quantities with the Grignard compound of the equivalent amount of neohexyl chloride. The condensation products which distilled between 220–250° at 1.2 mm. were brominated with phosphorus tribromide to convert the hydroxy ester into the bromo ester. The latter together with the unsaturated ester was extracted with ether, leaving behind a small amount of insoluble material which was identified as thapsic acid. Dehydrobromination and saponification of the ether-soluble products with 20% potassium hydroxide yielded a mixture of $\Delta_{15,16}$- and $\Delta_{16,17}$-19,19-dimethyleicosenoic acids. Catalytic hydrogenation of the free acids over platinum oxide in methanol under 30 lb./sq. in. and immediate esterification of the filtrate gave methyl 19,19-dimethyleicosanoate which distilled through a heated Vigreux column at 195° (0.7 mm.), $n^{20}D$ 1.4528. After saponification organic impurities had to be removed from the aqueous potassium soap solution by petroleum ether, since the potassium salt proved considerably soluble in ethyl ether. The neobehenic acid (19,19-dimethyleicosanoic acid) recrystallized from acetonitrile melted at 61.0–61.8°.

Anal. Calcd. for $C_{22}H_{44}O_2$: C, 77.58; H, 13.02; neut. equiv., 340.57. Found: C, 77.91; H, 13.43; neut. equiv., 342.6.

Preparation of Neolignoceric Acid.—An analogous condensation was carried out between 15-carbethoxypentadecanal and neoöctylmagnesium chloride. After refluxing with 10% potassium hydroxide in 80% ethanol for four hours and conversion into the free acids, extraction with petroleum ether left unreacted acid-aldehyde behind, which was identified after oxidation with potassium permanganate to thapsic acid. The mixture of C_{24} acids was reësterified with methanol, treated with phosphorus tribromide and subsequently with potassium hydroxide as in the preceding examples. The resulting unsaturated $\Delta_{15,16}$- and $\Delta_{16,17}$-21,21-dimethyldocosenoic acids were catalytically hydrogenated, again reesterified, and the methyl 21,21-dimethyldocosanoate distilled at 209° (0.8 mm.), $n^{20}D$ 1.4552.

Neolignoceric acid (21,21-dimethyldocosanoic acid) was obtained from the middle fraction of the methyl ester; recrystallized from acetonitrile, it melted at 63.8–64.5°.

Anal. Calcd. for $C_{24}H_{48}O_2$: C, 78.19; H, 13.13; neut. equiv., 368.62. Found: C, 78.94; H, 12.90; neut. equiv., 367.3.

Summary

The synthesis, properties and infrared absorption spectra of the neo isomers of the monobasic aliphatic acids with even numbers of carbon atoms from 16 to 24 are described.

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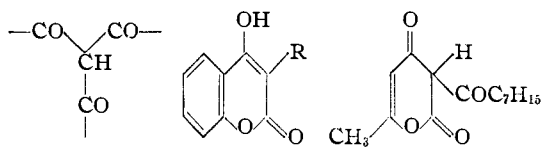
[CONTRIBUTION FROM THE SEVENTH DEPARTMENT OF THE INSTITUTE FOR INFECTIOUS DISEASES OF THE UNIVERSITY OF TOKYO]

The Antibacterial Properties of Compounds Containing the Tricarbonylmethane Group. IV. Syntheses of 3-Alkylated or 3-Acylated 4-Hydroxycoumarins and of a Related Pyrone

BY TYUNOSIN UKITA, SHOSHICHI NOJIMA AND MAKOTO MATSUMOTO

3-Acetyl-4-hydroxycoumarin, a compound containing the tricarbonylmethane group (I), has been found to possess remarkable activity against several bacteria.[1] In subsequent papers[2,3] interesting relations between structure and activity were reported for a number of 3-acyl- and 3-alkyl-4-hydroxycoumarins (II and III) possessing long side chains, and the related 6-methyl-4-hydroxy-3-octanoylpyrone-2 (IV) was also investigated. The present paper describes the syntheses of the compounds tested.



I II, R = acyl III, R = alkyl V, R = H IV

The known methods of preparing compounds of type II or III involve condensation of suitable derivatives of salicylic acid with β-keto esters[4] or alkylated acetoacetates[5]; further, 3-alkyl derivatives are available by condensation of phenol with alkylated malonic esters,[6] and also by alkali fusion of methyl acylsalicylates.[7] The last-named method also yields the parent compound (V) when applied to methyl acetylsalicylate,[8] and the same substance is easily obtainable by decarboxylation of the condensation product of malonic ester and acetylsalicylyl chloride.[4]

We attempted direct acylation of V in the 3-position. This type of condensation failed under the following conditions: treatment of V as its sodio derivative with an acid chloride, or treatment of V with an acid chloride and magnesium in benzene or toluene.[9,10] Heating V with acetyl chloride and sodium in toluene gave a yield of about 5% of the desired product. However, smooth reaction occurred when pyridine–piperidine was used as condensing solvent, and we obtained in good yield the thirteen 3-acyl-4-hydroxycoumarins listed in the table. The acetyl derivative, compound no. 1, was identical with an authentic specimen prepared by the Anschütz method,[4] and by analogy we regard our substances

(1) Ukita, Tamura, Matsuda and Kashiwabara, *Jap. J. Exp. Med.*, **20**, 109 (1949).
(2) Ukita, Tamura, Yamakawa and Nojima, in press.
(3) Ukita, Mizuno, Tamura and Nojima, in press.
(4) Anschütz, *Ann.*, **367**, 169 (1909).
(5) Heilbron and Hill, *J. Chem. Soc.*, 1705 (1927).
(6) Urbain and Mentzner, *Bull. soc. chim.*, **11**, 171 (1944).
(7) Stahmann, Wolff and Link, THIS JOURNAL, **65**, 2285 (1943).
(8) Pauly and Lockemann, *Ber.*, **48**, 28 (1915).
(9) Spassow, *ibid.*, **70**, 1926, 2381 (1937).
(10) Ogata, Nozaki and Takagi, *J. Pharm. Soc. Japan*, **59**, 105 (1939).

