TABLE I

C_{20} OXIMES AND SEMICARBAZONES OF 17(α)HYDROXYL-21-STEROID ACYLATES

Compound	R_1	R_2	Molecular Formula	Nitrogen Calc'd	Nitrogen Found	M.P., °C.	Ultraviolet Peaks (in methanol)[a] λ, mμ.	E
I	$-CH_3$[c]	$-NHCONH_2$	$C_{25}H_{36}N_6O_6$	16.27	15.97	>300°	268	34,800
II	$-CH_3$	$-OH$	$C_{23}H_{32}N_2O_6$	6.48	6.33	188° dec.	241	20,100
III	$-C_6H_5$[b]	$-NHCONH_2$	$C_{30}H_{38}N_6O_6$	14.52	14.50	212–220° dec.	230 267.5	27,900 29,900
IV	$-C(CH_3)_3$[b]	$-NHCONH_2$	$C_{28}H_{42}N_6O_6$	15.04	14.75	>300°	242 267.5	22,100 30,700
V	$-(CH_2)_{10}CH_3$[b]	$-NHCONH_2$	$C_{35}H_{56}N_6O_6 \cdot 2CH_3OH$	11.68	11.62	228–230° dec.	245 268	27,200 37,000
VI	$-CH_2C_6H_5$[b]	$-NHCONH_2$	$C_{31}H_{40}N_6O_6$	14.18	13.94	225° dec.	242 268	24,750 34,600
VII	$-C_6H_4(o\text{-}CH_3)$[b]	$-NHCONH_2$	$C_{31}H_{40}N_6O_6$	14.18	14.04	225° dec.	236 268	32,400 38,[illegible]00
VIII	3(α),17(α),21-trihydroxy-pregnane-11,-20-dione 20-semicarbazone 21-acetate	$-NHCONH_2$	$C_{24}H_{37}N_3O_6$	9.07	9.07	245° dec.	242.5	12,950

[a] The semicarbazones were first dissolved in ethylene glycol (15–20 mg./cc.), then diluted to 100 cc. with methanol. [b] The parent esters of these compounds were prepared by Drs. E. F. Rogers and J. Conbere of these laboratories (unpublished work). [c] Recently this compound was reported by Eugene P. Oliveto, Richard Rausser, Herbert Q. Smith, Corine Gerold, Lois Weber, Elliot Shapiro, David Gould, and E. B. Herschberg, *Abstracts of Papers, First Regional Meeting, Delaware Valley, American Chemical Society*, p. 43, February 16, 1956. The substance was prepared by essentially the same method as we have used; it subsequently was converted to hydrocortisone.

tion of 3000 cc. of water. After stirring the cooled mixture for 3 hours, the product was filtered, washed with water, and dried; wt. 107.9 g., m.p. 247° dec.

Anal. Cf. Table I.

For ultraviolet spectra, *cf.* Table I.

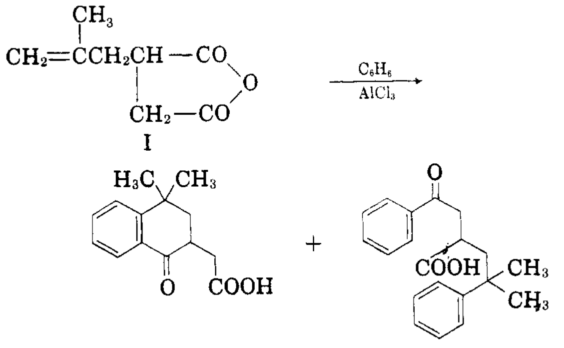
RESEARCH LABORATORIES
CHEMICAL DIVISION
MERCK & CO., INC.
RAHWAY, NEW JERSEY

A Novel Synthesis of Cyclohexenones by Intramolecular Acylation

DONALD D. PHILLIPS AND A. WILLIAM JOHNSON

Received February 2, 1956

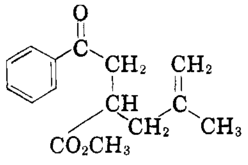
In a recent communication[1] we reported the synthesis of benzo[*c*]phenanthrene derivatives through a series of reactions that involved the tetraloneacetic acid (II) and the keto acid (III) as important intermediates. These acids were prepared in fair yield by the Friedel-Crafts' condensation between β-methallylsuccinic anhydride (I) and benzene. In the separation of these two acids (by distillation of their methyl esters) there was always obtained a substantial amount of a lower-boiling fraction whose identity at the time was not established. The infrared spectrum of this particular fraction (maxima at 5.77, 5.98, and 6.13 μ) led us to believe that the principal constituent was the monoacylated ester (IV), but an unequivocal synthesis of IV established their non-identity.



