[CONTRIBUTION NO. 1155 FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

The Dehydration of Some α,β-Dihydroxy Esters[1,2]

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Several α,β-dihydroxy esters were prepared and dehydrated. With potassium bisulfate the dehydration leads to a mixture of products including β-keto acid derivatives; no evidence of α-keto acid formation was obtained.

In the course of his work on the structure of auxin a Kögl[3] reported that this substance, an α,β-dihydroxylactone, was dehydrated to form a β-keto acid derivative, auxin b. In view of the reported discrepancies[4] between the properties of auxin b and synthetic analogs and considering the meager information in the literature[5] on acid-catalyzed dehydrations of α,β-dihydroxy acids, esters or lactones, it seemed desirable to examine the behavior of some model compounds under dehydration conditions.

It seems reasonable to expect dehydration either to α-keto acids or β-keto acids or products derived from them.

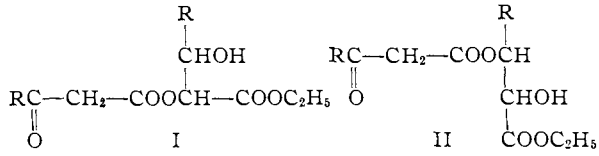
$$\mathrm{R{-}CHOHCHOHCOOR} \begin{cases} \nearrow \mathrm{RCH_2COCOOR'} \\ \searrow \mathrm{RCOCH_2COOR'} \end{cases}$$

On account of the known ease of dehydration of β-hydroxy acids one might be tempted to predict that loss of the β-hydroxyl group would predominate.

The preparation of simple α,β-dihydroxy esters was carried out either by oxidation of the corresponding unsaturated acids[6] and subsequent esterification or by hydrolysis of glycidic esters from Darzen's condensations. The former route was generally more convenient.

The stereochemistry of the products has been assumed from the method of preparation.[6] It is of interest that ethyl α,β-dihydroxycaproate prepared by way of the corresponding glycidic ester was found to have the *erythro* configuration.[6] Assuming the usual inversion on opening an epoxide ring in alkali, we may tentatively assign the *trans* configuration to the main product of the Darzen's condensation of butyraldehyde and ethyl chloroacetate.

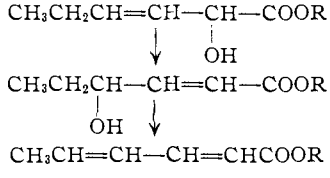
The dehydration of *erythro* α,β-dihydroxypelargonate, *erythro*-ethyl α,β-dihydroxycaproate and *erythro*-methyl α,β-dihydroxybutyrate over potassium hydrogen sulfate at 110–115° gave similar results. In all cases water and ethanol (or methanol) were evolved, condensed in a Dry Ice trap and identified. Fractionation of the neutral components of the mixtures gave in each case some starting material and a higher boiling ester mixture in addition to non-volatile decomposition products. These high boiling fractions were refractionated and obtained as thick liquids; they had infrared spectra resembling β-keto esters, gave colors with ferric chloride and decolorized bromine in carbon tetrachloride. The boiling point, molecular weight, saponification equivalents and hydrolysis products indicated the presence of structures of the type I or II.



The known ready transesterification of β-keto esters[7] even without catalyst makes the production of dimeric products of this sort not unreasonable.

Although the liquid ester mixtures could not be further purified by distillation and may not represent pure compounds, chromatography of the hydrolysis products of the α,β-dihydroxybutyric ester dimer added some evidence for this structure. Only acetone (from the decomposition of acetoacetic acid) and α,β-dihydroxybutyric acid could be found in significant amounts. The absence of α-ketobutyric acid and its degradation products shows that the dehydration under these conditions involves primarily loss of the α-hydroxyl group.

A comparison was made of the behavior of the *erythro*- and *threo*-forms of ethyl α,β-dihydroxycaproate toward dehydrating agents. With potassium hydrogen sulfate at 115° little difference was noted. With concentrated sulfuric acid the *threo*-form was recovered unchanged together with some of the free acid while the *erythro*-form, under the same conditions, yielded 19% ethyl sorbate and 3% sorbic acid. No unchanged starting material could be recovered from the reaction mixture of the *erythro*-form and more extensive coloration and decomposition apparently took place. The production of ethyl sorbate is best explained by an allylic rearrangement of an intermediate such as the ester of 3-hexene-2-ol-oic acid.