TABLE I

No.	Hydroxycoumarin	Formula	M. p., °C.	Coloration by $FeCl_3$ in alcohol	Yields, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	3-Acetyl-4-	$C_{11}H_8O_4$	134	Yellowish	40	...	...	..	..
2	3-Propionyl-	$C_{12}H_{10}O_4$	123	brown	22	66.06	65.86	4.59	4.58
3	3-Butyryl-	$C_{13}H_{12}O_4$	120–121	Reddish	42	67.24	67.15	5.17	5.48
4	3-Isobutyryl-	$C_{13}H_{12}O_4$	76.5–77	brown	42	67.24	67.38	5.17	5.31
5	3-*n*-Valeryl-	$C_{14}H_{14}O_4$	99	Orange	39	68.29	68.17	5.69	5.78
6	3-Isovaleryl-	$C_{14}H_{14}O_4$	75–76	Orange	33	68.29	68.56	5.69	5.57
7	3-Isocaproyl-	$C_{15}H_{16}O_4$	79–80	Orange	..	69.23	69.19	6.15	6.43
8	3-Octanoyl-	$C_{17}H_{20}O_4$	104–105	Orange	68	70.83	70.64	6.94	7.09
9	3-*n*-Decanoyl-	$C_{19}H_{24}O_4$	108	Pale	62	72.35	72.28	7.60	7.75
10	3-*n*-Dodecanoyl-	$C_{21}H_{28}O_4$	110	orange	57	73.25	73.03	8.14	8.29
11	3-*n*-Tetradecanoyl-	$C_{23}H_{32}O_4$	110.5	Pale	57	74.19	74.36	8.60	8.70
12	3-*n*-Hexadecanoyl-	$C_{25}H_{36}O_4$	111	orange	61	75.00	75.39	9.00	9.17
13	3-(α-Phenyl)-*n*-tetradecanoyl-	$C_{29}H_{36}O_4$	92	Pale orange	33	77.68	77.63	8.06	8.07
14	6-Methyl-2-hydroxy-3-octanoylpyrone-4	$C_{14}H_{20}O_4$	70	Orange red	35	66.67	66.86	7.94	8.06

as 3-acylated coumarins, an inference borne out by the positive ferric chloride test all of them give in alcoholic solution.

The method of acylation described could be extended to 6-methyl-2-hydroxypyrone-4 (or 6-methyl-2,4-diketo-2,3-dihydropyrane), obtainable by hydrolysis of dehydroacetic acid. In this fashion the octanoylhydroxypyrone IV was prepared, compound no. 14 in the table.

Direct alkylation by the method described did not prove successful, and we used a modification of Heilbron's procedure[5] to prepare the 3-*n*-butyl and the 3-*n*-decyl derivatives of V.

Experimental

General Acylation Procedure.—To an ice-cold solution of 1 g. of V in 8 cc. of pyridine containing one drop of piperidine was added 0.8 g. of acetyl chloride, and the mixture was kept at 37° for forty-eight hours. The red suspension was poured into ice-water, acidified with dilute hydrochloric acid and extracted with ether. The ethereal solution was extracted with 5% sodium carbonate solution, the alkaline extract was acidified and the precipitated solid, upon recrystallization from alcohol, afforded 0.5 g. of needles, m. p. 134°, not depressed by an authentic specimen of 4-hydroxy-3-acetylcoumarin.

In general, about 1.5 equivalents of acid chloride was added to 1 g. of V as above; for compounds nos. 2–7 the mixtures were heated for three hours on a water-bath, for no. 8–14 the solutions were boiled gently for twelve hours. The mixtures were processed as described. Yields, appearance, melting points, and analyses are reported in the table.

Mixed melting point determinations showed pronounced depressions for the following mixtures: 2 and 3; 4 and 5; 8 and 9, 10, 11, 12; 9 and 10, 11, 12; 10 and 11, 12; 11 and 2.

3-*n*-Butyl-4-hydroxycoumarin.—To 15 g. of diethyl *n*-butylmalonate in 30 cc. of dry ether was added 1.69 g. of sodium and 4.5 g. of acetylsalicylyl chloride. After heating on the water-bath for twelve hours the mixture was decomposed with hydrochloric acid and extracted with ether. Extraction of the ether with 5% sodium bicarbonate, acidification of the extract, and recrystallization from alcohol yielded 0.9 g. of colorless needles, m. p. 158°. Addition of ferric chloride to an alcoholic solution produced a yellow color.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.55; H, 6.42. Found: C, 71.53; H, 6.40.

3-*n*-Decyl-4-hydroxycoumarin.—A mixture of 11 g. of diethyl *n*-decylmalonate, 30 cc. of dry ether, and 2.44 g. of acetylsalicylyl chloride was treated as above, yielding 0.5 g. of colorless crystals, m. p. 121–122°; ferric chloride test yellow.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.50; H, 8.61. Found: C, 75.78; H, 8.91.

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Summary

1. The condensation of 4-hydroxycoumarin with acid chlorides in pyridine–piperidine has been used to prepare a number of 3-acyl-4-hydroxycoumarins. Similarly 3-octanoyl-6-methyl-2-hydroxypyrone-4 has been obtained.

2. The method fails when applied to alkylation reactions. Two 3-alkyl-4-hydroxycoumarins were prepared by orthodox procedures.

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