$C_8H_{14}O_4$: C, 55.2; H, 8.04. Found: C, 54.8, 54.6; H, 8.05, 8.08.

4-Acetamido-4,4-dicarbethoxypentanonitrile.—Ethyl oximinomalonate is prepared in accordance with the directions of Snyder and Smith.[9] Acetamidomalonic ester is prepared by reduction of ethyl oximinomalonate by a procedure analogous to that used by Albertson[10] for the reduction of ethyl oximinoacetoacetate. A 500-ml. flask is fitted with a reflux condenser, mechanical stirrer, and an addition funnel. The entire apparatus is carefully dried and protected from atmospheric water with a drying tube. Absolute ethanol (200 ml.), which has been dried and distilled from calcium hydride, and 5.7 g. (0.25 mole) of sodium is added to the flask. After the sodium has reacted with the ethanol, 56.7 g. (0.25 mole) of ethyl acetamidomalonate and 30.0 g. (0.32 mole) of 4-chlorobutyronitrile[11] is added. The reaction mixture is maintained at reflux temperature and stirred for eighteen hours, cooled, and filtered from the precipitate of sodium chloride. Distillation of the filtrate yields 12 g. of recovered 4-chlorobutyronitrile and 12 g. of 4-acetamido-4,4-dicarbethoxypentanonitrile (yield, 21.8%; b. p. 132° (5 mm.), n^{20}_D 1.4468, d^{20}_{20} 1.1083, M_D calcd. 69.23, M_D 68.94). *Anal.* Calcd. for $C_{13}H_{20}O_5N_2$: N, 9.85. Found: N, 9.50.

DL-**Lysine Dihydrochloride.**—In 100 ml. of freshly distilled acetic anhydride, 15 g. (0.053 mole) of 4-acetamido-4,4-dicarbethoxypentanonitrile is dissolved. Platinic oxide catalyst (0.5 g.) is added and reduction begun at a hydrogen pressure of three atmospheres. Three hours is required to complete the reduction. The catalyst is removed by filtration and the acetic anhydride carefully hydrolyzed with 25 ml. of water. The N,N-diacetyllysine is hydrolyzed by boiling the acetic acid solution with 100 ml. of hydrochloric acid (sp. gr. 1.19) for eighteen hours. Evaporation of this solution yields 9.0 g. of lysine dihydrochloride (yield, 77%; m. p. 175–180°). This crude lysine is reprecipitated from absolute ethanol with ether yielding pure lysine dihydrochloride (m. p. 187–188°).

Summary

Two syntheses for lysine and preparation of several possible intermediates has been described.

RECEIVED MAY 5, 1950

---

[9] Snyder and Smith, THIS JOURNAL, **66**, 350 (1944).

[10] Albertson, *et al.*, *ibid.*, **70**, 1150 (1948).

[11] Allen, "Organic Syntheses," Coll. Vol. I, p. 157, John Wiley and Sons, Inc., New York, N. Y., 1941.

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, LABORATORIES OF THE MOUNT SINAI HOSPITAL]

Neo-fatty Acids[1]

BY HARRY SOBOTKA AND FREDERIC E. STYNLER

The occurrence of branched fatty acids in nature is confined to a few exceptional cases. For example, the fat of the tubercle bacillus contains a fatty acid carrying a methyl group side-chain about the middle of the chain; the normal fatty acids in wool fat or "degras" are accompanied by small amounts of representatives of three other series, namely, α-hydroxy acids and two kinds of branched fatty acids.[2] The members of one series terminate in an isopropyl group $(CH_3)_2CH$- and have been designated iso acids, the others terminate in a *s*-butyl group $(CH_3)(C_2H_5)$-CH- and have been named anteiso acids. Some iso acids[3a,b] and anteiso acids[4a,b] have been synthesized and also acids with a methyl group nearer the middle of the chain,[4a,c] finally acids with a tertiary or a quaternary carbon atom carrying longer side chains.[5a,b,c]

Modification of the terminal portion in long chain aliphatic compounds by side-chains or cyclic groups causes changes in their physico-chemical properties which may become significant for their biochemical behavior and for their technical applications. For reasons, detailed in another publication, which will treat of the surface and colloidal properties of these compounds, we wished to compare fatty acids with two and with three terminal methyl groups.