The greater ease of dehydration of the *erythro*- relative to the *threo*-ester is difficult to explain. It is presumed due to the influence of association of the β-hydroxyl and the ester group which is favored in the preferred conformation of the *erythro*-form and not in the *threo*-form.

(1) Taken from a thesis submitted by D. L. Heywood in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Yale University, 1954.

(2) We are indebted to the Research Corporation for a grant in support of this work.

(3) F. Kögl, *Ber.*, **68A**, 16 (1935).

(4) J. B. Brown, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 3634 (1950).

(5) W. Kiosh, *Ber.*, **32**, 337 (1922); J. W. Howard and W. A. Fraser, *Org. Syntheses*, **4**, 63 (1925).

(6) J. English, Jr., and J. D. Gregory, THIS JOURNAL, **69**, 2120, 2123 (1947); J. Boeseken, *Rec. trav. chim.*, **41**, 199 (1922).

(7) A. R. Bader, L. O. Cummings and H. A. Vogel, THIS JOURNAL, **73**, 4195 (1951). H. Adkins, J. Connor and E. Cramer, *ibid.*, **52**, 5194 (1930).

As examples of aromatic structures *m*-nitrophenylglyceric ester and phenylglyceric ester were chosen. It was found that these did not dehydrate smoothly with potassium hydrogen sulfate; either unchanged starting material was recovered or extensive decomposition occurred. With concentrated sulfuric acid, however, *threo*-methyl *m*-nitrophenylglycerate was converted into a mixture of *m*-nitrophenylpyruvic acid (42% of theory) and methyl *m*-nitrophenylpyruvate (2% of theory). The identity of the product was confirmed by analysis and conversion to the known *m*-nitrophenylacetic acid. The formation of α-keto acids in these examples rather than β-keto acid derivatives observed in the aliphatic analogs may be ascribed in part at least to the resonant stabilization of the carbonium ion on the β-carbon which might be expected to facilitate loss of this hydroxyl.

In an attempt to obtain a better comparison with the reported dehydration of auxin a lactone, *d,l*-erythronic γ-lactone[8] and the δ-lactone of δ-cyclopentenyl-α,β,δ-trihydroxyvaleric[9] acid were prepared. All attempts to dehydrate these substances with potassium hydrogen sulfate, however, led either to recovery of unchanged starting material or to extensive decomposition.

Experimental

α,β-Dihydroxy Acids.—The aliphatic α,β-dihydroxy acids used in this work were known compounds and were prepared by oxidation of the corresponding *trans*-α,β-unsaturated acids by the method indicated in Table I.

TABLE I

DIHYDROXY ACIDS, RCHOHCHOHCOOH

R	Config.	M.p., °C.	Oxn. method
n-C_6H_{13}	*erythro*	118[6]	HCO_3H
n-C_3H_7	*erythro*	98[10]	HCO_3H
n-C_3H_7	*threo*	108[10]	$KMnO_4$[12]
CH_3	*erythro*	82[11]	HCO_3H

α,β-Dihydroxy Esters.—These esters were prepared by Fischer esterification of the above acids in the usual fashion. As they do not seem to have been characterized, their properties are reported in the Table II.

TABLE II

DIHYDROXY ESTERS, RCHOHCHOHCOOR'

R	R'	Config.	B.p. °C.	B.p. Mm.	$n^{25}D$	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Sapon. equiv. Calcd.	Sapon. equiv. Found
n-C_6H_{13}	C_2H_5	*erythro*	135	2	1.4474	60.52	59.92	10.16	10.50	218	216
n-C_3H_7	C_2H_5	*erythro*	99	0.8	1.4445	54.53	54.22	9.15	8.76	176	174
n-C_3H_7	C_2H_5	*threo*	95	0.4	1.4418	54.53	54.49	9.15	9.08	176	175
CH_3	CH_3	*erythro*[6]	112	12	1.4394	...	...	...	...	..	..