I

II

III



IV

The lack of absorption in the neighborhood of 6.25 μ indicated that this fraction was *not* aromatic in nature[2] and the ultraviolet absorption spectrum (λ_{max} 237 mμ, log ε 4.15 and 282 mμ, log ε 2.19) was characteristic of an α,β-unsaturated carbonyl

---

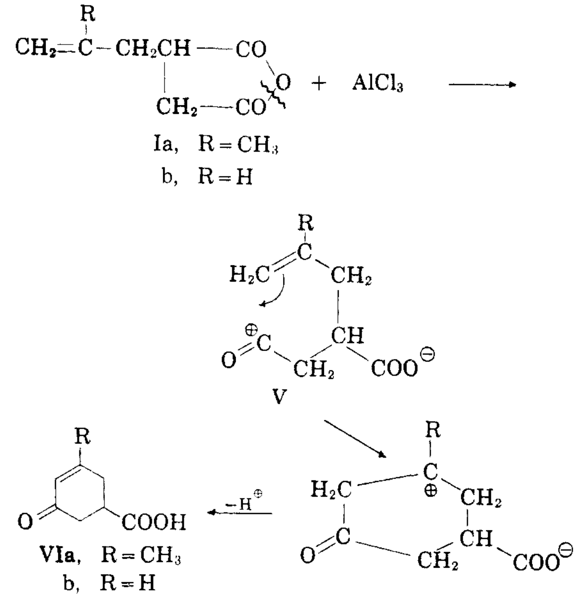
[1] Phillips and Johnson, *J. Am. Chem. Soc.*, **77**, 5977 (1955).

[2] Bellamy, *The Infra-Red Spectra of Complex Molecules*, Methuen and Co. Ltd., London, 1954, p. 60.

compound.[3] Since no reasonable structure involving this chromophore and a benzene ring could be envisaged, we concluded that the unknown compound was formed from the anhydride (I) and aluminum chloride and that benzene played no part in its formation. In support of this contention we were able to obtain the compound in question by allowing the anhydride and aluminum chloride to react in the presence of ethylene chloride alone.

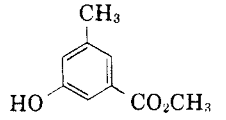
With this information available to us, it was then a relatively simple matter to arrive at a likely structure and we subsequently established that it was the cyclohexenone (VIa). We envisage its formation as outlined in Chart I.

CHART I

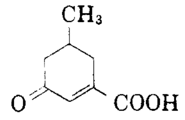


For simplicity we have omitted the aluminum chloride from intermediates such as V since the principal function of the catalyst seems to be the facilitation of the bond rupture as indicated in anhydride I. That this bond is preferentially broken in unsymmetrical anhydrides has been well established in other systems[4] and the argument is strengthened by our observation that the product is a cyclo*hex*enone rather than a cyclo*pent*enone.

The structure of VIa was established in a variety of ways. Hydrogenation data indicated the presence of two centers of unsaturation, one of which was rapidly reduced and the other much more slowly. Ultraviolet and infrared absorption studies were in agreement with the chromophore proposed and dehydrogenation of the methyl ester gave methyl 3,5-cresotate (methyl 3-hydroxy-5-methylbenzoate) (VII). When the carbonyl group in VIa was reduced and the resultant alcohol was dehydrogenated, *m*-toluic acid was obtained.

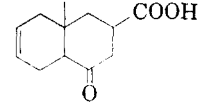


VII



VIII

It is difficult to propose a synthetic scheme for the preparation of VIa that would approach in simplicity the sequence outlined in this paper. For instance, the Birch reduction, which has been invaluable in the preparation of cyclohexenones,[5] would probably give rise to the fully conjugated acid (VIII) rather than to VIa. Because compounds similar to VIa are desirable as synthetic intermediates, especially in the total synthesis of steroids,[6]



IX

we were interested in establishing the generality of this intramolecular acylation as a preparative method for cyclohexenones of this type. In this regard, we have investigated the reaction between allylsuccinic anhydride (Ib) and aluminum chloride. In this instance there was obtained a 34% yield of VIb, indicating that the methyl group in Ia is not a necessary structural feature in the anhydride for the reaction to occur. Since both anhydrides Ia and Ib are readily available materials we believe that this sequence represents a useful method for the preparation of this type of cyclohexenone and other examples of this interesting isomerization are presently being studied.

