TABLE I

UNSATURATED HYDROXY ESTERS: R—CHCH$_2$CH=CHCOOC$_2$H$_5$ (OH)

R =	Yield, %	B. p., °C. (1 mm.)	$n^{25}D$	Formula	% Composition Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Phenyl	21	143–145.5	1.5298	$C_{13}H_{16}O_3$	70.89	70.45	7.32	7.40
Cyclohexyl	14	125–127	1.4893	$C_{13}H_{22}O_3$	68.99	68.39	9.80	10.50
Cyclopentyl	23	116–117	1.4865	$C_{12}H_{20}O_3$	67.89	67.44	9.50	9.57
1-Cyclopentenyl	7.5	101–104	1.495	$C_{12}H_{18}O_3$	68.55	68.70	8.62	8.57
2-Furyl	35	101–107	1.4973	$C_{11}H_{14}O_4$	...	...	..	...

5-Phenyl-5-hydroxyvaleric Acid.—The above hydroxy acid was hydrogenated in absolute ethanol with Adams catalyst, and the product was crystallized from a mixture of chloroform and carbon tetrachloride; m. p. 65.5–66°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.06; H, 7.27; neut. equiv., 194. Found: C, 67.63; H, 7.26; neut. equiv., 193.

5-Cyclohexyl-5-hydroxy-2-pentenoic Acid.—Ethyl 5-cyclohexyl-5-hydroxy-2-pentenoate was saponified with aqueous-alcoholic potassium hydroxide on the steam-bath for one hour. After removal of most of the alcohol and acidification, an oil appeared which crystallized slowly. Several recrystallizations from a mixture of benzene and ligroin gave small needles of hydroxy acid, m. p. 91.5–92°.

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15; neut. equiv., 198. Found: C, 66.90; H, 9.44; neut. equiv., 198.

5-Cyclohexyl-5-valerolactone.—A sample of the above acid, reduced in absolute ethanol with Adams catalyst, absorbed 0.97 mole of hydrogen per mole of acid. Evaporation of the solvent left a solid, which was recrystallized in an ice-bath from low-boiling petroleum ether containing a little ethyl acetate, as bunches of needles, constant m. p. 59.5–60°. The analysis and properties indicated that the product had lactonized to 5-cyclohexyl-5-valerolactone.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.29; H, 9.54.

The complete hydrogenation of ethyl 5-phenyl-5-hydroxy-2-pentenoate with a particularly active sample of Adams catalyst, followed by saponification, gave a product with the same properties as the above lactone. A mixed melting point showed no depression.

5-Cyclopentyl-5-hydroxy-2-pentenoic Acid.—Ethyl 5-cyclopentyl-5-hydroxy-2-pentenoate was saponified in the same manner as the cyclohexyl analog. The solid hydroxy acid was crystallized from a mixture of benzene and ligroin in tiny needles to constant m. p. 84.5–85°.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76; neut, equiv., 184. Found: C, 64.93; H, 8.79; neut. equiv.. 184.

This hydroxy acid, on reduction in absolute ethanol with Adams catalyst, absorbed 1.00 mole of hydrogen per mole of acid, but no crystalline product could be isolated.

Summary

The Reformatsky reaction has been employed in the synthesis of some 5-substituted-5-hydroxy-2-pentenoic esters of the general form RCHOH-CH$_2$CH=CH—COOC$_2$H$_5$. R represents phenyl, cyclohexyl, cyclopentyl, 1-cyclopentenyl, and furyl group.

The corresponding acids have been prepared from the phenyl, cyclohexyl and cyclopentenyl analogs.

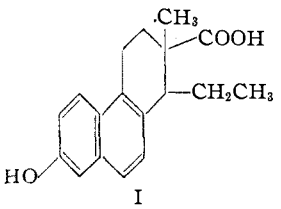
NEW HAVEN, CONN. RECEIVED APRIL 25, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

The Synthesis of Certain Hydroxyacids with Possible Estrogenic Activity

BY JAMES H. HUNTER AND JEROME KORMAN

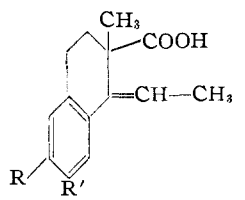
In a series of recent articles Miescher and co-workers reported the synthesis of bisdehydrodoisynolic acid (I) and certain homologs and analogs.[1]



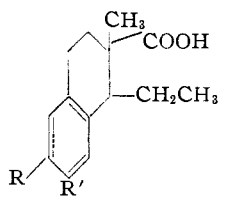
I

In connection with a more general investigation of synthetic sex hormones in progress in this Laboratory, the present communication describes the synthesis of analogs of I containing the tetrahydronaphthalene nucleus in which the position of the hydroxyl group has been varied.[2]

In our work both the 7- and 6-hydroxy compounds were prepared by the same series of reaction. Following the procedure of Bachmann and



IIa R = OCH_3, R′ = H
IIb R = H, R′ = OCH_3



IIIa R = OH, R′ = H
IIIb R = H, R′ = OH

(1) (a) Miescher, *Helv. Chim. Acta*, **27**, 1727 (1944); (b) Heer, Billeter and Miescher, *ibid.*, **28**, 1342 (1945); (c) Heer and Miescher, *ibid.*, **28**, 1506 (1945); (d) Anner and Miescher, *ibid.*, **29**, 586 (1946).