***threo*-β-(*m*-Nitrophenyl)-glyceric Acid.**—To a stirred solution of 20 g. of *m*-nitrocinnamic acid and 5.34 g. of potassium hydroxide in 2 l. of water was added 16.6 g. of potassium permanganate in 500 ml. of water. The addition was carried out at −10° over a period of 5 hours after which the solution was allowed to come to room temperature and stand overnight. The slight excess permanganate was then destroyed by bisulfite, the solution filtered and concentrated *in vacuo* to 150 ml. On acidification some starting material separated; this was filtered and washed with water. The combined filtrate and washings (350 ml.) was extracted once with 50 ml. of ether to remove a further amount of unreacted *m*-nitrocinnamic acid and then continuously extracted with ether. Concentration of the ether extract yielded 5.52 g. (23.8%) of crude product. Recrystallization from water gave fine white needles of *threo*-β-(*m*-nitrophenylglyceric acid), m.p. 189–190°.

Anal. Calcd. for $C_9H_9O_6N$: C, 47.6; H, 3.99; N, 6.17. Found: C, 47.9; H, 4.15; N, 6.40.

The methyl ester was prepared in the usual manner by reaction with methanol and *p*-toluenesulfonic acid catalyst in 92% yield, m.p. 129–130°.

Anal. Calcd. for $C_{10}H_{11}O_6N$: C, 49.8; H, 4.56; N, 5.81. Found: C, 49.8; H, 4.50; N, 6.14.

The ethyl ester, m.p. 90–91°, was also prepared.

Anal. Calcd. for $C_{11}H_{13}O_6N$: C, 51.8; H, 51.13; N, 5.48. Found: C, 51.8; H, 5.20; N, 5.60.

Ethyl α,β-Epoxycaproate.—This ester was prepared by the Darzens condensation of butyraldehyde and ethyl chloroacetate in the usual manner.[13] The yield of refractionated pure ester, b.p. 91–92 (12 mm.), $n^{25}D$ 1.4322, was only 17%.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.1; H, 8.85; sapon. equiv., 158. Found: C, 59.9; H, 8.76; sapon. equiv., 156.

***erythro*-Ethyl α,β-Dihydroxycaproate.**—The most efficient method of converting ethyl α,β-epoxycaproate to the corresponding α,β-dihydroxy compound was as follows.

Potassium hydroxide (15.45 g., 0.276 mole) in 150 cc. of water was added with stirring and cooling during ½ hour to 14.5 g. (0.092 mole) of ethyl α,β-epoxycaproate. The homogenous solution was allowed to remain at room temperature overnight and then heated at 60–80° for 2 days; the cooled solution was acidified with 20 cc. 12 *N* hydrochloric acid and concentrated to as near dryness as possible *in vacuo*. Much difficulty with foaming was encountered in this operation. Acidification of a portion of this solution at this point allowed separation of crystalline *erythro*-α,β-dihydroxycaproic acid, m.p. and mixed m.p. with authentic acid, 97–98°.

Water was removed by codistillation with 50 cc. of benzene in a Dean–Stark apparatus until no further separation of layers was evident; a solution of 1 g. of sulfuric acid in 150 cc. of absolute ethanol was added and the mixture refluxed for 2 days. During the course of this time portions of the refluxing vapors were condensed and withdrawn and replaced by dry ethanol in the reaction flask three times. The salt-containing mixture was then concentrated to ½ volume *in vacuo*, taken up in twice its volume of ether, and the ether layer washed thoroughly with saturated aqueous sodium bicarbonate solution and dried. After removal of solvent the residue was distilled giving 9.69 g. of pure *erythro*-ethyl α,β-dihydroxycaproate, b.p. 90–91° (0.4 mm.), $n^{25}D$ 1.4449. The infrared absorption spectrum of this ester was identical with that of the ester from *erythro*-α,β-dihydroxycaproic acid, prepared by performic acid oxidation of *trans*-α,β-hexenoic acid. The yield for the over-all saponification and re-esterification was 60%.

Dehydration of α,β-Dihydroxy Esters with Potassium Bisulfate (Table II).—The esters were mixed with an equal weight of potassium bisulfate and heated at 110–115° at 15–20 mm. pressure in an apparatus equipped with a Dry Ice trap to catch volatile products. The mixture was then cooled, treated with water and extracted with ether; the ether layer was washed with sodium bicarbonate solution, dried and evaporated to yield the crude mixture of dehydration products. These were fractionally distilled *in vacuo*. In the case of the water-soluble α,β-dihydroxybutyric ester

(8) J. Thiele, *Ann.*, **319**, 144 (1902); R. Gilmour, *J. Chem. Soc.*, **105**, 74 (1914).

(9) J. English, Jr., J. D. Gregory and J. R. Trowbridge, THIS JOURNAL, **73**, 615 (1951).

