Summary

The synthesis of N-succinylglycine dimethyl ester has been described.

A Dieckmann cyclization of this compound gave rise to 2,5-diketo-1-pyrrolidineacetic acid methyl ester. The structure of the latter was confirmed by an independent synthesis using a method known to give rise to the 2,5-diketopyrrolidine ring.

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[Contribution from the Chemical Laboratory of Smith College]

High Molecular Weight Hydrocarbons. II. Five New Hydrocarbons Derived from Sebacic Acid

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The highly purified hydrocarbons prepared in the present undertaking[2] are 1,14-diphenyltetradecane, 1-phenyl-12-*n*-propylpentadecane, 4-phenyl-13-*n*-propylhexadecane, and the cyclohexyl analogs of the latter two.

Dimethyl sebacate was a convenient starting material serving all of these syntheses. Partial saponification under proper conditions gave the diacid and the acid-ester in the ratio required for the subsequent work. These acids, through their acid chlorides, were converted by treatment with di-β-phenylethylcadmium to 1,14-diphenyl-3,12-tetradecadione and to methyl 10-keto-12-phenyldodecanoate; the acid ester through its acid chloride, by treatment with diphenylcadmium, was converted to methyl 10-keto-10-phenyldecanoate.

The symmetrical hydrocarbon was obtained by Wolff–Kishner reduction of the diketone and the same method, applied to the 18-carbon keto-acid derived from the corresponding ester, above, gave rise to 12-phenyldodecanoic acid. These reductions were carried out at atmospheric pressure[3] in single operations which in the case of the keto-acid involved as much as 700 g. of starting material.

The branched phenyl alkanes were obtained from the methyl ester of the latter acid, and from the 9-keto-dodecanoic ester, by treatment with excess *n*-propylmagnesium bromide, dehydration of the tertiary mono- and di-alcohols, and hydrogenation of the resulting olefins (1-phenyl-12-*n*-propylpentadecene and 4-phenyl-13-*n*-propylhexadecadiene).

The selective hydrogenation of the ethylenic linkages in the presence of the aromatic nucleus required special study. The difficulties involved in effecting this type of preferential attack on a quantitative basis have been remarked by Whitmore, *et al.*,[4] who in a similar case used a nickel catalyst. Inasmuch as nickel is generally recognized as "the most satisfactory catalyst for the hydrogenation of the benzenoid nucleus"[5] it appeared to us that the selectivity of the reaction might be enhanced by the use of a catalyst more indifferent to this part of the molecule.[6] The results of a large number of trial hydrogenations with copper–chromium oxide and several with Adams catalyst indicated that the desired conversion could be carried out most effectively by high pressure hydrogenation over copper–chromium oxide at *ca.* 225°.

The cyclohexyl derivatives were obtained by high pressure hydrogenation with Raney nickel.

In planning these syntheses emphasis was placed upon the selection of reactions involving a minimum of difficultly separable by-products, and throughout the work special pains were taken to insure the purity of the products. None of the substances in these synthetic series except the simple derivatives of sebacic acid have appeared previously in the literature.

Experimental

Monomethyl Sebacate and Sebacic Acid.—In a typical batch preparation a cold solution of 841.5 g. of C.P. potassium hydroxide (87.6% potassium hydroxide, 13.1 moles) in 3 liters of absolute methanol was stirred into a solution of 3965 g. (17.22 moles) of pure[7] dimethyl sebacate (m. p. 26.5–27.5°) in 11 liters of the same solvent. While a voluminous precipitate of the potassium salts separated,

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[2] Preceding paper in this series: Sherk, Augur and Soffer, This Journal, **67**, 2239 (1945). This work is being carried out at Smith College in coöperation with the Technical and Research Division of the Texas Company.

[3] Soffer, Soffer and Sherk, This Journal, **67**, 1435 (1945); Huang-Minlon, *ibid.*, **68**, 2487 (1946).

[4] Whitmore, Crosby, Sloatman and Clarke, *ibid.*, **64**, 1801 (1942).

[5] Gilman, "Organic Chemistry," 2 ed., Vol. 1, 1943, p. 817. See also Adkins, "Reactions of Hydrogen, etc.," The University of Wisconsin Press, Madison, Wis., 1937, p. 57.

