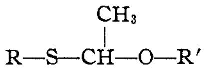
TABLE I

1-ALKOXY-1-ALKYLTHIOETHANES



$R—S—\overset{CH_3}{\overset{|}{C}H}—O—R'$

R	R'	B.p., °C.	B.p., Mm.	Yield, %	Formula	Analyses,[a] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Ethyl	*n*-Butyl	28–30	2.5	40	$C_8H_{18}OS$	59.21	59.92	11.18	11.37
n-Butyl	Ethyl	46–9	4	44	$C_8H_{18}OS$	59.21	59.24	11.18	11.30
Ethyl	Ethyl	33–5	5	40	$C_6H_{14}OS$	53.68	53.99	10.51	10.50

[a] Analyses by Oakwold Laboratories, Alexandria, Virginia.

above 15° (30 minutes). After addition was complete, the mixture was maintained at that temperature for two hours and then allowed to stand at room temperature for 14 hours. The solution was then washed with saturated potassium carbonate solution, dried with calcium sulfate, filtered, and the volatiles stripped at slightly reduced pressure. The residue was fractionated through a 35-cm. Vigreux column at 45–48° (4 mm.) to give the mixed O,S-acetal in 44% yield. The residue from the fractionation was distilled at 84–85° (4 mm.) to give 10 g. of acetaldehyde di-*n*-butylmercaptal.

Anal. Calcd. for $C_{10}H_{22}S_2$: S, 31.07. Found: S, 31.17.

Properties and analyses for related products are given in Table I.

MORRIS PLAINS, NEW JERSEY RECEIVED OCTOBER 10, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, SOUTHWESTERN MEDICAL SCHOOL OF THE UNIVERSITY OF TEXAS]

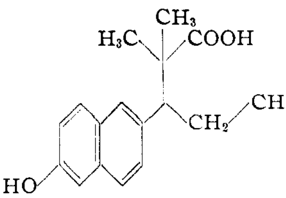
5-Hydroxy-4,4-dimethyl-3-(6-hydroxynaphthyl-2)-pentanoic Acid Lactone

BY JAMES ASHMORE[1a] AND MAX N. HUFFMAN[1b]

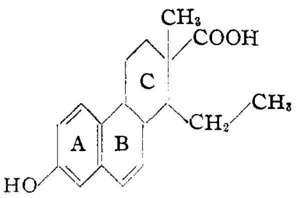
The synthesis of the lactone of 5-hydroxy-4,4-dimethyl-3-(6-hydroxynaphthyl-2)-pentanoic acid is described in detail. This compound represents a simplified 2-hydroxymethylpolyhydrophenanthryl-1-acetic acid lactone in the same manner that 2,2-dimethyl-3-(6-hydroxynaphthyl-2)-pentanoic acid represents a simplified doisynolic acid, namely, by the absence of an intact steroidal Ring C.

Horeau and Jacques[2] have recently shown that it is possible to prepare certain simplified doisynolic acids which possess a considerable degree of estrogenic potency. The most active compound of Horeau and Jacques—2,2-dimethyl-3-(6-hydroxynaphthyl-2)-pentanoic acid (I)—differs from the bisdehydrodoisynolic acid (II) of Miescher[3,4] and collaborators in not possessing an intact Ring C; in fact, the compound of the French workers possesses no carbon atom comparable to that steroidal C_{11}, and furthermore contains only one asymmetric carbon atom.

We have recently prepared from the naturally occurring steroidal hormones a series of lactones of 2-hydroxymethylpolyhydrophenanthryl-1-acetic acids.[5] Thus, from estrone was prepared the lactone III, in which it is to be observed that C_{16} of the original steroid skeleton is in the highest state of oxidation. We decided that it would be of interest to synthesize a compound of the Horeau–Jacques type which possessed the lactone configuration of our original steroidal lactones. Such a compound was realized in VIII.