(10) G. Braun, *ibid.*, **52**, 3188 (1930).

(11) J. W. E. Glattfeld and W. G. Straitiff, *ibid.*, **60**, 1384 (1938).

(12) *erythro*-Methyl α,β-dihydroxybutyrate was prepared by hydroxylation of methyl crotonate with performic acid. The free acid (m.p. 82°) was obtained by saponification.

(13) R. P. Linstead and J. T. W. Mann, *J. Chem. Soc.*, 2070 (1930).

TABLE III

DEHYDRATION OF α,β-DIHYDROXY ESTERS, RCHOHCHOHCOOR'

R	R'	Ester, g.	H_2O, g.	Ester recovered, g.	B.p. °C.	B.p. Mm.	Dimer, g.	B.p. °C.	B.p. Mm.
C_6H_{13}	C_2H_5	7.8	..	2.6	137–140	3	2.3	200–204	3
C_3H_7	C_2H_5	17.2	0.12	12.3	88–94	0.2	2.4	~180	0.2
CH_3	CH_3	15.5	.33	4.1	73–74	0.4	5.0	139–144	0.4

it was necessary to extract the dry reaction mixture with methyl acetate and neutralize the solution with methanolic barium acetate before distillation.

Water was detected in the Dry Ice trap by titration with Karl Fischer reagent and methanol or ethanol identified by formation of the corresponding dinitrobenzoate, m.p. and mixed m.p. 107–108° and 92–93° with authentic samples.

erythro-**Ethyl α,β-Dihydroxypelargonate.**—From 7.8 g. of pure ester there was obtained 2.3 g. of dehydration product, b.p. 200–204° (3 mm.). Refractionation through a 10″ Podbielniak type column gave a viscous oil, b.p. 188–192° (1.1 mm.), $n^{25}D$ 1.4618, which was analyzed. This product gave a greenish violet color with $FeCl_3$ and rapidly decolorized Br_2 in CCl_4.

Anal. Calcd. for $C_{20}H_{34}O_5$: C, 67.8; H, 9.67; mol. wt., 354; sapon. equiv., 177. Found: C, 67.7; H, 10.10; mol. wt. (Menzies–Wright), 346; sapon. equiv., 174.

The above product (0.27 g.) was hydrolyzed in 2 *N* KOH in 50% alcohol to yield a small neutral fraction (0.06 g.) containing some ketone that could not be identified and an acid fraction which on recrystallization from ethyl acetate yielded pure *erythro*-α,β-dihydroxypelargonic acid, m.p. 117–118°.

erythro-**Ethyl α,β-Dihydroxycaproate.**—The pure ester, 17.2 g., was dehydrated as described above to yield a smaller amount (2.4 g.) of high boiling fraction, b.p. 96–180° (0.2 mm.), in addition to unchanged starting material. Refractionation through a 10″ Podbielniak type column of the products from a number of such experiments led to a colorless liquid which distilled at 85–90° bath temp. in a short path apparatus at 0.01 mm. pressure. The distillate gave greenish violet color with $FeCl_3$ and decolorized bromine in CCl_4. Calcd. for $C_{14}H_{22}O_5$: sapon. equiv., 135. Found: sapon equiv., 129.

erythro-**Methyl α,β-Dihydroxybutyrate.**—Dehydration of 15 g. of this ester yielded an analogous high boiling fraction 5.0 g., b.p. 139–144° (0.4 mm.), $n^{25}D$ 1.4561. This was refractionated through a 12″ Podbielniak type column to yield a pale yellow viscous oil, b.p. 130–136° (0.5 mm.). Slight decomposition was evident during the fractionation and there was a large distillation residue.

The product was hydrolyzed with 2 *N* HCl at 70°—conditions that were found with acetoacetic ester to yield 92% of acetone—and the acetone produced caught in a trap containing a saturated 2 *N* hydrochloric acid solution of 2,4-dinitrophenylhydrazine. There was obtained 82% (calculated on one mole of acetone per $C_9H_{14}O_6$) of crude acetone dinitrophenylhydrazone. Chromatographic analysis of the crude product on supported silicic acid developed with 5% ether in petroleum ether[14] gave acetone dinitrophenylhydrazone, m.p. 124–125°, as the major and only isolable component. The hydrochloric acid was evaporated *in vacuo* from the remainder and the water-soluble acid mixture was chromatographed[15] in paper with formic acid, benzene, ether, water (1.35:2.88:5.77:1) as the mobile phase; the paper was dried and sprayed with brom phenol blue. Under these conditions good control separations of α,β-dihydroxybutyric acid (R_f 12) from α-ketobutyric acid (R_f 81) could be obtained. The only acid detectable in the solution by this means was α,β-dihydroxybutyric acid.

