Syntheses of 1,1,2,2-Tetraacylcyclopropane Derivatives by Photochemical Rearrangement of 2,2,4-Triacyl-2,3-dihydrofurans

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In 1925 Radulescu and Georgescu reported formation of 1,1,2,2-tetraacylcyclopropane (**1a**), mp 211–212 °C, by reaction of the dimedone–formaldehyde adduct with iodine in absolute ethanol.[1] The structural formula was, however, corrected by Kondrat'eva and Greenberg to a derivative of 2,2,4-triacyl-2,3-dihydrofuran (**2a**) from spectroscopic analysis.[2] We now wish to report a facile photochemical rearrangement of **2a** to **1a**.[3]

A number of dihydrofurans (**2a–c**) have already been prepared by treatment of disodio derivatives of aldehyde–dimedone adducts with iodine in absolute ethanol[1] or by the reaction of the adducts with bromine in glacial acetic acid.[4] We modified this synthetic procedure so as to carry out the reaction with iodine–sodium iodide in aqueous alkaline solution. This saved much trouble in preparation of the substrates (see Experimental Section). While the adduct of cyclohexa-1,3-dione with formaldehyde did not give the corresponding dihydrofuran (**6**) in this manner, 2,2,4-triacetyl-2,3-dihydrofuran (**4**) was obtained by the same procedure even in low yield.

A solution of each dihydrofuran derivative dissolved in acetonitrile was irradiated by a low pressure mercury arc lamp through quartz for 6–7 h under nitrogen at room temperature. The results are summarized in Table I. In the irradiation diethyl ether was also used instead of acetonitrile, but some dihydrofurans were not dissolved in this solvent at the initial stage of the rearrangement. Surprisingly the photorearrangement was very clean and complete without contamination by any by-product. Dihydrofurans (**2a–c** and **4**) show UV absorption maxima near 255 nm in the region of strongest emission by the low-pressure mercury lamp. On the other hand, the products (**1a–c** and **3**) do not absorb light appreciably near this wavelength but show their maxima near 280 nm and are quite stable under the above irradiation. Thus, selectivity has been superior to the other photochemical rearrangements of dihydrofurans.[5]

To assure the structure proposal proton-decoupled ^{13}C FT-NMR spectra of **1a** and **3** were measured in $CDCl_3$ using

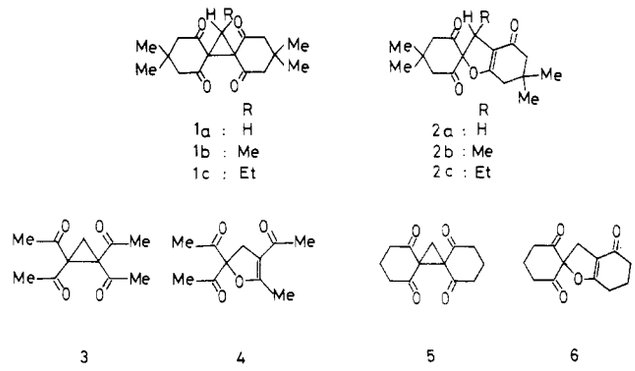

Figure 1.

Me_4Si as an internal standard and each signal was assigned as shown in Figure 2. Reduction of the tetraacylcyclopropanes with zinc dust and acetic acid resulted in recovery of the adduct of β-diketones with formaldehyde in 70–80% yield. Since this reductive ring opening has been generally observed in the case of 1,2-diacylcyclopropane derivatives,[6] the result provides chemical evidence for the proposed structures.

Another synthetic procedure of tetraacylcyclopropane (**5**) was reported by Mattsson and his collaborators[7] who oxidized the adduct of cyclohexa-1,3-dione with formaldehyde with $Fe[Fe(CN)_6]$ in aqueous solvent. This gave a mixture of the tetraketone hydrate and the corresponding dihydrofuran; consequently separation and dehydration was necessary for purification of the tetraketone.

Experimental Section

All melting points are uncorrected. Infrared spectra were recorded with a Hitachi 215 grating infrared spectrophotometer. Nuclear magnetic resonance measurements were carried out on a Varian T-60 instrument, using tetramethylsilane as an internal reference. Ultraviolet absorption spectra were measured by a Hitachi 124 spectrophotometer. The authors are indebted to Dr. S. Sato and Mr. K. Kushida of Nichiden-Varian Inc., Tokyo, for the measurement of ^{13}C NMR spectra.

