Photosensitized *cis–trans* Isomerization of Methyl Oleate

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Received March 18, 1964

The photosensitized *cis–trans* isomerization of methyl oleate has been performed using benzophenone as a sensitizer. In a typical experiment a degassed sample of 0.352 M methyl oleate dissolved in benzene containing 5.5×10^{-2} M benzophenone was photolyzed with 366-mμ light for 1357 min. and 23% *trans* isomer was obtained. The quantum yield for this process was determined to be 0.34; however, the yield decreases as the stationary state is approached.

Since the isolated double bond in methyl oleate absorbs in the vacuum ultraviolet[2] and shows virtually no absorption at 366 mμ, the isomerization is most probably proceeding through the triplet state *via* energy transfer in solution. Recent work[3–5] has established that the triplet state of benzophenone is populated with unit efficiency at 366 mμ.

Benzophenone has been used to photosensitize the *cis–trans* isomerization of a conjugated diene such as piperylene (1,3-pentadiene)[6,7]; however, it was predicted in that work that the sensitized isomerization of an isolated double bond would occur very inefficiently, if at all. This was demonstrated by Hammond and co-workers[7] for the isomerization of a simple unconjugated alkene. Isomerization experiments in the vapor state have been performed with butene-2[8–11]; however, this work was done using 2537-Å. excitation and the triplet state of benzene, which is more energetic than the benzophenone triplet.

The occurrence of this isomerization process *via* the triplet state of methyl oleate is indicative of a low-lying triplet state in this molecule, which may be important in understanding the photooxidation processes that occur in fats and oils.

The direct photolysis of a degassed sample of 0.337 M methyl oleate in benzene at 366 mμ for 3114 min. produced no isomerization or significant change in the infrared spectrum. Similarly, the photolysis of 5.5×10^{-2} M benzophenone in benzene for 1337 min. indicated no significant changes. This latter result was also recently reported by Bell and Linschitz.[12]

Although the photolysis of benzophenone in benzene produced no significant changes in benzophenone, it was observed that, during the sensitized runs, some benzophenone was consumed, and its disappearance was faster when isomerizing *trans–cis* rather than the reverse. This side reaction is probably due to hydrogen abstraction from the olefin, *i.e.*, $(C_6H_5)_2CO + RH \rightarrow (C_6H_5)_2\dot{C}OH + \dot{R}$. A referee has pointed out that an alternate method for explaining the partial depletion of benzophenone is by addition to the olefin to form an oxetane.[13] In either event, the reaction is in competition with the energy-transfer process which is essential for the isomerization.

The reversibility of the isomerization reaction has been verified by isomerizing methyl elaidate. In a typical experiment, photolysis by degassed 0.152 M methyl elaidate in benzene containing 5.5×10^{-2} M benzophenone for 1603 min. resulted in 23% oleate, and the quantum yield for this process was determined to be 0.14. Since the isomerization process is reversible, with the rates for the forward and reverse reactions decreasing as the equilibrium state is approached, benzene solution of mixtures of methyl oleate and elaidate were photolyzed in the presence of benzophenone. Results indicate that, when the ratio of *trans* to *cis* isomer is near three, the quantum yield becomes negligibly small; consequently, it appears that the equilibrium state exists with 75% *trans* isomer.

The *cis–trans* isomerization of methyl oleate has been performed using oxides of nitrogen,[14] elemental selenium,[15] and ionizing radiation.[16] Conjugated long-chain fatty acid esters have been isomerized photochemically with iodine[17,18]; however, to the author's knowledge, this is the first unconjugated long-chain fatty acid ester which has been isomerized *cis–trans* in the presence of a photosensitizer. The occurrence of this isomerization reflects the large energy difference between the first excited singlet and triplet in the $\pi \rightarrow \pi^*$ transitions of alkenes.

Since the triplet state energy of methyl oleate is unknown, its determination may be made with different sensitizers as suggested by Hammond, *et al.*[6] The extension of this isomerization method to fatty acid chemistry is an obvious one.

Experimental

The 366-mμ light was isolated from a General Electric BH-6 high pressure mercury lamp by a Farrand UV monochromator. The light intensities were determined with the potassium ferrioxalate actinometer[19] to be approximately 4.7×10^{15} quanta/sec. Photolysis runs were performed at 24.5 ± 0.5° in 1-cm. fused silica cells, with all samples vacuum degassed prior to lamp exposure. Fresh solutions were prepared for each run. At the end of each photolysis experiment, the cell was opened to air and the solution was subjected to infrared analysis for the generation of methyl elaidate at 10.34 μ.[20] It is noteworthy that the fatty acid structure of the ester was not significantly changed during the photolysis. Ultraviolet spectroscopy and gas chromatography (column: 23% ethylene glycol glutarate on 75% 60-80-

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mesh Chromosorb W with 2% phosphoric acid) provided an estimate of the purity of the fatty acid esters, the extent of side reactions, and the partial depletion of benzophenone. Gas chromatograms indicated that the isomerization is not accompanied by significant side reactions. A Beckman IR-5A spectrophotometer was used for the quantitative measurements and the length of the sodium chloride cells was determined by counting interference fringes.