In the following we describe the synthesis and some of the properties of the neo isomers of the fatty acids with 16, 18, 20, 22 and 24 carbon atoms. In the course of this work we extended the chain of neohexyl chloride by means of ethylene oxide to neoöctyl alcohol.

Preliminary experiments have shown us that in the case of neohexyl chloride the reaction of its Grignard compound with an aldehyde proceeds more smoothly and with better yields than the condensation of the cadmium compound with an acyl chloride. Hence, we prepared the monoethyl ester-aldehydes corresponding to sebacic acid, dodecanedioic acid, and thapsic acid. Their condensation with neohexyl and neoöctyl magnesium chloride leads to products with 16 to 24 carbon atoms including a terminal *t*-butyl group. Because of spontaneous dehydration upon decomposition of the Grignard condensation product, mixtures were usually obtained of a 10- or 12- or 16-hydroxy acid with a pair of satellite mono-unsaturated acids. For their eventual conversion to the saturated acids, we followed in several features the procedures used by Velick and English[4b] for the synthesis of 14-methylpalmitic acid.

Table I summarizes the melting points of the new acids and the refractive indices and boiling points of their methyl esters (concerning the

---

[1] We wish to acknowledge support for this work by the Office of Naval Research (NR 057-101).

[2] Weitkamp, THIS JOURNAL, **67**, 447 (1945).

[3] (a) Fordyce and Johnson, *ibid.*, **55**, 3368 (1933); (b) Cason, *ibid.*, **64**, 1106 (1942).

[4] (a) Cason and Prout, *ibid.*, **66**, 46 (1942); Cason, Pippen, Taylor and Wynans, *J. Org. Chem.*, **15**, 135, 139, 148 (1950); (b) Velick and English, *J. Biol. Chem.*, **160**, 473 (1945); (c) Ställberg-Stenhagen, *Arkiv Kemi*, **A22**, no. 19 (1946); **A26**, no. 12 (1948).

[5] (a) Stanley, Jay and Adams, THIS JOURNAL, **51**, 1261 (1929); (b) Polgar and Robinson, *J. Chem. Soc.*, 615 (1943); (c) Cason, *J. Org. Chem.*, **13**, 227 (1948).

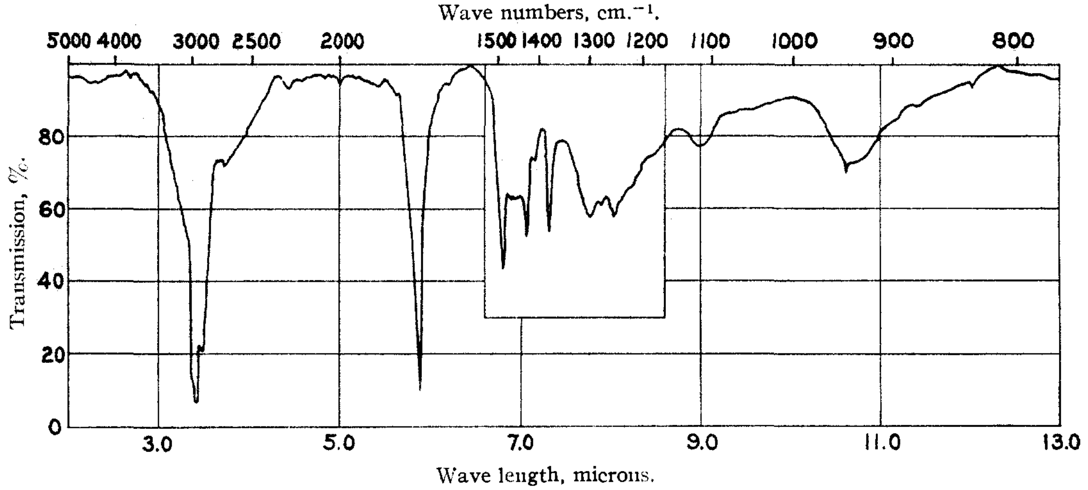


Fig. 1.—Infrared absorption spectrum of neostearic acid: the rectangular cutout contains that region of the spectrum which is significant for the terminal configuration.

difference in melting point between normal and branched acids *cf.* ref. 5c).