The volatile materials (1.61 g.) in the cold trap from this dehydration were analyzed for water (20.35% by Karl Fischer titration) and qualitatively for methanol (3,5-dinitrobenzoate, m.p. and mixed m.p. 106.5–108°). Carbonyl compounds were analyzed by paper and column chromatography of the dinitrophenylhydrazones. Again acetone dinitrophenylhydrazone was the main component. A very small amount of an unknown dinitrophenylhydrazone, m.p. 147–148°, was also isolated; comparison with authentic samples by m.p., mixed m.p. and chromatography showed this to be different from the derivatives of propionaldehyde, acetaldehyde, methyl acetoacetate, methyl α-ketobutyrate and α-ketobutyric acid, but the amount was insufficient for further identification.

Simultaneous Dehydration of *erythro*- and *threo*-Ethyl α,β-Dihydroxycaproate with Sulfuric Acid.—The following solutions were heated for 4 minutes on the steam-bath simultaneously: 2.506 g. of *erythro*-ethyl α,β-dihydroxycaproate and 3.44 g. of sulfuric acid; 1.875 g. of *threo*-ethyl α,β-dihydroxycaproate and 2.58 g. of sulfuric acid. Color developed more quickly and was darker at the end in the solution containing the *erythro* isomer than the *threo* isomer.

Both were cooled in ice, added to three times their volume of ice-water and extracted twice with ether. The ether extracts were washed twice each with saturated aqueous sodium bicarbonate solution, the ether solutions dried over sodium sulfate and solvent removed to give two neutral fractions, E-N and T-N. The bicarbonate washes were acidified with hydrochloric acid and extracted twice each with ether giving, after drying and removing solvent, the two acid fractions, E-A and T-A. Weights of the dried fractions thus obtained are: E-N, 0.699 g.; E-A, 0.090 g.; T-N, 0.407 g.; T-A, 0.058 g.

E-N and T-N were then taken up in 5 cc. of 95% ethanol and saponified for 45 minutes on steam—with 3.5 and 4.5 cc. of 10% potassium hydroxide, respectively. Each solution was acidified with 6 *N* hydrochloric acid, warmed briefly and allowed to cool slowly. E-N deposited 0.320 g. (19%) of sorbic acid, white needles, m.p. 128–131°, undepressed on admixture with authentic sorbic acid.

The mother liquor of this filtration and the acidified solution from T-N (from which nothing crystalline had deposited) were extracted with ether, the ether dried and solvent removed. The residue from T-N solidified and, after one recrystallization from chloroform, gave 0.048 g. of *threo*-α,β-dihydroxycaproic acid, m.p. 107–108°,[10] undepressed on mixture with the authentic acid. No *erythro* acid could be obtained from the residue from E-N.

Inspection of the infrared absorption spectra of E-A and T-A, neither of which crystallized, showed the presence of the sorbic acid diene system (bands at 6.06 and 6.15 μ) in E-A, absent in T-A.

Dehydration of *threo*-Methyl β-(*m*-Nitrophenyl)-glycerate with Sulfuric Acid.—*threo*-Methyl β-(*m*-nitrophenyl)-glycerate, 1.00 g., was heated with 4.0 cc. of concentrated sulfuric acid for three minutes on the steam-bath, at the end of which time the solution was light brown and effervesced slightly. Immediately after cooling and adding 15 cc. of ice-water the solution was extracted with three 10-cc. portions of ether and the combined ether solutions extracted four times with saturated sodium bicarbonate solution. The extracted ether layer was concentrated to dryness, leaving 208 mg. of semi-solid neutral fraction; the sodium bicarbonate extract was acidified with 1 *N* hydrochloric acid, extracted three times with ether, and the ether removed, depositing a solid acid fraction of 422 mg.