[6] Adkins, ref. 5, p. 48, has advised that "the use of Cu–Cr oxides is desirable if there is any possibility that nickel will induce the hydrogenation of a benzenoid ring in the compound," and that "quantitative preferential hydrogenation of the alkene linkages may be easily accomplished" in the presence of benzenoid nuclei (*ibid.*, pp. 121–122). While some later evidence (Folkers, This Journal, **58**, 1559 (1936); see also Durland and Adkins, *ibid.*, **59**, 135 (1937)) made it plain that the original claims for complete inactivity of this catalyst toward the benzenoid nucleus were not valid in cases of extreme treatment, there never has been any question of its marked relative inertness toward simple aromatic rings.

[7] Except where otherwise indicated all primary starting materials were the best samples obtained by fractionation of the Eastman "White Label" product through a Fenske column with an efficiency of approximately twenty plates. Only those fractions of the distillate which had a constant boiling point and a constant index of refraction ±0.0001), and in the case of solids a constant melting point, were accepted. In the case of dimethyl sebacate, 6.20 kg. of the commercial product gave 5.46 kg. of material satisfying these criteria.

the reaction mixture was refluxed until (*ca.* forty-five minutes) fresh samples were no longer alkaline to phenolphthalein. After removal of methanol at reduced pressure the residue was distributed between water and ether. The washed and dried ether extract yielded 1386 g. (6.02 moles) of crystalline diester which was recycled in another batch saponification.

The aqueous extract was washed with ether and treated with excess hydrochloric acid and ether. The ethereal solution was washed well with water and finally with saturated solution of sodium chloride. Removal of solvent left a solid mixture of acid–ester and diacid (melting range 41–91°). This product was fractionated[8] in 450-g. batches at high vacuum, through a 120-cm. perforated-disk column (five theoretical plates) specially designed to permit a minimum pressure gradient. The main component, 1621 g. (7.50 moles) was monomethyl sebacate; b. p. 148° at 0.025 mm., 157° at 1 mm., m. p. 42.5–43°.[9]

The yields, based on the amount of diester consumed, were 67% monoester and 429 g. of residual diacid (19%); total 86%. The yields on the basis of total amount of starting material used, *i. e.*, per cent. conversion, were 35% recovered diester, 44% monoester and 12% diacid; total 91%.

In another run the saponification was carried out completely in the homogeneous liquid phase by increasing the proportion of solvent. In this case 1643 g. of the diester (7.12 moles) and 348 g. (5.45 moles) of potassium hydroxide (87.6% potassium hydroxide) in 13 liters of methanol gave by the same treatment 627 g. (2.72 moles) of diester, 693 g. (3.20 moles) of the purified monoester and 221 g. (1.09 moles) of residual diacid. The yields, in the same order as before, were 73 and 25; total 98%, and the "conversions" were 38 diester, 45 monoester and 15 diacid; total 98%.

The combined residues (1.1 kg.) from several fractionations of the mixed acids were freed from last traces of monoester by raising the temperature throughout the column until pure sebacic acid began to come over. A little more than 1 kg. of pure sebacic acid was obtained from the final residual material by recrystallization from water to constant melting point (133.5–134°).

9-Carbomethoxynonanoyl chloride, b. p. 143° at 3.5 mm., m. p. 16.5–17°[10] (yield 96%), and sebacyl dichloride, b. p. 168° at 12 mm., and 128° at 1.3 mm., m. p. −2.5°[10] (yield 67%) were obtained as water white oils by the usual treatment of the acids with thionyl chloride and distillation at reduced pressure. A solution of 20 g. of 9-carbomethoxynonanoyl chloride[11] in 35–60° petroleum ether was saturated with dry ammonia. The snow-white precipitate of ammonium chloride and ester amide was distributed between ether and water, and the washed ether extract was evaporated. Recrystallization of the residue from 4:1 methanol–water gave 15.1 g. (83%) of 9-carbomethoxynonanamide, m. p. 74.5–76°.[12]

A solution of 12.5 g. (0.058 mole) of the foregoing ester-amide in 21 ml. (0.29 mole) of purified thionyl chloride was kept at 45° for six hours, and then refluxed for fifteen minutes. After evaporation at reduced pressure, the pale-yellow residue was taken up in ether and washed with sodium bicarbonate solution, dried and treated with Norite. Removal of solvent and distillation gave 10.8 g. (95%) of 9-carbomethoxynonanonitrile as a water-white oil, b. p. 131–132° at 1.6 mm., which crystallized readily, m. p. 3–4°.[10,13]