TABLE I

PHYSICAL CONSTANTS OF "NEO" ACIDS

Number of C atoms	M. p. of acid, °C. "Neo"	M. p. of acid, °C. Normal	Methyl ester B. p. °C.	Methyl ester B. p. mm.	n^{20}_{D}
16	43.8–44.2	62.8	144	1.6	1.4450
18	48.8–50.2	69.6	160	1.0	1.4485
20	57.2–57.7	75.4	178	0.9	1.4500
22	61.0–61.8	79.9	195	0.7	1.4528
24	63.8–64.5	84.1	209	0.8	1.4550

In order to confirm that the synthetic products were of the postulated structure, we submitted samples of the C_{16} and C_{18} members of the series to Mr. E. F. Binkerd for infrared examination.[6] Together with neopalmitic and neostearic acid, we obtained infrared spectrograms of samples of the corresponding normal and iso acids and of the related anteiso acids with 17 and 19 carbon atoms. According to Mr. Binkerd "the curves obtained for palmitic and stearic acids are identical with curves of the fatty acids in our file. A distinct difference is noted, however, in the spectrum of the iso acids. In both the isopalmitic and isostearic a doublet occurs in the 1360–1380 cm.$^{-1}$ range. This absorption is attributed directly to the isopropyl group $-CH(CH_3)_2$, further proving the structure. In the case of both the neopalmitic and the neostearic acid, a similar doublet is observed in the same region as that demonstrated by the iso acids. Here, however, it is to be noted that the relative intensities of the absorptions are different, the higher frequency being considerably weaker than the low frequency. This type of absorption is characteristic of the tertiary butyl group $-C(CH_3)_3$ and so coincides with the structure of the neo acids."

In the case of 14-methylpalmitic and 16-methylstearic acids "it is observed that no significant absorption wave length is manifested by the branched-chain acid. However, the intensity of the absorption at 7.25 μ [1380 cm.$^{-1}$], attributed to $-CH_3$, is stronger than is shown by the regular straight-chain acids. It would appear that the absorption of the two methyl groups is additive in this case, though an instrument having a higher resolving power in this range of the spectrum might show the presence of a doublet as in the case of the iso and neo acids."

Experimental

Microanalyses were carried out by the Elek Micro Analytical Laboratories, Los Angeles, Calif. Melting points were determined in a Hershberg apparatus using Anschuetz thermometers divided in 0.1° with completely immersed mercury column. All distillations were carried out under nitrogen. Infrared absorption spectra were obtained on 0.4 *N* solutions of the acids in carbon tetrachloride, using the same solvent in the compensation cell.

Preparation of Neopalmitic Acid.—Ethyl hydrogen sebacate[7] was treated with thionyl chloride, which had been freshly distilled over quinoline and over boiled linseed oil. The yield of 9-carbethoxypelargonyl chloride of b. p. 142° (0.5 mm.) and 156° (4 mm.), was 88%.[8] This chloride was hydrogenated according to Rosenmund[9] with palladium freshly precipitated on barium sulfate and poisoned with sulfur and quinoline. The 9-carbethoxy-nonylaldehyde, b. p. 145° (2.5 mm.), 134° (1 mm.) was obtained in 65% yield; n^{22}_{D} 1.4410.

Sixty-one grams (0.5 mole) of neohexyl chloride[10] was converted into the Grignard compound in ether solution. This was slowly added over three to four hours at −25° to a solution of 96 g. (0.45 mole) of ester-aldehyde in 500 ml. of ether. Since the gummy precipitate tended to stop the

---

[6] We are indebted to Dr. J. D. Porsche, Director of the Chemical Research and Development Department of Armour and Co., Chicago, and to Mr. Binkerd for their coöperation and for permission to publish the spectrograms and interpretations.

[7] "Org. Synth.," Coll. Vol. II, p. 276, New York, N. Y., 1943.

[8] *Cf.* the corresponding methyl ester of b. p. 171–172° (12 mm.), Cason, THIS JOURNAL, **64**, 1106 (1942).

[9] Rosenmund and Zetsche, *Ber.*, **56**, 1481 (1923); *Org. Synth.*, **21**, 84, 110 (1941).

[10] We are indebted to Dr. L. Schmerling of Universal Oil Products Company, Riverside, Ill., for a generous supply of this compound.