Spiro[4-keto-6,6-dimethyl-5,6,7,8-tetrahydrobenzofuran-2-(3*H*)1′,4′,4′-dimethylcyclohexane-2′,6′-dione] (2a). Into a solution of methylenebis(4,4-dimethyl-2,6-dioxocyclohexyl) (an adduct of dimedone with formaldehyde), mp 192–193 °C (lit.[8] mp 191–191.5 °C) (5.65 g, 0.024 mol), dissolved in water (150 mL) containing sodium hydrogen carbonate (6.3 g, 0.075 mol) was slowly added an aqueous solution (75 mL) of sodium iodide (22.5 g, 0.15 mol) and iodine (12.7 g, 0.05 mol), then the mixture was stirred at room temperature overnight. The resultant precipitates were filtered and washed successively with 5% aqueous sodium thiosulfate, 5% aqueous sodium hydrogen

Table I. Spectral Data for 1,1,2,2-Tetraacylcyclopropanes (1a–c and 3)

	registry no.	yield	mp, °C dec	IR (Nujol), cm^{-1}	UV (EtOH), nm	NMR ($CDCl_3$), δ CH_3	CH_2	cyclopropane		anal. C, %	H, %
1a	54283-18-0	78	147–148	1720 1740	282 (ε 286)	1.04 (s) 1.15 (s)	2.62 (bs)	2.23 (s)	found calcd for $C_{17}H_{22}O_4$	70.32 70.21	7.64 7.59
1b	54283-19-1	81	109–110	1690 1720	288 (ε 300)	1.08 (s) 1.17 (s)	2.60 (bs)	1.46 (3 H, d, J = 6.7 Hz) 2.66 (1 H, q, J = 6.7 Hz)	found calcd for $C_{18}H_{24}O_4$	71.03 70.92	7.95 8.02
1c	22381-64-2	70	136–137	1700 1730	288 (ε 440)	1.06 (s) 1.13 (s)	2.56 (bs)	1.09 (3 H, t, J = 6.9 Hz) 1.74 (2 H, m) 2.51 (1 H, t, J = 6.8 Hz	found calcd for $C_{19}H_{26}O_4$	71.67 71.50	8.23 8.27
3	54283-20-4		96–97	1700	280 (ε 150)	2.28 (s)		2.14 (s)	found calcd for $C_{11}H_{14}O_4$	62.81 62.85	6.72 6.71

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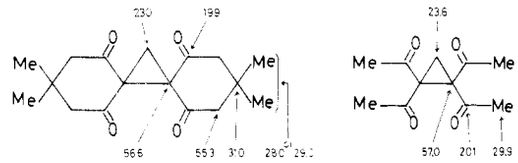

1a 3

Figure 2. ^{13}C FT-NMR spectra of **1a** and **3**.

carbonate, and water. Recrystallization from a mixture of ethanol and petroleum–ether gave **2a**, mp 205–210 °C (lit.[4] mp 211–213 °C) (4.4 g), in 78% yield.

By means of the same method, the methyl derivative of **2a** (**2b**) (mp 202–203 °C, (lit.[4] mp 197–198 °C)) and the ethyl derivative (**2c**) (mp 151–153 °C (lit. mp 149–150 °C)) were prepared in 81 and 75% yield, respectively.

3,3,10,10-Tetramethyldispiro[5.0.5.1]trideca-1,5,8,12-tetraone (1a). A solution of a dihydrofuran derivative (**2a**) (3 g) dissolved in acetonitrile (600 mL) was irradiated by low-pressure mercury arc lamp (Eiko-sha, 60 W) under a bubbling nitrogen stream at room temperature for 6 h. Evaporation of the solvent under reduced pressure left colorless product, which was recrystallized from a mixture of benzene and petroleum ether to give the tetraketone (**1a**) (mp 147–148 °C; 2.34 g) in 78% yield. If diethyl ether was used as the solvent instead of acetonitrile, **2a** was dispersed in the beginning of irradiation, then gradually dissolved in ether developing a yellow color as the reaction proceeded. But the yield of the tetraketone (**1a**) was almost the same as above.

3,3,10,10,13-Pentamethyldispiro[5.0.5.1]trideca-1,5,8,12-tetraone (**1b**), mp 109–110 °C, and 13-ethyl-3,3,10,10-tetramethyldispiro-[5.0.5.1]trideca-1,5,8,12-tetraone (**1c**), mp136–137 °C, were prepared by the same procedure as described above from **2b** and **2c**, respectively. Experimental data for these compounds are summarized in the Table I.