The neutral fraction was then saponified with 0.1 g. of potassium hydroxide in 10 cc. of 50% aqueous ethanol on the steam-bath for one-half hour, concentrated to half-volume, acidified with 3 cc. of 1 *N* hydrochloric acid, warmed for five minutes on steam and finally extracted twice with ether. This ether solution was then extracted four times with saturated sodium bicarbonate solution, which, after acidification, was extracted with ether. After evaporation of the solvent, 149 mg. of an acid remained, the infrared absorption spectrum of which was identical in every respect with the spectrum of the original acid fraction. The non-saponifiable portion of the neutral fraction (above) amounted to 11 mg. of oily residue which gave a slight turbidity with 2,4-dinitrophenylhydrazone test solution and from which nothing identifiable could be isolated.

A portion of the acid fraction, recrystallized twice from

(14) B. E. Gordon, *et al.*, *Anal. Chem.*, **23**, 1754 (1951).

(15) C. A. Hargreaves, private communication.

nitrobenzene–petroleum ether, was sublimed at bath temperature 145° (0.08 mm.), to give pure *m*-nitrophenylpyruvic acid, m.p. 158–159°, sintering at 152°. *m*-Nitrophenylpyruvic acid exhibits an intense green ferric chloride color test.

Anal. Calcd. for $C_9H_7O_5N$: C, 51.68; H, 3.37; N, 6.71. Found: C, 51.98; H, 3.69; N, 7.06.

m-Nitrophenylpyruvic acid, 35 mg., was dissolved in 350 mg. of concentrated sulfuric acid and heated on the steam-bath for 1.5 hours, by which time the solution was dark brown and gas evolution had ceased. Eight cc. of water was added to the cooled solution, the suspension centrifuged, and the filtrate extracted with ether. Evaporation of the ether extract left 15 mg. of crystalline yellow residue; two recrystallizations from water brought the m.p. to 116–117°, mixed m.p. with authentic *m*-nitrophenylacetic acid, synthesized by the method of Gabriel and Borgmann[16] showed no depression.

(16) S. Gabriel and O. Borgmann, *Ber.*, **16**, 2065 (1883).

Dehydration of *threo*-Methyl β-Phenylglycerate[17] with Sulfuric Acid.—A solution of 0.190 g. of *threo*-methyl β-phenylglycerate and 0.35 g. of concentrated sulfuric acid was heated for 3 minutes on the steam-bath, at the end of which time the color was dark brown. On adding ice-water and cooling, a red oil appeared which was extracted with ether. Extraction of the ether solution with aqueous sodium bicarbonate three times, followed by acidification of the combined bicarbonate extracts, deposited an amorphous mass. This was distilled (short path, 120° (0.2 mm.)) and recrystallized from benzene. The colorless phenylpyruvic acid melted at 156–157° with decomposition; estimated yield was 15%. Literature values are given variously as 154–155°, 156° and 159–160°.[18] The acid gives a strong green color with acidic ferric chloride.

(17) K. Rüber, *ibid.*, **54**, 1960 (1921); R. P. Linstead, L. N. Owen and R. F. Webb, *J. Chem. Soc.*, 1218 (1953).

(18) C. Granacher, *Helv. Chim. Acta*, **5**, 613 (1922).

NEW HAVEN, CONN.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MARYLAND]

Quinolinequinones. III. Derivatives of 6-Hydroxy-5,8-quinolinequinone[1]

BY YOLANDA T. PRATT WITH NATHAN L. DRAKE

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7-Alkyl-6-hydroxy-5,8-quinolinequinones have been prepared by the alkylation of 6-hydroxy-5,8-quinolinequinone (I) with diacyl peroxides and these products have been converted, by means of Hooker oxidation, to 6-alkyl-7-hydroxy-5,8-quinolinequinones with one less carbon in the side-chain. 7-Aminomethyl-6-hydroxy-5,8-quinolinequinones have been obtained by treating 6-hydroxy-5,8-quinolinequinone (I) with formaldehyde and a primary or secondary amine.

Numerous biologically active compounds have been prepared from 2-hydroxy-1,4-naphthoquinone by the introduction of side-chains at the 3-position. The 3-alkyl derivatives obtained by the action of diacyl peroxides on the parent compound[2] or by Hooker oxidation of the next higher 3-alkyl homolog[3] are active as antimalarials; the 3-aminomethyl derivatives, synthesized by means of the Mannich reaction,[4] have been patented as parasiticides. In the present work, the application of these three reactions to the analogous 6-hydroxy-5,8-quinolinequinone[5,6] (I) (6-hydroxy-5,8-dihydroquinolinedione) has been investigated in the hope that pharmacological tests on representative examples of the resulting products will furnish clues as to the most promising types of derivatives for further studies.