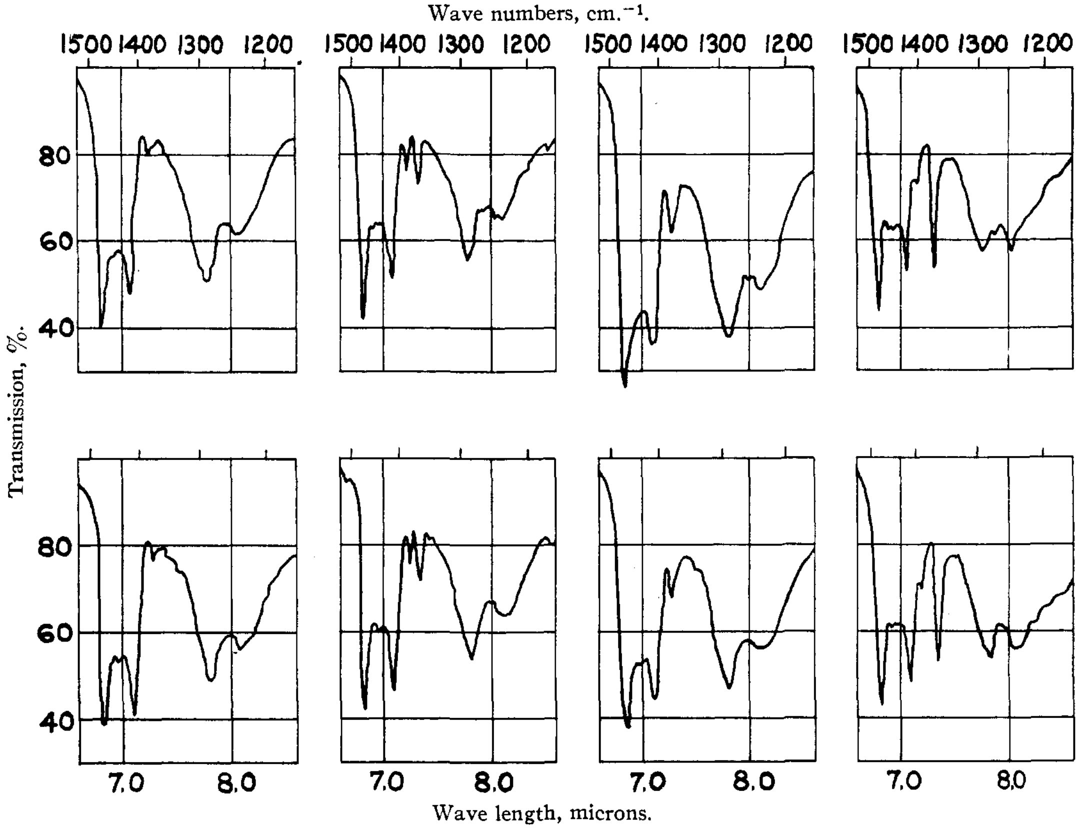


Fig. 2.—Infrared absorption spectra of branched fatty acids in the region significant for the terminal configuration: upper row, stearic acids; lower row, palmitic acids. From left to right: 1, normal acid; 2, iso acid; 3, anteiso acid C_{n+1}; 4, neo acid. All spectra with 0.4 *N* solutions in carbon tetrachloride.

stirrer, another 200 ml. of ether was added at the end of this period and the reaction permitted to proceed for eight more hours. After decomposition with saturated ammonium chloride solution, the reaction mixture was worked up in the usual manner, the ether extracts dried over anhydrous sodium sulfate. In order to purify the product, the resulting crude ethyl 10-hydroxy-13,13-dimethyltetradecanoate (yield 70%) was saponified and the acid reësterified, this time with methanol, yielding **methyl 10-hydroxy-13,13-dimethyltetradecanoate.** Neither the ethyl nor the methyl ester may be distilled. The methyl ester (7.5 g., 0.025 mole) of this hydroxy acid was treated with one-half of its weight of phosphorus tribromide at 0° for thirty min.[4b] After heating the mixture another thirty minutes on the steam-bath, it was decomposed with ice-water and the bromo-ester extracted with ether. After removal of the ether from the washed and dried ether extract, the substance was dehydrobrominated with 750 ml. of a 20% alcoholic potassium hydroxide solution, allowed to stand twelve hours at room temperature and refluxed for three hours. After removal of the greater part of the solvent, the residue was diluted with water, acidified with concentrated hydrochloric acid and the supernatant oily 13,13-dimethyltetradecenoic acid extracted with petroleum ether. The crude acid, dissolved in absolute methanol, was hydrogenated at 30 lb./sq. inch pressure with 3% of its weight of platinum oxide catalyst. The yield of the resulting saturated acid was 60% on the basis of the hydroxy acid. A parallel run with chlorination by phosphorus trichloride gave a substantially lower yield. The crude 13,13-dimethyltetradecanoic acid was esterified with methanol and the methyl 13,13-dimethyltetradecanoate distilled through a heated Vigreux column; b. p. 144° at 1.6 mm., n^{20}_{D} 1.4420. The ester was saponified with 25% potassium hydroxide in 80% ethanol.