(2) While this work was in progress the synthesis of IIa and IIIa was reported.[1d,3]

(3) Horeau, *Compt. rend.*, **222**, 961 (1946).

Thomas[4] 7-methoxytetralone-1 was converted to 7-methoxy-2-methyl-2-carbomethoxy-1-keto-1,2,-3,4-tetrahydronaphthalene. Addition of slightly more than the equivalent amount of ethylmagnesium bromide at room temperature gave the 1-hydroxy-1-ethyl compound. Dehydration of the tertiary alcohol was accomplished by either formic acid or anhydrous hydrogen chloride in benzene. The 6-methoxy compound was also dehydrated by conversion to the chloride followed by dehydrohalogenation.[5] Dehydration of the 6-methoxy derivative by any of these methods gave the same unsaturated compound reported previously,[1d,3] *i. e.*, 6-methoxy-2-methyl-2-carbomethoxy-1-ethylidene-1,2,3,4-tetrahydronaphthalene.

Treatment of the 7-methoxy unsaturated ester with aqueous potassium hydroxide gave excellent yields of crude acid from which two isomers could be obtained; with methanolic potassium hydroxide only tars resulted from which none of the free acid could be separated. Conversely aqueous alkali had little effect on the 6-methoxy ester whereas methanolic potassium hydroxide gave excellent yields of free acid.

Hydrogenation of the acid over palladium–charcoal gave the saturated acid which was demethylated with pyridine hydrochloride,[6] since it was found that demethylation proceeded poorly when acetic acid–hydrobromic acid in a nitrogen atmosphere was used. Only one of the two possible isomeric acids IIIa and IIIb could be isolated.

Attempts to obtain the free unsaturated phenols were unsuccessful since demethylation with either acidic or basic reagents caused decomposition, apparently decarboxylation; therefore bioassays were conducted on the methyl ethers IIa and IIb.

Preliminary tests[7] by the Kahnt–Doisy method, employing white rats, indicated that all compounds were inactive in doses up to 100 γ. IIIa has been reported to be inactive in rats in 1000 γ doses.

Experimental[8,9]

Methyl 7-methoxy-1-keto-1,2,3,4-tetrahydronaphthalene-2-glyoxalate.—Condensation of 17.6 g. of 7-methoxytetralone-1 in the manner described by Bachmann and Thomas[4] for the 6-methoxy compound gave 26.2 g. (100%) of the desired compound which was used without further purification. A sample recrystallized from methanol formed fine needles; m. p. 80–81°.

Anal. Calcd. for $C_{14}H_{14}O_5$: C, 64.12; H, 5.34. Found: C, 64.19; H, 5.40.

7-Methoxy-2-carbomethoxy-1-keto-1,2,3,4-tetrahydronaphthalene.—Decarbonylation of 26.2 g. of the above glyoxalate with 12 g. of powdered soft glass at 185° gave 22 g. (84%) of product which could be used without further purification. A portion of the residual oil after removal of the acetone was distilled at 0.2 mm. A yellow-orange oil resulted which could be made to crystallize only with great difficulty. A solid 2,4-dinitrophenylhydrazone was prepared which, after recrystallization from ethanol, melted at 177–178°.

Anal. Calcd. for $C_{19}H_{18}O_7N_4$: C, 55.07; H, 4.38; N, 13.52. Found: C, 54.97; H, 4.12; N, 13.62.

7-Methoxy-2-methyl-2-carbomethoxy-1-keto-1,2,3,4-tetrahydronaphthalene.—Methylation of 20 g. of the above compound according to the procedure of Bachmann and Thomas[4] gave 15.5 g. (73%) of product melting at 91–92.5°. A sample recrystallized from petroleum ether (55–75°) formed colorless prisms; m. p. 92–93°.

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.74; H, 6.45. Found: C, 67.70; H, 6.53.