The alkylation of I with diacyl peroxides was carried out according to the method of Fieser, Leffler and co-workers[2b] except that a 10% excess of the peroxides was used. The yield of the propyl derivative[6a] II was somewhat lower (18%), and that of the undecyl derivative IV was higher (11%) than those reported for the corresponding naphthoquinones. The undecyl derivative IV is not only related to the naphthoquinone antimalarials but contains the side-chain of embelin, a dihydroxybenzoquinone derivative which is reportedly an anthelmintic.[7]

TABLE I

DERIVATIVES OF 5,8-QUINOLINEQUINONE

Cmpd.	M.p.,[a] °C.	Yield, %	Carbon, % Calcd.	Carbon, % Found[b]	Hydrogen, % Calcd.	Hydrogen, % Found[b]
II	151.0–152.5	46[c]	66.35	66.56	5.11	5.13
III	134.0–135.0	39[c]	67.52	67.64	5.67	5.57
IV	91.5–92.5	44	72.91	72.77	8.26	8.04
V	203.5–206.0[d]	37[e]	65.02	65.25	4.47	4.45
VI	138.0–139.0	75	66.35	66.59	5.11	4.88
VII	110.0–111.0	68	72.35	72.27	7.99	8.01
VIII	167.0–168.5[d]	81	64.60	64.47	6.20	6.25
IX	203.0–203.5[d]	93	66.16	65.95	5.92	5.96
X	151.5–152.0[d]	78	66.64	66.82	7.04	7.12

[a] Melting point of the purest sample. [b] Averages of duplicates. [c] Based upon the amount of starting material taken although much of it was recovered (25% in II and 20% in III). [d] Decomposes below the melting point; sample placed in the bath at 10° below the melting point and heated at the rate of 2° a minute. [e] By the hydrogen peroxide–copper sulfate method.

Hooker[3a] found that under the influence of alkaline permanganate 3-alkyl-2-hydroxy-1,4-naphthoquinones undergo ring opening and reclosure to form the next lower homologs with the positions of the

(1) This investigation was supported by a research grant (PHS E-665) from the National Microbiological Institute of the National Institutes of Health, Public Health Service.

(2) (a) L. F. Fieser and A. E. Oxford, THIS JOURNAL, **64**, 2060 (1942); (b) L. F. Fieser, M. T. Leffler, *et al.*, *ibid.*, **70**, 3174 (1948).

(3) (a) S. C. Hooker, *ibid.*, **58**, 1163–1179 (1936); (b) L. F. Fieser and M. Fieser, *ibid.*, **70**, 3215 (1948).

(4) M. T. Leffler and R. J. Hathaway, *ibid.*, **70**, 3222 (1948); M. T. Leffler, U. S. Patent 2,541,473 (1951) [*C. A.*, **45**, 7149f (1951)].

(5) Y. T. Pratt with N. L. Drake, THIS JOURNAL, **77**, 37 (1955).

(6) In related studies of the mode of addition of various reagents to 5,8-quinolinequinone, we have found that 5,6,8-triacetoxyquinoline may be isolated in 47% yield after the addition of acetic anhydride (Thiele reaction; J. Thiele and E. Winter, *Ann.*, **311**, 347 (1900); L. F. Fieser, THIS JOURNAL, **70**, 3165 (1948)). This triacetoxyquinoline may be converted to I by methods used for the analogous conversion in the naphthoquinone series (L. F. Fieser, *loc. cit.*). Since 5,8-quinolinequinone is obtained from the readily available 8-hydroxyquinoline (O. Fisher and E. Renouf, *Ber.*, **17**, 1644 (1884)), this series of reactions provides a suitable alternative synthesis for I. Details will be published in a later communication.

(6a) Previously prepared by a different procedure by R. Long and K. Schofield, *J. Chem. Soc.*, 3919 (1953).

(7) A. S. Paranjpé and G. K. Gokhalé, *Arch. intern. pharm.*, **42**, 212 (1932) [*C. A.*, **27**, 1400 (1933)]; L. F. Fieser and E. M. Chamberlain, THIS JOURNAL, **70**, 71 (1948).