Neopalmitic acid (**13,13-dimethyltetradecanoic acid**) was recrystallized from acetonitrile,[11] m. p. 43.8–44.2°.

Anal. Calcd. for $C_{16}H_{32}O_2$: C, 74.94; H, 12.58; neut. equiv., 256.42. Found: C, 75.00; H, 12.39; neut. equiv., 257.0.

Preparation of Neostearic Acid.—As starting materials for the synthesis of this acid one may have recourse to dodecanedioic acid and neohexyl chloride or to sebacic acid and neoöctyl chloride. We chose the latter alternative and prepared neoöctyl alcohol, 5,5-dimethylhexanol-1, from neohexyl chloride. All the following operations were carried out under nitrogen and with stirring. Three moles of neohexyl chloride (362 g.), dissolved in 2 liters of dry ether, was added to the equivalent amount (73 g.) of magnesium in 600 ml. of ether at room temperature. After twenty-four hours the formation of the Grignard compound was completed. One hundred thirty-two grams of condensed ethylene oxide was dropped into the Grignard solution at −10°. After refluxing at room temperature for one hour about one-third of the liquid was distilled off under continued stirring and the viscous residue was diluted with 1 liter of dry benzene. Refluxing was resumed for one additional hr. and after decomposition with 1 liter of ice-cold water, 300 ml. of 50% sulfuric acid was added to dissolve the precipitate. The extraction and fractionation by steam distillation followed the outline for the preparation of *n*-hexyl alcohol in "Organic Syntheses."[12] The crude neoöctyl alcohol (330 g., 2.5 moles) was distilled through a heated Vigreux column under ordinary pressure in a nitrogen atmosphere; 260 g. (two

---

[11] Obtained through the courtesy of Niacet Chemicals Division of U. S. Vanadium Corporation of Niagara Falls, N. Y.

[12] "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 299.

moles = 67% yield) of pure product was obtained of b. p. 181.5–182° (760 mm.). Its smell is quite different from that of other octyl alcohols and has a terpenoid quality, d^{20}_4 0.8270, $n^{20}\mathrm{D}$ 1.4260.

Anal. Calcd. for $C_8H_{18}O$: C, 73.38; H, 13.93; mol. refr. 40.45. Found: C, 73.62; H, 14.05; *MR* 40.34.

α-Neoöctyl 3-nitrophthalate was prepared[13] by heating 0.65 g. of 3-nitrophthalic anhydride with 0.33 g. of neoöctyl alcohol over a free flame. The reaction product, recrystallized from benzene, consisted of fine white needles of m. p. 156°.

Neoöctyl chloride was prepared from neoöctanol according to Clark and Streight[14] with thionyl chloride. To 260 g. (2 moles) of the alcohol, dissolved in 500 ml. of dry benzene, was added during one hour 475 g. (4 moles) of thionyl chloride in 500 ml. of dry benzene at 0°. Stirring was continued for three hours at 0° and the mixture was then heated under reflux for eight hours. The remaining thionyl chloride was decomposed with a few ml. of formic acid and, after removal of the more volatile products, neoöctyl chloride distilled at normal pressure at 166.5°; yield 252 g. (85%); sp. gr. d^{20}_4 0.8655, $n^{20}\mathrm{D}$ 1.4270.

Anal. Calcd. for $C_8H_{17}Cl$: C, 64.62; H, 11.53; Cl, 23.85; *MR*, 43.87. Found: C, 64.66; H, 11.86; Cl, 23.85; *MR*, 43.98.