7-Methoxy-2-methyl-2-carbomethoxy-1-ethyl-1-hydroxy-1,2,3,4-tetrahydronaphthalene.—The above ketone (10.3 g.) was dissolved in 125 cc. of dry ether and 50 cc. of dry benzene contained in a 250-ml. three-necked flask, fitted with a reflux condenser, mechanical stirrer and dropping funnel with gas inlet tube. Stirring was started and the apparatus flushed with dry nitrogen; 40 cc. of an ethereal solution of ethylmagnesium bromide containing 0.00125 mole of Grignard reagent per cc. (by titration against standard hydrochloric acid) was added dropwise. The reaction mixture was stirred at room temperature for one-half hour, and then decomposed with cold 5% sulfuric acid. The aqueous layer was separated, extracted twice with ether, the combined ethereal layers washed with sodium bicarbonate solution, water, and dried over anhydrous sodium sulfate. Spontaneous evaporation of the solvent gave 9.53 g. (82%) of white crystalline material. Recrystallization from petroleum ether gave the product; m. p. 53.5–54.5°.

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 68.71; H, 7.88. Found: C, 68.72; H, 7.48.

7-Methoxy-2-methyl-2-carbomethoxy-1-ethylidene-1,2,3,4-tetrahydronaphthalene.—The carbinol (3.75 g.) and 10 cc. of 85% formic acid was heated on the steam-bath for one hour. Formic acid was removed *in vacuo* at 40° and the residual oil taken up in benzene. The solution was washed with sodium bicarbonate solution, then water, and distilled. The fraction boiling at 140–145° (0.08 mm.) was collected, and amounted to 2.79 g. (81%).

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.85; H, 7.69. Found: C, 73.85; H, 8.08.

7-Methoxy-2-methyl-2-carboxy-1-ethylidene-1,2,3,4-tetrahydronaphthalene.—Four grams of the unsaturated ester was refluxed for twelve hours with 30 cc. of 45% aqueous potassium hydroxide. Water was added, the solution clarified somewhat with Norite, and filtered. The cold solution was acidified with 5% hydrochloric acid whereupon the acid precipitated. There was obtained 3.3 g. (85%) of crude acid; m. p. 118–163°. Recrystallization from methanol gave one form; m. p. 178–178.5° (A). Recrystallization of the residue from petroleum ether after removal of methanol gave a second form; m. p. 128–130° (B).

Anal. Calcd. for $C_{15}H_{18}O_3$: (A) C, 73.17; H, 7.32; (B) C, 73.17; H, 7.32. Found: (A) C, 73.44; H, 7.39; (B) C, 73.02; H, 7.70.

7-Methoxy-2-methyl-2-carboxy-1-ethyl-1,2,3,4-tetrahydronaphthalene.—Hydrogenation of 2.53 g. of the unsaturated acid (A) in 100 cc. of 95% ethanol over palladium–carbon at room temperature and atmospheric pressure gave a colorless oil after evaporation of solvent. On cooling and scratching the oil solidified to a white solid; m. p. 114.5–116.5°. Recrystallization from petroleum ether gave the compound; m. p. 115–116.5° in 89% yield (2.2 g.).

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.60; H, 8.11. Found: C, 72.97; H, 8.36.

7-Hydroxy-2-methyl-2-carboxy-1-ethyl-1,2,3,4-tetrahydronaphthalene.—A mixture of 0.7 g. of the ether and

(4) Bachmann and Thomas, THIS JOURNAL, **64**, 94 (1942).

(5) Bachmann, Cole and Wilds, *ibid.*, **62**, 824 (1940).

(6) Prey, *Ber.*, **74B**, 1219 (1941).

(7) Grateful acknowledgment is made to Messrs. Nelson and Lyster of this Laboratory for carrying out the bioassays.

(8) All melting points are uncorrected.

(9) All microanalyses were performed by Mr. Harold Emerson and staff of our microanalytical laboratory.

8.6 g. of pyridine hydrochloride was heated at 185–195° for three hours. After cooling it was poured into water, extracted repeatedly with ether, the ethereal layer washed with dilute hydrochloric acid, water and dried. Evaporation of the solvent gave 0.54 g. (82%) of the naphthol which after recrystallization from methylcyclohexane melted at 169–171°.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 71.81; H, 7.74. Found: C, 71.69; H, 7.86.

6-Methoxy-2-methyl-2-carbomethoxy-1-keto-1,2,3,4-tetrahydronaphthalene.—This compound was prepared according to the procedure of Bachmann and Thomas.[4] Recrystallization from petroleum ether (55–75°) gave needles, m. p. 91.5–92°.

6-Methoxy-2-methyl-2-carbomethoxy-1-ethyl-1-hydroxy-1,2,3,4-tetrahydronaphthalene.—Ten and three-tenths grams of the above ketone was treated with 40 cc. of ethylmagnesium bromide solution as described for the 7-methoxy compound. Evaporation of the solvent gave 9.8 g. (87%) of product. A sample washed once with anhydrous ether melted at 100.5–101°.