I



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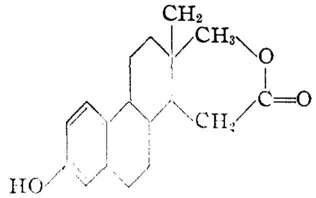
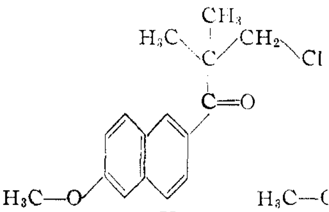
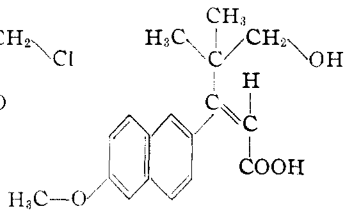


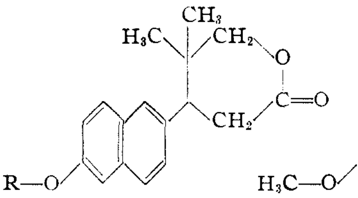
III



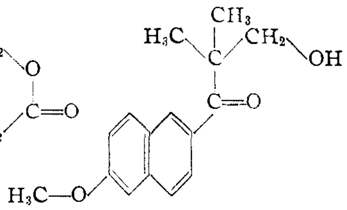
V



VI



VII (R = CH₃)
VIII (R = H)



IX

Haworth and Sheldrick[6] have shown that in the Friedel–Crafts reaction *β*-naphthyl methyl ether

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[1] (a) Department of Biochemistry, Saint Louis University, Saint Louis, Missouri. (b) Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma.

[2] A. Horeau and J. Jacques, *Compt. rend.*, **224**, 862 (1947); R. Courrier, A. Houreau and J. Jacques, *ibid.*, **224**, 1401 (1947); A. Horeau and J. Jacques, *Bull. soc. chim. France*, 707 (1948); J. Jacques and A. Horeau, *ibid.*, 711 (1948).

[3] J. Heer, J. R. Billeter and K. Miescher, *Helv. Chim. Acta*, **28**, 991 (1945).

[4] K. Miescher, *Chem. Revs.*, **43**, 367 (1948).

[5] M. N. Huffman, M. H. Lott and J. Ashmore, THIS JOURNAL, **70**, 4268 (1948).

[6] R. D. Haworth and G. Sheldrick, *J. Chem. Soc.*, 864 (1934).

(2-methoxynaphthalene) and an acid chloride react to place a substituent in the number six position on the naphthalene nucleus if nitrobenzene is used as the solvent. We therefore submitted β-naphthyl methyl ether to reaction with β-chlorotrimethylacetyl chloride in nitrobenzene in the presence of powdered aluminum chloride and obtained pure 3-chloro-2,2-dimethyl-1-(6-methoxynaphthyl-2)-1-propanone (V) in 25% yield. By using amalgamated zinc in a mild Reformatsky reaction, it was found possible to condense ethyl bromoacetate with this ketone (V) without the reductive removal of its chlorine atom. Dehydration of the resulting Reformatsky alcohol with acetic anhydride followed by treatment with alkali resulted in the formation of the unsaturated hydroxy acid VI in 38% yield (V → VI). In compound VI the carboxylic acid group is undoubtedly *cis* to the naphthalene nucleus as evidenced by its failure to give a lactone. The double bond in the unsaturated hydroxy acid VI was reduced by the method of Bachmann, Cole and Wilds[7] using 2% sodium amalgam in alkali. The saturated hydroxy acid easily lactonized in the presence of mineral acid to produce the lactone of 5-hydroxy-4,4-dimethyl-3-(6-methoxynaphthyl-2)-pentanoic acid (VII) (55% yield from VI). Demethylation with pyridine hydrochloride at 190° gave the free naphtholic lactone (VIII) in 70% yield.

It is possible to obtain the hydroxy ketone IX from the chloro ketone V by cautious treatment with methanolic potassium hydroxide. However, alkaline degradation of V cleaves the molecule to the naphthoic acid state, as shown by the recovery (after demethylation) of pure 6-hydroxy-2-naphthoic acid. This alkaline degradation, it is to be noted, constitutes proof of the assigned position of the chloro ketone radical on the naphthalene nucleus.

Compounds VII and VIII are now being investigated for biological activity.