The methyl oleate used in this work was better than 99% pure and obtained from the Applied Science Laboratories, State College, Pa. In addition to chromatographic analysis, the purity of the fatty acid ester was estimated by the absence of absorption in the ultraviolet region. At 250 $m\mu$, in isopropyl alcohol, the molar extinction coefficient was 4.5. Methyl elaidate was prepared by esterification of elaidic acid (Chemical Procurement Laboratories, Inc., College Point, N. Y.) with methanol and sulfuric acid. A low-temperature recrystallization in acetone of the prepared ester removed an impurity, which appeared to be eleostearic acid from its ultraviolet absorption. The purity of the elaidate sample was determined to be 99% by gas chromatography and the molar extinction coefficient at 250 $m\mu$, in isopropyl alcohol, was determined to be 4.8.

Baker's analytical reagent grade benzene was used as solvent, and benzophenone (Matheson Coleman and Bell) was recrystallized from ethanol and hexane.

Methyl (Cortison-21-yl 2,3,4-tri-*O*-acetyl-β-D-glucosid)uronate[1]

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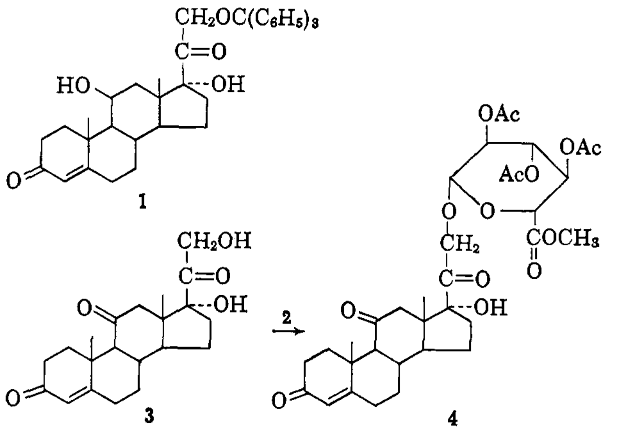
February 11, 1964

In an effort to secure C-21 2-deoxyglycosides of hydrocortisone (11β,17α,21-trihydroxy-4-pregnene-3,20-dione) as potential antiinflammatory agents, we investigated a glycosidation procedure described[3] by Bredereck and co-workers. When, however, 21-tritoxyhydrocortisone (11β,17α-dihydroxy-21-tritoxy-4-pregnene-3,-20-dione, **1**) was treated in the presence of silver perchlorate with various 2-deoxy acylglycosyl halides, the isolation of crystalline products was not realized.

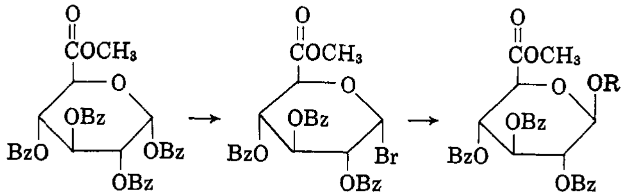
Also investigated was the preparation of some adrenocortical C-21 glucosiduronic acids as possible water-soluble derivatives. Whereas methyl 2,3,4-tri-*O*-acetyl-1-bromo-1-deoxy-α-D-glucuronate (**2**) coupled readily with cortexone (21-hydroxy-4-pregnene-3,20-dione) to give the desired glucosiduronate in good yield,[4] treatment of hydrocortisone with **2** under identical conditions failed to give crystalline material, even after chromatography of the reaction products on silicic acid.

We next turned our attention to the corresponding methylated and fully acetylated C-21 glucosiduronic acid (**4**) prepared from cortisone (**3**) and previously reported by Wotiz and co-workers.[5] Whereas these workers were able to isolate the crystalline intermediate directly from the reaction mixture, it was necessary for us to chromatograph the material on silicic acid. The crystalline material thus obtained had properties (melting point, rotation) which differed from the data reported by Wotiz for the coupling product (**4**). Also, combustion analysis for our compound (**4**) gave values for carbon and hydrogen closely fitting $C_{34}H_{44}O_{14}$ (the correct molecular formula), while Wotiz' values more nearly correspond to the formula $C_{34}H_{46}O_{14}$ which is the one assigned erroneously to **4** in his paper.

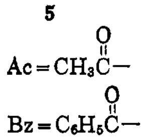


1

3 **4**



5 **6** **7**, R = CH_3 **8**, R = C_2H_5



$\mathrm{Ac} = \mathrm{CH_3}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-$

$\mathrm{Bz} = \mathrm{C_6H_5}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-$

In the absence of further published information, we infer that Wotiz' compound may have been impure (in view of the sharp melting point reported this does not seem likely) or that it possibly represents an incorrectly named coupling product of **2** with some dihydro derivative or cortisone. The synthesis of **4** reported herein represents, then, the first successful coupling of cortisone (**3**) with D-glucuronic acid.

Saponification of **4** yielded amorphous material which could not be crystallized. The material was readily soluble in water giving a solution which was acidic to litmus. It was homogeneous as disclosed by paper-grams and, when hydrolyzed by means of β-D-glucuronidase and again chromatographed on paper, showed two spots, exactly coincident in position with cortisone (**3**) and D-glucuronic acid, respectively.

In a further attempt to secure a C-21 glucosiduronic acid from hydrocortisone, we investigated benzoylated derivatives of D-glucuronic acid owing to the superior crystallizing properties of carbohydrate benzoates. Methyl D-glucuronate[6] was readily converted to the tetrabenzoate (**5**), which is provisionally assigned to the α-anomeric configuration because of its strongly positive specific rotation (+125.2°). Treatment of **5** with hydrogen bromide–acetic acid solution gave the expected methyl 2,3,4-tri-*O*-benzoyl-1-bromo-1-deoxy-α-D-glucuronate (**6**), which underwent methanolysis to

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[1] This work was supported in part by U. S. Public Health Service Grant AM02764.

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