6-Methoxy-2-methyl-2-carbomethoxy-1-ethylidene-1,2,3,4-tetrahydronaphthalene.—Dehydration of 5 g. of the carbinol with 20 cc. of 85% formic acid gave, after working up as described above, 3.7 g. (80%) of the unsaturated ester as an oil; b. p. 135–140° (0.08 mm.).

6-Methoxy-2-methyl-2-carboxy-1-ethylidene-1,2,3,4-tetrahydronaphthalene.—The above ester (3.32 g.) was refluxed for twelve hours with 30 cc. of 15% methanolic potassium hydroxide. The alcohol was distilled and the solid residue taken up in water. The solution was extracted once with ether to remove a small amount of neutral material, and then acidified with 5% hydrochloric acid. After standing overnight in the ice box there was obtained 2.63 g. (84%) of material; m. p. 109–114° (dec.). Recrystallization from dilute methanol gave material melting at 113–115° (dec.); yield, 2.2 g.

6-Methoxy-2-methyl-2-carboxy-1-ethyl-1,2,3,4-tetrahydronaphthalene.—One gram of the unsaturated acid in 40 cc. of 95% ethyl alcohol was hydrogenated over palladium charcoal at room temperature and atmospheric pressure. Removal of the solvent gave an oil which crystallized on cooling and scratching. Recrystallization from methanol gave 0.6 g. of material, m. p. 131–132°.

6-Hydroxy-2-methyl-2-carboxy-1-ethyl-1,2,3,4-tetrahydronaphthalene.—A mixture of 0.53 g. of the above ether and 6 g. of pyridine hydrochloride was heated in an oil-bath for three hours at 185–195°. After cooling it was poured into water and extracted repeatedly with ether. The ethereal layer was washed with dilute hydrochloric acid, then water, and dried. Removal of the ether gave an oil which crystallized on cooling and scratching; yield 0.3 g. (60%). Recrystallization from methylcyclohexane gave the compound, m. p. 150.5–152°.

Summary

1. Two analogs of bisdehydrodoisynolic acid containing the naphthalene ring system have been prepared.

2. Preliminary tests indicate that these compounds are estrogenically inactive in doses up to 100 γ.

KALAMAZOO, MICHIGAN RECEIVED APRIL 5, 1947

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NATIONAL RESEARCH COUNCIL, AND THE RESEARCH LABORATORIES, DOMINION RUBBER COMPANY]

The Alkaloids of Lycopodium Species. IX. *Lycopodium Annotinum* Var. *Acrifolium*, Fern. and the Structure of Annotinine[1]

BY RICHARD H. F. MANSKE AND LÉO MARION

A previous examination of *Lycopodium annotinum* L.[2] has yielded eight alkaloids, the chief of which was a new one named annotinine. This alkaloid seemed to be one of the large group of Lycopodium alkaloids which would be more amenable to chemical study because of functional groups in the molecule. It was therefore desirable to obtain larger quantities of annotinine and for this purpose a second lot of a plant presumed to be *L. annotinum* L. was worked up. The authors are greatly indebted to Professor P. L'Ecuyer, Laval University, who generously placed this material at their disposal. It was collected in the vicinity of Duchesnay, Que.

Chemical examination soon disclosed, however, that the two lots of plants were definitely distinct and evinced differences that could not be accounted for by accidental variations in isolation procedure. Indeed the distinction was so marked as to suggest taxonomic differences and accordingly Mr. C. A. Weatherby of the Gray Herbarium, Harvard University, was consulted. He reported that the plant in question was *Lycopodium annotinum* var. *acrifolium* Fern., thus confirming the differences of kind. Although the plants are not too readily recognizable they are more distinct, taxonomically, than for instance *L. flabelliforme* and *L. complanatum* which are both given specific rank. The presence of lycopodine which occurs in this plant calls for no comment; its absence would definitely arouse interest. The occurrence of annotinine, which is the chief alkaloid, indicates an affinity with the type species but the absence of alkaloids L6, L8, L9, L11 and L12, all found in the type and the presence of five new ones, indicates that this affinity can be only remote. Even obscurine (L6) which has been found in *L. flabelliforme*[3] and *L. obscurum*[4] was either absent or present only in doubtful traces. In view of such marked differences between the type and the variety; in view also of the fact that the variety possesses morphological characteristics by means of which it can be differentiated from the type by a relatively experienced observer,

(1) Published as National Research Council Bull. No. 1529.

(2) R. H. F. Manske and L. Marion, *Can. J. Research*, **B21**, 92 (1943).

(3) (a) R. H. F. Manske and L. Marion, *ibid.*, **B20**, 87 (1942); (b) *ibid.*, **B22**, 1 (1944).

(4) R. H. F. Manske and L. Marion, *ibid.*, **B22**, 53 (1944).