Acknowledgment. The authors are grateful to the Research Corporation for their generous support of this work in the form of a Frederick Gardner Cottrell grant.

EXPERIMENTAL[7]

Starting materials. β-Methallylsuccinic anhydride (Ia) was prepared as previously described.[1] α-Methallylsuccinic anhydride (Ib) was obtained in 60% yield from the reaction

---

[3] Fieser and Fieser, *Natural Products Related to Phenanthrene*, Reinhold Publishing Corp., New York, N. Y., 1949, p. 190.

[4] See E. Berliner in *Org. Reactions*, **5**, 242 (1949).

[5] Birch, Quartey, and Smith, *J. Chem. Soc.*, 1768 (1952); Birch, *Quart. Revs.* **4**, 69 (1950); Watt, *Chem. Revs.*, **46**, 317 (1950).

[6] A useful reaction that might serve to introduce the angular methyl group in a potential steroid intermediate would be the Diels-Alder condensation between VI and butadiene. The expected product (IX) contains a multiplicity of functional groups, the elaboration of which offers several possibilities. These reactions are presently under investigation.

[7] Melting points and boiling points are both uncorrected. Ultraviolet absorption spectra were measured with a Beckman model DK automatic recording spectrophotometer in 95% ethanol as solvent. Infrared spectra were determined using a Perkin-Elmer model 21 double-beam spectrophotometer; the solid samples were pressed in potassium bromide. All distillations were through a 30-inch Podbielniak type column with partial reflux head. Analyses are by Geller Labs., Hackensack, N. J.

between propylene and maleic anhydride at 180°.[8] At the temperatures (200–250°) suggested by Alder, *et al.*,[8] the yields were extremely low.

1-Methylcyclohexene-2-one-5-carboxylic acid (VIa). a. *From β-methallylsuccinic anhydride and aluminum chloride in the presence of benzene.* This experiment has been described in our previous paper[1] but we wish to record the pertinent data that have been accumulated for this compound and its derivatives.

The *methyl ester* had b.p. 110–111° (1.0 mm.); n_D^{20} 1.4980; d_4^{20} 1.089. The ultraviolet absorption spectrum had maxima at 237 mμ (log ε 4.15) and 282 mμ (log ε 2.19) while the principal peaks in the infrared absorption spectrum were at 5.77, 5.98, and 6.13 μ. The ester decolorized aqueous permanganate solutions and bromine in carbon tetrachloride but was recovered unchanged when reductive ozonolysis was attempted.

The *2,4-dinitrophenylhydrazone* of the methyl ester formed as red microneedles from alcohol-ethyl acetate, m.p. 149.5–150.5°; λ_{max} 383 mμ (log ε 4.56).

Anal. Calc'd for $C_{15}H_{16}N_4O_6$: C, 51.74; H, 4.63; N, 16.09. Found: C, 51.71, H, 4.68; N, 16.05.

The *free acid* (VIa) formed as a microcrystalline powder from acetone-hexane, m.p. 92–94°.

Anal. Calc'd for $C_8H_{10}O_3$: Neut. Eq., 154.1. Found: Neut. Eq., 157.0.

(*b*) *From β-methallylsuccine anhydride and aluminum chloride in the presence of ethylene chloride.* To a cooled (0°) solution of 5.0 g. (0.03 mole) of anhydride (Ia) in 50 ml. of ethylene chloride was added over one-half hour 4.4 g. (0.33 mole) of aluminum chloride. The resultant green complex was stirred at room temperature for 24 hours, poured onto a mixture of ice and water, and the organic material was taken up in ether. The ethereal layer was extracted with carbonate solution and on acidification there was deposited 0.93 g. of VIa as a semisolid mass. On the basis of anhydride consumed (1.0 g. was recovered from the neutral fraction) the yield was 23%.

Quantitative hydrogenation. A solution of 0.115 g. of the methyl ester corresponding to VIa was dissolved in 10 ml. of glacial acetic acid containing 25 mg. of prereduced platinum oxide catalyst. At a pressure of 740 mm., one mole (19.1 ml.) of hydrogen was taken up in 72 minutes but the second mole (19.0 ml.) required 93 hours. The product was not characterized.