1,14-Diphenyl-3,12-tetradecadione.—A di-β-phenylethylcadmium reagent was prepared as described previously[2] from 692 g. (3.72 moles) of β-phenylethyl bromide,[7] 91.5 g. (3.76 gram-atoms) of magnesium, and 365 g. (1.99 moles) of powdered anhydrous cadmium chloride in an atmosphere of dry nitrogen. After treatment with a solution of 359 g. of sebacyl chloride in dry benzene, the reaction mixture was worked up, essentially according to the previous procedure,[2] for the neutral, non-saponifiable fraction. Distillation of the product at reduced pressure gave 33 g. of rejected material and 365.4 g. (64.5%) of colorless distillate, b. p. 259° at 1.4 mm., m. p. 67–68°. Recrystallization from ethanol or from petroleum·ether did not change the melting point.

Anal. Calcd. for $C_{26}H_{34}O_2$: C, 82.5; H, 9.1. Found: C, 82.1, 82.5; H, 9.0, 9.2.

1,14-Diphenyltetradecane.—The preparation of this hydrocarbon from the diketone above has been described previously.[3] The crude product was purified by the procedure used for 1-phenyleicosane.[2] In the final fractionation, the central 80% of the distillate exhibited a constant boiling point, 187° at 0.02 mm., and constant melting point, 39.5°, and a constant refractive index, $n^{49.5}\text{D}$ 1.5042 ± 0.0001.

Anal. Calcd. for $C_{22}H_{38}$: C, 89.1; H, 10.9. Found: C, 89.1, 89.2; H, 11.1, 10.7.

Methyl 10-Keto-12-phenyllaurate.—A di-β-phenylethylcadmium reagent was prepared[2] from 147.2 g. (6.06 gram-atoms) of magnesium, 185 g. (6.00 moles) of the bromide,[7] 595 g. (3.24 moles) of cadmium chloride and a total of 6.5 liters of anhydrous ether. After solvent replacement at reduced pressure the product in 1.5 liters of dry benzene was treated with a solution of 1134 g. (4.83 moles) of 9-carbomethoxynonanoyl chloride in 2 liters of the same solvent. The mixture gradually became more viscous during the slightly exothermic addition of the acid chloride, and finally became too thick and lumpy to allow complete mixing of the reactants in the ordinary way.[14] After stirring for three hours at room temperature the dark clay-like sediment was allowed to settle. Still working in an atmosphere of dry nitrogen, the colorless benzene solution was decanted and the sedimentary mass was immersed in benzene and ground to a fine mud to separate occluded acid chloride from the mixture of inorganic halides. All the components were then combined and the mixture was efficiently stirred at reflux temperature for three hours.

After treatment of the cooled reaction mixture with excess dilute hydrochloric acid and removal of all cadmium and magnesium salts with water, the benzene extract was washed with aqueous sodium bicarbonate until no water-insoluble material was obtained on acidification of successive washings. The combined alkaline washings gave, on acidification, 30 g. of monomethyl sebacate representing unreacted ester-acid chloride.

Removal of solvent at reduced pressure from the washed and dried benzene extract and rapid distillation of the residue through a Claisen flask at about 1 mm. pressure gave the following: Fraction I, 35.6 g. of low boiling material consisting of 1,4-diphenylbutane (m. p. 51.5–52.5°

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(8) In order to ensure a minimum of disproportionation (acid–ester to diacid and diester) by prolonged treatment at high temperature, the fractionation of large quantities of acid–ester were carried out in separate batches, at low pressure, in a low pressure-drop column, and unnecessarily high reflux ratios were avoided. Since some trace of equilibration must invariably take place, and since the diester is the most volatile component, it is probably impossible to effect a completely quantitative purification of the half-ester by fractionation alone. This fact, however, imposes no significant limitation on the synthetic method because the impurity is removed automatically in the subsequent synthetic operations.

(9) Noller and Adams, THIS JOURNAL, **48**, 1074 (1926); who obtained the compound by oxidation of methyl undecylenate, reported m. p. 40–41°. Morgan and Walters, *J. Chem. Soc.*, 903 (1936), who prepared the substance, b. p. 208° at 20 mm., from sebacic acid, from the di-ester, and from a mixture of both of these, did not report the melting point.