Seventy-five grams (0.5 mole) of neoöctyl chloride was converted into the Grignard compound in 500 ml. of ether and slowly added to a solution of 96 g. (0.45 mole) of 9-carbethoxynonylaldehyde at −20°. The procedure was the same as in the case of the C_{16}-acid. The crude 10-hydroxy-15,15-dimethylhexadecanoic acid ester was obtained in 63% yield after all unreacted ester-aldehyde had been removed by a quick distillation through a heated column. After saponification and reësterification with methanol the methyl ester was treated with phosphorus tribromide as in the previous example and the bromo-acid was dehydrobrominated. The resulting 15,15-dimethylhexadecenoic acid (45 g.) was hydrogenated in methanol solution and methyl 15,15-dimethylhexadecanoate was distilled through a heated Vigreux column; b. p. 160° (1.0 mm.); $n^{20}\mathrm{D}$ 1.4485.

Neostearic acid (15,15-dimethylhexadecanoic acid) was obtained by saponification and purified by evaporative distillation and by recrystallization from acetonitrile; boiling range 145–153° at 0.05 mm.; m. p. 49.8–50.2°.

Anal. Calcd. for $C_{18}H_{36}O_2$: C, 75.99; H, 12.76; neut. equiv., 284.47. Found: C, 75.88; H, 12.73; neut. equiv., 285.7.

Preparation of Neoarachidic Acid.—The starting material for this synthesis, dodecanedioic acid, was prepared according to Chuit[15]; however, the Bouveault reduction of ethyl sebacate to decanediol-1,10 was replaced by the reduction of sebacic acid itself with lithium aluminum hydride.[16] Because of the slight solubility of sebacic acid in ether we proceeded as follows: Twenty-two grams of lithium aluminum hydride was dissolved in 1500 ml. of ether in a three-neck flask with stirrer, reflux condenser, and a Soxhlet extractor with condenser. The Soxhlet thimble was charged with 77 g. of sebacic acid. The flask was slightly heated until the first extract syphoned into the flask. The ensuing vigorous reaction kept the ether boiling with the reflux condenser coming into play; at the same time the evaporating ether maintained the function of the extractor. The extraction was completed by slight heating. From the beginning of the reaction, the diol complex precipitated as a white flocculent mass. After cooling below 0°, the lithium aluminum decanediolate was decomposed with 300 ml. of 10% aqueous sulfuric acid. The ether washings of the aqueous layer were combined with the ether layer, dried and freed of ether. The residue was dissolved in boiling dry benzene and yielded the crystalline decanediol of m. p. 71°; yield, 86%. It was converted with gaseous hydrogen bromide[17] into 1,10-dibromodecane (b. p. 150° at 2 mm.), which was transformed into the dinitrile of dodecanedioic acid. The nitrile was saponified with the calculated amount of potassium hydroxide in 50% ethanol. The yield of dodecanedioic acid calculated on decanediol was 72%; m. p. 126°; acid equiv. calcd. 115.15, found 116.8.

The diethyl ester of dodecanedioic acid was then prepared; it boils under 1.2 mm. at 160° and solidifies slightly below room temperature; $n^{20}\mathrm{D}$ 1.4414. A mixture of 100 g. of the acid and 60 g. of the diethyl ester was used for the preparation of the monoethyl ester in analogy to the preparation of ethyl hydrogen sebacate.[7] After distillation and fractionation 66 g. of ethyl hydrogen dodecanedioate was obtained, representing a yield of 59% calculated on the free acid used; 69 g. of the diethyl ester (115% of the amount used) was recovered in pure form. The **monoethyl ester** melts at 33° and boils at 172° (1.2 mm.); $n^{20}\mathrm{D}$ 1.4395.

Sixty-six grams of the monoethyl ester of dodecanedioic acid, chlorinated with thionyl chloride, yielded 64 g. (90% yield) of pure 11-carbethoxyundecanoyl chloride of b. p. 160° (1.0 mm.); m. p. 13.5°; $n^{20}\mathrm{D}$ 1.4475.

The chloride was reduced with palladium/barium sulfate catalyst[9] and yielded **11-carbethoxyundecanal** in 89% yield (50 g. from 64 g. of chloride); b. p. 160° (1.3 mm.); $n^{20}\mathrm{D}$ 1.4415.