Aromatization of methyl 1-methylcyclohexene-3-one-5-carboxylate. The methyl ester (1 g.) was intimately mixed with 0.2 g. of a 10% palladium on charcoal catalyst and heated to 250° for 1.5 hours. The melt was taken up in ether, filtered, and the ether was evaporated. The oil then was triturated with hexane and the amorphous brown solid that precipitated was sublimed to give colorless microneedles of methyl 3,5-cresotate (VII), m.p. 90.5–91.5°; lit.,[9] m.p. 92–93°.

Anal. Calc'd for $C_9H_{10}O_3$: C, 65.04; H, 6.06. Found: C, 65.10; H, 6.04.

On saponification, this ester yielded 3,5-cresotic acid, m.p. 205–206°; lit.,[10] m.p. 208°.

Reduction and aromatization of VIa *to m-toluic acid.* To a solution of 0.80 g. (4.8 millimoles) of VIa (methyl ester) in 15 ml. of methanol was added 0.10 g. of sodium borohydride. After the exothermic reaction had subsided the solution was heated on the steam-bath for five minutes and then was quenched with dilute acid. The alcohol then was extracted with ether and evaporated to an oil.

To the oil was added 80 mg. of a 10% palladium on charcoal catalyst and the mixture was heated to 245° for 2 hours. The melt was taken up in ether, the solvent was removed, and the residual oil was saponified in the usual manner. After one recrystallization the acid melted at 107–108.5°, undepressed on admixture with authentic *m*-toluic acid, m.p. 107.5–108.5°.

Methyl cyclohexene-3-one-5-carboxylate (*VIb, methyl ester*). When 5.0 g. of anhydride Ib[11] was treated with aluminum chloride in ethylene chloride as described above for Ia, there was recovered 1.0 g. of unreacted anhydride and 1.35 g. (34%) of crude acid, VIb. This was esterified with absolute methanol and the methyl ester was fractionally distilled; b.p. 125–128° (1.1 mm.); n_D^{20} 1.4712. The infrared absorption spectrum had maxima at 5.75, 5.95, 6.15, and 6.24 μ while the ultraviolet absorption maxima were at 243 mμ (log ε 3.85) and 280 mμ (log ε 3.12).

The *2,4-dinitrophenylhydrazone* crystallized from 90% alcohol as dull orange microneedles, m.p. 144–146°; λ_{max} 384 mμ (log ε 4.40).

Anal. Calc'd for $C_{14}H_{14}N_4O_6$: C, 50.30; H, 4.22; N, 16.77. Found: C, 50.26; H, 3.93; N, 17.03.

BAKER LABORATORY OF CHEMISTRY
CORNELL UNIVERSITY
ITHACA, NEW YORK

---

[8] Alder, Pascher, and Schmitz, *Ber.*, **76**, 47 (1943).

[9] Jacobsen, *Ber.*, **14**, 2357 (1881).

[10] Meldrum and Perkin, *J. Chem. Soc.*, **95**, 1889 (1909).

[11] We are grateful to Trevor B. Hill of this laboratory for preparing this anhydride in connection with another problem.

The Preparation of 2,3,6-Trihydroxybenzoic Acid and Its Methyl Ester[1]

A. KREUCHUNAS[2] AND ROBERT E. MOSHER[3]

Received February 9, 1956

A method has been developed for the preparation of 2,3,6-trihydroxybenzoic acid (I) by demethylating 2,3,6-trimethoxybenzoic acid (II) using anhydrous aluminum chloride in a mixture of benzene and chlorobenzene.

Hotii, *et al.*,[4] attempted to prepare I by the potassium persulfate oxidation of *gamma*-resorcylic acid; however, a syrup was obtained and the pure acid was not isolated. The presence of I could only be shown by the methylation of the syrup with the subsequent isolation of the corresponding trimethoxy derivative, II.

The preparation of II by the carbonation of 2,3,6-trimethoxyphenyllithium has been described by Gilman and Thirtle.[5]

Since I is easily decarboxylated, especially at temperatures in excess of 100°, any method for its preparation had to take this into account. Our experience with the aluminum chloride demethylation of 2,3-dimethoxybenzoic acid indicated that the reaction would be incomplete in refluxing benzene.

---

[1] This work was supported in part by the Michigan Heart Association.

[2] Lark Research Laboratory, P. O. Box 3922, Detroit 27, Michigan.

[3] Address: Department of Research, Providence Hospital, Detroit 8, Michigan.

[4] Hotii, Komiyama, Otsuki, and Yamamura, *J. Pharm. Soc. Japan*, **72**, 1520 (1952).

[5] Gilman and Thirtle, *J. Am. Chem. Soc.*, **66**, 858 (1944).