amer. Chem. Soc.*, **80**, 6360 (1958); R. J. Light and C. R. Hauser, *J. Org. Chem.*, **26**, 1716 (1961); T. M. Harris and C. R. Hauser, *ibid.*, **29**, 1391 (1964).