Experimental[8]

β-Chlorotrimethylacetyl Chloride.—This compound was prepared by the procedure of Kharasch and Brown.[9] It was purified by fractionation through a Widmer column, the fraction distilling at 85–86° (58 mm.) being collected. The amide was prepared and found to have a melting point of 108–109° as given by Kharasch and Brown.

3-Chloro-2,2-dimethyl-1-(6-methoxynaphthyl-2)-1-propanone (V).—A solution of 15.8 g. of β-naphthyl methyl ether plus 17.2 g. of β-chlorotrimethylacetyl chloride in 70 ml. of nitrobenzene was cooled well in an ice-bath. To this solution were added gradually and with stirring 26.7 g. of anhydrous aluminum chloride (finely powdered). When all of the aluminum chloride had gone into solution, stirring was discontinued and the reaction mixture allowed to remain at room temperature for 24 hours. The mixture was then added with stirring to dilute hydrochloric acid plus crushed ice. The organic layer was taken up in ethyl ether and washed once with an equal volume of water, washed twice with equal volumes of 5% sodium hydroxide, and finally washed twice with water. Evaporation of the ether gave an oil which was steam distilled until the distillate was free of nitrobenzene. The resulting material was again dissolved in ether, and the ethereal phase washed well with water and evaporated, the last traces of solvent being removed under diminished pressure. This residue of crude product was recrystallized twice from benzene–Skellysolve B and once from Skellysolve B to yield 7.0 g. of long flat needles (V), m.p. 85–85.5° (25%).

Anal. Calcd. for $C_{16}H_{17}O_2Cl$: Cl, 12.81. Found: Cl, 12.79, 12.65.

5-Hydroxy-4,4-dimethyl-3-(6-methoxynaphthyl-2)-2-pentenoic Acid (VI).—Zinc metal (40 mesh), in amount 20 g., was amalgamated by shaking with 100 ml. of 3% hydrochloric acid containing 0.20 g. of mercuric chloride followed by washing with water, alcohol and ether. Of this amalgamated zinc, one-half was added to a solution of 3.0 g. of chloro ketone (V), m.p. 84–85°, in 75 ml. of dry benzene. To this solution were added 1.2 ml. of ethyl bromoacetate followed by 25 ml. of absolute ethyl ether. The mixture was refluxed gently on the steam-bath with moisture protection for a period of 3 hours, the remainder of the amalgamated zinc being added in portions at 30-minute intervals. (After one hour of refluxing another 1.2-ml. portion of ethyl bromoacetate was added followed by 25 ml. of absolute ether.) At the end of the reflux, the solution was cooled and distributed between ethyl ether and 1 *N* sulfuric acid. The separated ethereal phase was washed with water, washed with equal volumes of 3% ammonia until the ammonia was no longer colored, and finally washed well with water and evaporated on the steam-bath. To the residue was added 50 ml. of acetic anhydride, and the resulting solution was then heated on the steam-bath for 2 hours, after which the solvent was removed *in vacuo* at 90°. After removal of the last traces of anhydride, 50 ml. of methanol and 25 ml. of 26% potassium hydroxide were added, and the alkaline solution refluxed for 2 hours. At the end of the reflux period, the bulk of the methanol was removed by distillation, and the remaining alkaline solution cooled, diluted with water, and washed with ethyl ether. The aqueous phase was strongly acidified with sulfuric acid and shaken with an equal volume of ether during the course of twenty minutes, after which the acid layer was separated and discarded. The ether was washed twice with water and then extracted three times with 3% sodium bicarbonate. The combined bicarbonate extracts were acidified, allowed to stand overnight in the ice-box, and the crude acid filtered. Upon recrystallization from aqueous methanol, the product weighed 1.58 g. (m.p. 167–170°). The acid was recrystallized once from benzene–acetone to give 1.25 g. of microscopic crystals (VI) melting at 187–189° (38%). This melting point may be raised to 189–190° by further recrystallization from benzene–acetone.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.99, 71.94; H, 6.74, 6.77.