(10) The melting point has not been reported previously.

(11) The material used in this case was prepared from Eastman Kodak Co., White Label products without further purification.

(12) Biggs and Bishop, THIS JOURNAL. **63**. 944 (1941), reported the melting point as 77.4°.

(13) Previous workers (ref. 12) who prepared the substance by different methods reported only the boiling point: 178° at 16 mm.; 170° at 14 mm.

(14) This difficulty was not encountered in preliminary small-scale experiments which could be conveniently carried out at greater dilution and which gave better yields.

after recrystallization from 50:1 methanol-water) and the ether exchange[15] product (ethyl methyl sebacate); Fractions II-VII, 1150 g. (78.3%) of crude crystalline keto-ester; and Fraction VIII, 3 g. of a higher boiling component, (b. p. *ca.* 250° at 1 mm., m. p. 61-62°) which was not investigated further. Three central fractions (III, IV, and V) consisting of purer keto-ester, m. p. 43-45° had a combined weight of 1032 g. (70.3%).

The combined crude product (II-VII) was refractionated in three batches through the low pressure-drop column at high vacuum.[16] The accepted fractions of the pure keto-ester (836.9 g., 57%) appeared as a water-white distillate, b. p. 169° at 0.03 mm., crystallizing in long, well defined, needles, m. p. 45.5-46.5°. The melting point was not changed by recrystallization from 20-40° petroleum ether.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 75.0; H, 9.3. Found: C, 75.0, 74.6; H, 9.2, 9.3.

One interesting difficulty encountered in preliminary experiments is worthy of mention. In a run in which the reaction mixture was inadvertently contaminated with metallic mercury from the stirrer-seal some of the metal was found to have been converted to a mixture of mercurous bromide and chloride. Since these salts are both insoluble in water and appreciably soluble in the organic media and have a volatility approximating that of the high molecular compounds involved, their quantitative elimination from the keto-ester was an additional complication in these experiments. Most of the mercurous halides were removed by filtration of a methanol solution of the neutral fraction, and the traces that remained were finally eliminated by short heating with metallic aluminum followed by removal of the free mercury and the aluminum halides.

10-Keto-12-phenyldodecanoic Acid.—The foregoing keto-ester 826 g. (2.72 moles) was saponified in aqueous ethanol. After removal of most of the alcohols and dilution with water, the solution was adjusted to *p*H 11 with hydrochloric acid in order to reduce the tendency toward emulsification. The alkaline solution was then washed with ether and the product isolated by acidification and extraction with ether. Successive recrystallizations from contrasting solvents, *i. e.*, 3:1 methanol-water and 60-68° petroleum ether, to constant melting point gave 720 g. of pure keto-acid (2.48 moles, 91.5%), m. p. 71.3-71.5°.

Anal. Calcd. for $C_{18}H_{26}O_3$: neut. equiv., 290. Found: neut. equiv., 289.

12-Phenyldodecanoic Acid.—Seven hundred grams (2.41 moles) of pure 10-keto-12-phenyldodecanoic acid, dissolved in a solution made up of 457 g. of sodium (19.9 gram-atoms) and 482 ml. (9.64 moles) of hydrazine hydrate in 6.3 liters of diethylene glycol,[3] was refluxed (liquid temperature 182°) for eighty-three hours. The mixture, which congealed to a soapy mass on cooling, was dissolved in water and filtered to remove siliceous material. After extraction of a sample indicated the absence of any neutral fraction, the solution was acidified with hydrochloric acid and extracted with ether. The extracts were washed with water until the washings gave a negative test for hydrazine with acidified permanganate, and was dried. The crude crystalline product, obtained in quantitative yield on removal of solvent, was recrystallized to constant melting point from both methanol-water (*ca.* 6:1, containing a small amount of acetone) and a nonpolar solvent mixture (7:1 isopentane-benzene). The final colorless product, 520 g. (78%), separated from the hydrocarbon solvent in perfect rhombic blades, m. p. 60.5-61.5°. A mixture of this product with the keto acid melted at 54-59°.

Anal. Calcd. for $C_{18}H_{28}O_2$: neut. equiv., 276. Found: neut. equiv., 276.