One-fifth mole (50 g.) of this ester-aldehyde was condensed with the Grignard compound of one-fifth (30 g.) of neoöctyl chloride at −20°. The reaction product (57 g.) was saponified, the alcohol distilled off, and the potassium salts taken up in hot water. After acidification, the mixture of the 12-hydroxy-17,17-dimethyloctadecanoic acid and its unsaturated dehydration products were extracted with low-boiling petroleum ether, and esterified with methanol. They were treated with phosphorus tribromide at −5° to convert the ester of the hydroxy-acid into that of the bromo-acid; after decomposition with ice-water, the bromo ester with the accompanying unsaturated ester was extracted and treated with 20% potassium hydroxide in 95% ethanol. The free acids (23 g.) were isolated and hydrogenated in methanol solution with platinum oxide catalyst under 30 lb./sq. inch pressure. Without previous isolation, the saturated acid was esterified with methanol. The resulting **methyl 17,17-dimethyloctadecanoate** was distilled through a heated Vigreux column at 178° (0.9 mm.); $n^{20}\mathrm{D}$ 1.4500. Saponification with 25% potassium hydroxide in 80% ethanol yielded **neoarachidic acid** (17,17-dimethyloctadecanoic acid) of m. p. 57.2–57.7° after recrystallization from acetonitrile.

Anal. Calcd. for $C_{20}H_{40}O_2$: C, 76.86; H, 12.90; neut. equiv., 312.52. Found: C, 76.70; H, 12.76; neut. equiv., 311.2.

For the preparation of **neobehenic acid** and **neolignoceric acid** thapsic acid[18] served as starting material. One hundred and seven g. (0.375 mole) of this acid was esterified with ethanol in the presence of 84 g. (0.25 mole) of diethyl thapsate of m. p. 36.5°, following the procedure used for the monoesterification of sebacic and dodecanedioic acid. The **ethyl hydrogen thapsate** was separated from diethyl thapsate by fractional distillation, the diester distilling at 205° (1.5 mm.), the monoester at 217°; m. p. 48°. The yield was 112 g. corresponding to 95% yield on the thapsic acid employed; the diester was quantitatively recovered.

Chlorination with thionyl chloride afforded the **15-carbethoxypentadecanoyl chloride** of b. p. 215° (1.0 mm.) in 66% yield; it melts at 36°.

Hydrogenation according to Rosenmund gave the **15-carbethoxypentadecanal** in 95% yield; purified by distillation under 1 mm. at 202°, it melted at 35°.

This ester aldehyde was condensed in quarter-mole

---

(13) McKenzie, *J. Chem. Soc.*, **79**, 1135 (1901).

(14) Clark and Streight, *Trans. Roy. Soc. Can.*, Section III, **23**, 77 (1929).

(15) Chuit, *Helv. Chim. Acta*, **9**, 264 (1926); *cf.* Sobotka and Goldberg, *Biochem. J.*, **26**, 555 (1932).

(16) Nystrom and Brown, THIS JOURNAL, **69**, 2548 (1947).

(17) "Organic Syntheses," Coll. Vol. II, 338 (1943).

(18) Obtained through the courtesy of Firmenich et Cie., Geneva, Switzerland.

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 $\Delta_{16,16}$- 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.

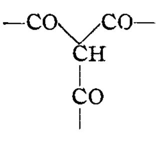
NEW YORK 29, N. Y. RECEIVED JANUARY 23, 1950

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

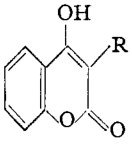
The Antibacterial Properties of Compounds Containing the Tricarbonylmethane Group. IV. Syntheses of 3-Alkylated or 3-Acylated 4-Hydroxycoumarins and of a Related Pyrone

BY TYUNOSIN UKITA, SHOSHICHI NOJIMA AND MAKOTO MATSUMOTO

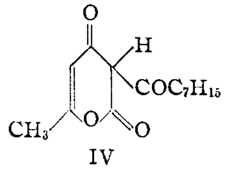
3-Acetyl-4-hydroxycoumarin, a compound containing the tricarbonylmethane group (I), has been found to possess remarkable activity against several bacteria.[1] In subsequent papers[2,3] interesting relations between structure and activity were reported for a number of 3-acyl- and 3-alkyl-4-hydroxycoumarins (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).