The Lactone of 5-Hydroxy-4,4-dimethyl-3-(6-methoxynaphthyl-2)-pentanoic Acid (VII).—The hydroxypentenoic acid (VI), 1.15 g. melting at 187–189°, was dissolved in 1.10 ml. of 26% potassium hydroxide and 25 ml. of water. To this solution were added 60.0 g. of 2% sodium amalgam, and the mixture shaken with intermittent heating on the steam-bath for 30 minutes. After this treatment the solution was decanted from the amalgam and the latter washed with 1% potassium hydroxide. The combined alkaline solutions were extracted once with ethyl ether and the ether discarded. The alkaline phase was then strongly acidified with sulfuric acid and allowed to stand for 1.5 hours, followed by intermittent shaking with ether for an additional half hour. The aqueous acid phase was then removed, and the ether washed successively with water, 3% sodium bicarbonate, and water and, after the addition of 1 drop of acetic acid, evaporated to dryness. The resulting residue was crystallized from aqueous ethanol to give 0.60 g. of material (VII) melting at 148–149° (55% yield). Treatment with charcoal and recrystallization from 95% ethanol raised the melting point to 150.5–151.5°.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.84, 75.74; H, 7.01, 7.07.

The Lactone of 5-Hydroxy-4,4-dimethyl-3-(6-hydroxynaphthyl-2)-pentanoic Acid.—One part of lactone methyl ether (VII), m.p. 148–149°, was fused for 2 hours at 190° with five parts of pyridine hydrochloride. The melt was then cooled, partitioned between water and ethyl ether, and the latter washed with 3% hydrochloric acid, washed well with water, and then evaporated. The resulting residue was recrystallized once from aqueous methanol and once

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[7] W. E. Bachmann, W. Cole and A. L. Wilds, THIS JOURNAL, **62**, 824 (1940).

[8] All melting points are uncorrected. Analyses are by Dr. E. W. D. Huffman, Denver, Colo.

[9] M. S. Kharasch and H. C. Brown, THIS JOURNAL, **62**, 925 (1940).

from acetone–cyclohexane to give a 70% yield of free naphtholic lactone (VIII) melting at 191–192°. Subsequent recrystallization from aqueous acetone (with 10% loss) raised the melting point to 192–193° (microscopic crystals).

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.48, 75.59; H, 6.84, 6.77.

3-Hydroxy-2,2-dimethyl-1-(6-methoxynaphthyl-2)-1-propanone (IX).—Four-tenths of a gram of chloro ketone (V), m.p. 85.0–85.5°, was dissolved in 13 ml. of methanol plus 3 ml. of 26% potassium hydroxide and the resulting solution refluxed on the steam-bath for 2 hours. The hot solution was diluted with water (to turbidity) and left overnight in the ice-box. The resulting crystals were filtered and washed with water. Recrystallization from aqueous acetone gave 0.12 g. of product melting at 105–107°. A recrystallization from acetone–Skellysolve B followed by a recrystallization from Skellysolve F–ethyl ether gave 0.04 g. of silky needles (IX), m.p. 119°. This melting point was not improved upon subsequent recrystallization.

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.39; H, 7.03. Found: C, 74.05, 74.19; H, 6.73, 6.67.

Alkaline Degradation of 3-Chloro-2,2-dimethyl-1-(6-methoxynaphthyl-2)-1-propanone (V) to 6-Hydroxy-2-naphthoic Acid.—To 0.28 g. of pure chloro ketone (V) was added a solution of 10 g. of 85% potassium hydroxide in 10 ml. of water plus 30 ml. of ethanol. The alkaline solution was heated under reflux for 2 hours, cooled, and then acidified with dilute sulfuric acid. After 24 hours at room temperature, the precipitated acid was filtered, washed with water, and dried in the oven. The yield was 0.12 g. of crude 6-methoxy-2-naphthoic acid. This was demethylated by fusing with pyridine hydrochloride at 190° for 2 hours. The cooled fusion mixture was diluted with 100 ml. of water and, after a few hours, filtered from a dark brown precipitate. The filtrate, upon standing in the ice-box overnight, deposited 52 mg. of white crystals, m.p. 235–239°. Recrystallization of these white crystals from aqueous methanol and from benzene–Skellysolve B raised the melting point to 241–242°. Butler and Royle[10] record a melting point of 240–241° for 6 hydroxy-2-naphthoic acid.

Anal. Calcd. for $C_{11}H_8O_3$: C, 70.21; H, 4.29. Found: C, 70.15; H, 4.36.