In preliminary experiments the same product was obtained less satisfactorily by the Clemmensen method. In one case 2.00 g. of the keto acid was refluxed with amalgamated zinc and concentrated hydrochloric acid for six days. The course of the reaction was followed by periodic determinations of the melting point of the crude organic components. During these interruptions the spent inorganic reactants were separated and replaced with fresh material. Recrystallization from aqueous methanol gave 1.51 g. (80%) of crude reduced acid, m. p. 58-59°, and a small amount of a less soluble amorphous material which was assumed to be the bimolecular reduction product. Further recrystallization from both absolute methanol and 20-40° petroleum ether gave 0.48 g. (25%) of the constant melting product.

Methyl 12-Phenyldodecanoate.—A solution of 510 g. (1.85 moles) of the foregoing acid and 120 ml. of concentrated sulfuric acid in 3000 ml. of absolute methanol was refluxed for six hours and worked up for the neutral fraction in the usual way. No unchanged starting material was recovered by acidification of the alkaline washings. Fractionation at high vacuum gave a small fore-run (3 g.) and fifteen fractions (521.5 g.; 97%), b. p. 159° at 0.03 mm., which had the same index of refraction, $n^{20}D$ 1.4871 ±0.0001, and melted between 19.4 and 19.7°. Twelve central fractions (506.3 g., 94%) melted sharply at 19.6-19.7°. The substance is a water-white oil which crystallizes readily in transparent, well-defined rectangular prisms.

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 78.6; H, 10.4. Found: C, 78.2, 78.3; H, 10.1, 10.2.

1-Phenyl-12-*n*-propylpentadecene.—A Grignard solution prepared from 201 g. (8.27 gram-atoms) of magnesium, 1005 g. (8.17 moles) of *n*-propyl bromide,[7] and 6 liters of ether was treated with 509 g. (1.75 moles) of the foregoing ester. After decomposition with excess snow and ammonium chloride, and working up the product in alkaline and neutral media, **1-phenyl-12-*n*-propyl-12-pentadecanol** was obtained as a viscous oil in quantitative yield. The product formed a hard transparent glass at −80° and did not crystallize from common solvents.

A mixture of 571 g. of the crude tertiary alcohol and 1000 g. of 90% formic acid was refluxed for sixteen hours and worked up for the olefin in the usual way. Distillation over sodium at reduced pressure in an atmosphere of nitrogen gave 542 g. (97%) of the olefin,[17] b. p. 182-183° at 0.9 mm., $n^{20}D$ 1.4906, as a water-white mobile oil which gave instant tests for ethylenic unsaturation.

1-Phenyl-12-*n*-propylpentadecane.—The results of trial experiments which established the optimum conditions for the selective hydrogenation of 1-phenyl-12-*n*-propylpentadecene are summarized in Table I. In each case 10% by weight of copper chromium oxide catalyst was used. No solvent was employed and the reaction products were examined without further treatment after removal of catalyst.

TABLE I

No.	Starting material	Average p. s. i.	Time, hr.	Temp., °C.	$n^{20}D$	Br_2 test %
1	33 g. olefin	1350	4.5	125	1.4895	+85
2	Product from 1	1450	4.0	175	1.4827	+45
3	33 g. olefin	2200	2.3	200	1.4848	+ Very high
4	Product from 3	2400	3.3	205	1.4813	+ low
5	Product from 4	2600	2.0	225	1.4805	−
6	Product from 5	2600	2.0	230	1.4803	−
7	33 g. olefin	1400	6.0	200-245	1.4803	Trace, <0.1

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[15] Products arising from the acid chloride-ether exchange were invariably obtained in limited amounts from these reactions (see also Cason and Prout, THIS JOURNAL, **66**, 46 (1944)). Apparently, some ether is retained in a relatively stable complex with the organocadmium derivative under the conditions[3] used in the solvent replacement. See also Cason, *Chem. Rev.*, **40**, 22 (1947).

[16] These conditions (see ref. 8) served to minimize the possibility of ester-exchange reaction with any ether-exchange product not completely removed in the previous distillation.

[17] The hydrocarbon may be a mixture of several theoretical dehydration products of the foregoing carbinol.