This photochemical rearrangement of **2a** could be accomplished within 20 min by irradiation with a high-pressure mercury lamp, contaminated with a small amount of unidentified products, when a 2.0×10^{-3} M solution in acetonitrile was used. Then, the product (**1a**) was gradually decomposed under the conditions and gave a complex mixture after irradiation for 5 h.

5-Methyl-2,2,4-triacetyl-2,3-dihydrofuran (4). Into a solution of 1,1,3,3-tetraacetylpropane (21 g, 0.10 mol)[9] dissolved in water (400 mL) containing sodium hydrogen carbonate (17 g, 0.20 mol) was added an aqueous solution (300 mL) of iodine (22.5 g, 0.10 mol) and sodium iodide (45 g, 0.30 mol) under stirring at room temperature for 1 h, then the mixture was stirred for 30 h. The resultant light-brown solution was continuously extracted with ether. Evaporation of the solvent left an oil after ordinary workup of the ether layer. The yield was lower than the former case and varied with each experiment. It showed absorption bands at 1680, 1720, and 1740 cm^{-1} in its IR spectrum (neat) and the following signals in NMR spectrum (CCl_4): two singlets at 2.25 (3 H) and 2.23 (6 H), a triplet at 2.36 (3 H, J = 2 Hz), and a quartet at 3.35 (2 H, J = 2 Hz). The sample was employed in the photochemical rearrangement without further purification.

1,1,2,2-Tetraacetylcyclopropane (3). A solution of the crude dihydrofuran (**4**) (3.0 g) dissolved in anhydrous ether (300 mL) was irradiated in the same way as above for 21 h. The product (1.0 g, 33% yield) was recrystallized from a mixture of benzene and petroleum ether, mp 96–97 °C.

Reduction of the Tetraketone (1b) with Zinc Dust in Acetic Acid. A mixture of **1b** (60 mg), zinc dust (500 mg), and glacial acetic acid (5 mL) was stirred at room temperature for 24 h. Being poured into cold water (30 mL) the mixture was extracted with chloroform. After the chloroform solution was washed with aqueous sodium hydrogen carbonate and then with water, dried solution (with anhydrous sodium sulfate) was concentrated under reduced pressure to give the product (51.4 mg). The product was sufficiently pure and identical with the authentic sample of ethylidenebis(4,4-dimethyl-2,6-dioxocyclohexyl) in all respects. Ethanol could not substitute for acetic acid in the reaction. By means of the same procedure, **1a** and **1c** gave the corresponding adducts of dimedone with aldehydes in a similar yield.

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Registry No.—**2a**, 1984-51-6; **2b**, 19997-18-3; **2c**, 19997-19-4; **4**, 54283-17-9; methylenebis(4,4-dimethyl-2,6-dioxocyclohexyl), 2181-22-8.

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Side Reactions in Peptide Synthesis. 8.[1] On the Phenacyl Group in the Protection of the β-Carboxyl Function of Aspartyl Residues

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The ready conversion of aspartyl peptides to aminosuccinyl derivatives is one of the most disturbing side reactions in peptide synthesis. The benzyl ester grouping, a widely used form of protection for the β-carboxyl of aspartic acid, is conducive to ring closure under both acidic and basic conditions (Figure 1). Opening of the ring, e.g., with dilute alkali, is no remedy; mainly β-aspartyl peptides are obtained. Therefore, the proposal of Yang and Merrifield,[3] the application of the phenacyl group[4] for the protection of the side chain carboxyl of aspartyl residues, was a welcome contribution. These authors, however, investigated the ring closure only under the conditions of acidolysis, with HF or HBr used for the removal of completed peptide chains from the insoluble support. In solid phase peptide synthesis,[5] the intermediates are exposed to basic conditions only very briefly, namely, during the conversion of the hydrochlorides or trifluoroacetates of the partially deprotected peptidyl polymers to the corresponding free amines. On the other hand, in syntheses carried out in solution, the amine salts are often brought into reaction as such and the amino groups to be acylated are "liberated" by the addition of a tertiary amine. Thus, the often time-consuming coupling reactions are carried out in the presence of a base. Such conditions promote the formation of aminosuccinyl derivatives, especially when the aspartyl residue is followed in the sequence by serine, threonine or glycine.[1] Therefore, the proposed improvement, protection of β-carboxyls with the phenacyl group, could not be adopted for syntheses in solution without a reexamination from the point of view of ring closure under basic conditions. Also, some concern was felt about the application of phenacyl esters because they can be regarded as methyl esters substituted with the electron-withdrawing benzoyl group. Compared with benzyl esters, which are methyl esters substituted with a

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