The ethyl ester of this acid, prepared according to Butler and Royle,[10] melted sharply at 110°. (Butler and Royle record 111–112°.)

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.20; H, 5.59. Found: C, 72.01; H, 5.87.

Acknowledgment.—The support of this research by G. D. Searle and Company is gratefully acknowledged.

[10] C. Butler and F. A. Royle, *J. Chem. Soc.*, 1654 (1923).

OKLAHOMA CITY 4, OKLA. RECEIVED OCTOBER 9, 1950

[CONTRIBUTION FROM THE THOMPSON LABORATORY OF THE PHILLIPS EXETER ACADEMY]

The Tautomeric Forms of Some 1,1-Diaroylethanes

BY CHARLES L. BICKEL AND ROBERT MORRIS[1]

This report describes the preparation of the enolic forms of four diaroylethanes. These substances easily revert to the parent diketones but may be recrystallized without change from ether. The bromo derivatives of the enols have also been prepared and these have, in turn, been converted into the parent diketones by the use of hydriodic acid.

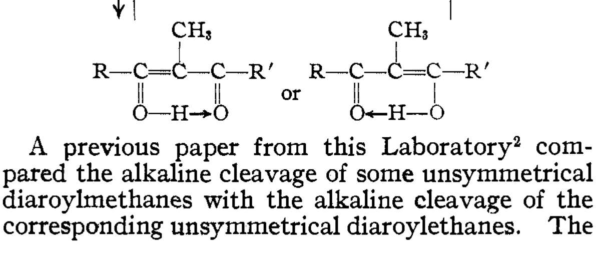
The investigation of a large number of diaroylmethanes has shown that these substances are completely enolic in solution, indicating that the enolic forms are more stable than the tautomeric ketonic forms.

Conversely, fragmentary reports on diaroylethanes indicate that the introduction of the methyl group suppresses the enolization almost completely.[2–4] These compounds give no coloration with ferric chloride and there is no evidence of bromine addition or copper salt formation. By the acidification of a sodium alcoholate solution of 1-anisoyl-1-benzoylethane, Weygand[5] obtained a solid which appeared to be the enolic form of the diaroylethane but which reverted to the diketone upon recrystallization.[6] Dieckmann[7] applied the same method to 1,1-dibenzoylethane and obtained a substance which gave the characteristic reactions of the enol but which reverted to the keto form on standing in alcoholic solution.

This paper reports the preparation of the pure enolic forms of four diaroylethanes by the action of an alcoholic solution of potassium hydroxide on the ethanes, followed by the addition of an excess of hydrochloric acid. Each of the enols can be recrystallized from ether without ketonization; in one case the enol was recovered unchanged after standing for several months in ether solution. The enols revert to the tautomeric diketones when heated in ordinary glass melting point tubes so that the melting points must be determined on a metal block. At the melting point the enols revert fairly rapidly to the diketones.

Chloroform solutions of the enols instantaneously absorb the calculated quantity of bromine, liberating hydrogen bromide and giving the corresponding 1,1-diaroyl-1-bromoethanes. These bromine compounds are quantitatively converted by potassium iodide and acid into the diaroylethanes from which the enols were prepared.

The above changes are summarized structurally



A previous paper from this Laboratory[2] compared the alkaline cleavage of some unsymmetrical diaroylmethanes with the alkaline cleavage of the corresponding unsymmetrical diaroylethanes. The

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[1] The 1,1-diaroylethanes used in this problem were prepared by Robert Morris, a senior in the Phillips Exeter Academy during the school year 1949–1950.

[2] Bickel, THIS JOURNAL, **67**, 2204 (1945).

[3] Kohler, Tishler and Potter, *ibid.*, **57**, 2518 (1935).

[4] Sprague and Adkins, *ibid.*, **56**, 2672 (1934).

[5] Weygand, *Ber.*, **61**, 687 (1928).

[6] Weygand reported a melting point of 80° for this solid. The pure enol melts at 112° while the diketone melts at 72°. The solid obtained by Weygand was, therefore, undoubtedly a mixture of the tautomeric forms.

[7] Dieckmann, *Ber.*, **55**, 2481 (1922).