In runs no. 2, 4, 5 and 6, the starting material was partially hydrogenated products from the previous runs as indicated. In run 7 the temperature was held at 200° for five and one-half hours and allowed to rise to 245° during the final thirty minutes. The last column indicates the per cent. olefin in the product as estimated from bromine titrations of the pure olefin and of the hydrogenated products. For comparison, the index of refraction is $n^{20}\mathrm{D}$ 1.4906 for the olefin and $n^{22}\mathrm{D}$ 1.4613 for the perhydro analog (*vide infra*).

In preliminary experiments with Adams catalyst, hydrogen uptake proceeded very slowly both in ethanol and in the absence of a solvent. The reaction proceeded at a satisfactory rate in a solvent mixture of ethyl acetate, absolute ethanol and glacial acetic acid (2:2:1), in which the olefin was completely soluble, but a study of refractive indices showed that under these conditions there was appreciable reduction of the benzene ring. In one such experiment the product ($n^{20}\mathrm{D}$ 1.4800), which still contained olefinic unsaturation, on the basis of bromine tests, was treated with copper chromite under conditions identical with those employed in run 5 (Table I). The new product gave negative tests for ethylenic unsaturation, but had an obviously low index of refraction ($n^{20}\mathrm{D}$ 1.4751), indicating that considerable reduction to the cyclohexyl derivative had taken place in the presence of the platinum catalyst.

On the basis of these trial experiments, 170 g. of the pure olefin was shaken for five and seven-tenths hours at 200–205° with 10% of copper–chromium oxide and an average pressure of 2000 p. s. i. of hydrogen. The charge in the bomb which appeared, by index of refraction ($n^{20}\mathrm{D}$ 1.4813) and bromine tests, to contain a small amount of unchanged olefin was then shaken for two hours more with 2600 p. s. i. of hydrogen at 225–228°. The product was a water-white oil, $n^{20}\mathrm{D}$ 1.4804, which gave negative tests for unsaturation. The same product was obtained in a similar run on a mixture of 149 g. of olefin and 20 g. of under-hydrogenated hydrocarbon from the earlier experiments with copper chromite. For final purification the combined material (315 g.) was carefully fractionated through a Fenske column of approximately twenty plates. Sixteen accepted fractions comprising 75% of the total distillate had a constant boiling point, 153.5° at 0.1 mm., and a constant index of refraction, $n^{24}\mathrm{D}$ 1.4781 ± 0.0001.[18]

Anal. Calcd. for $C_{24}H_{42}$: C, 87.2; H, 12.8. Found: C, 86.9, 86.7; H, 13.1, 12.8.

1-Cyclohexyl-12-*n*-propylpentadecane.—Accumulated hydrocarbon (180 g.) consisting of rejected material from the purification of the foregoing hydrocarbons, and over-hydrogenated products from preliminary experiments, was shaken for twenty hours at 225° with 20 g. of Raney nickel and 1500–2500 p.s.i. of hydrogen. Almost the entire theoretical quantity of hydrogen was taken up during the first six hours, and no perceptible amount was absorbed during the last two hours. The water-white oil was distilled over sodium from a Claisen flask at reduced pressure and finally fractionated as in the case of the previous hydrocarbon. Thirteen accepted fractions, b. p. 158° at 0.07 mm., comprising 89% of total distillate, had exactly the same indices of refraction, $n^{22}\mathrm{D}$ 1.4613.

Anal. Calcd. for $C_{24}H_{48}$: C, 85.6; H, 14.4. Found: C, 85.4, 85.5; H, 14.1, 14.2.

Methyl 10-Keto-10-phenyldecanoate.—The procedure was similar to that described for the previous keto-ester, using the following quantities of starting materials: 1180 g. (7.5 moles) of bromobenzene,[7] 185 g. (7.6 gram-atoms) of magnesium, 6 liters of ether, 742 g. (4.05 moles) of cadmium chloride, 11 liters of benzene and 1416 g. (6.04 moles) of pure 9-carbomethoxynonanoyl chloride. As in the previous case mechanical difficulties were encountered in the large-scale reaction at increased concentration.[14] By a rapid distillation at reduced pressure the poorly crystalline neutral fraction was roughly divided into three main components as follows: 84 g. of crystalline material consisting principally of biphenyl (identified by m. p. 68.5–69° and by m. m. p.); 42 g. of an intermediate liquid fraction[16]; and 1056 g. (63%) of crude crystalline keto-ester. The central fraction (772 g., 46%) of the main component melted at 35.5–37°.

The crude product was fractionated at high vacuum, in batches, through the low pressure-drop column, and all fractions melting above 37.5° were refractionated. The accepted fractions of water-white product (666 g., 40%), b. p. 164° at 0.06 mm., crystallized in long, well-defined needles, m. p. 38.5–39.5°. The melting point was not changed by recrystallization from petroleum ether.

In a preliminary experiment a small sample of relatively pure keto-ester[11] (m. p. 36–38°) was saponified for purposes of identification. One recrystallization from aqueous acetone gave **10-keto-10-phenyldecanoic acid** in thin, iridescent rhombic plates, m. p. 84.5–85°.[19]

4-Phenyl-13-*n*-propylhexadecadiene.—According to the previous procedure a reaction between *n*-propylmagnesium bromide from 10.85 moles of starting materials[7] and 635 g. (2.30 moles) of the foregoing keto-ester gave **4,13-dihydroxy-4-phenyl-13-*n*-propylhexadecane** in quantitative yield. The ditertiary alcohol was an extremely viscous liquid which formed a brittle glass at −40° and did not decolorize bromine in carbon tetrachloride.

The crude glycol (830 g.) was refluxed for eleven hours with 1000 g. of 90% formic acid, and the dehydration product was isolated in the usual way. Distillation over sodium at reduced pressure in an atmosphere of nitrogen removed traces of oxygen-containing material, and appeared to involve some additional loss with the formation of high molecular weight material.[20] The diolefin[17] (587 g., 76%) was a water-white mobile oil, b. p. 194° at 0.5 mm., $n^{21}\mathrm{D}$ 1.5040, which gave instant tests for unsaturation and was slowly resinified by concentrated sulfuric acid.

4-Phenyl-13-*n*-propylhexadecane.—Satisfactory conditions for complete reduction of the ethylenic linkages in 4-phenyl-13-*n*-propylhexadecadiene were determined in preliminary hydrogenations, as in the previous case. The results of these experiments, each involving 34 g. (0.1 mole) of the pure olefin, 3.4 g. of copper–chromium oxide catalyst, and a three-hour reaction period with about 1800 p. s. i. of hydrogen, are shown in Table II

TABLE II

Temp., °C.	125	150	175	205	225	[a]
$n^{21}\mathrm{D}$	1.4883	1.4854	1.4843	1.4817	1.4817	1.4817
Br_2 test	+	+	+	−	−	−

[a] In this run the temperature was kept at 175° except for accidental heating up to 300° for about ten minutes.

These results showed that the desired conversion was brought about (compare $n^{21}\mathrm{D}$ 1.5040 for the diolefin, and $n^{21}\mathrm{D}$ 1.4650 for the perhydro derivative) in the reactions at 205–225°. Three more hydrogenations involving a total of 361 g. of hydrocarbon and essentially these conditions gave the same final products; $n^{21}\mathrm{D}$ 1.4816, 1.4816 and 1.4817. The combined products were dissolved in anhydrous petroleum ether and washed through a 4-ft. tube of activated silica gel.[2]

Initial fractionations of the solvent-free material through a five-plate column failed to give a satisfactory separation of material satisfying the previous[7] criteria of purity. Subsequent fractionation of 310 g. of combined hydrocarbon through a twenty-plate Fenske column removed a small amount of a difficultly separable, highly refractive impurity, and gave 240 g. (16 fractions, 88% of the total distillate) with indices of refraction ranging from $n^{20}\mathrm{D}$ 1.4810 to 1.4817. Careful refractionation of this material

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(18) All of the branched hydrocarbons formed hard colorless glasses at Dry Ice temperature.

(19) This substance has been prepared before by a different method; m. p. 78–79° [Anger, *Ann. chim. phys.*, [6] **22**, 364 (1891)], and m. p. 85–86° [Borsche and Wollemann, *Ber.*, **44**, 3186 (1911)].

(20) This activity is probably due to the conjugation between Δ^4 and the benzene ring: *cf*. Gilman, ref. 5, p. 668.

gave 168 g. (78% of the total distillate) of product with indices of refraction of $n^{20}D$ 1.4813 ± 0.0002. Ten central fractions, 114 g., comprising 53% of the total distillate had a constant boiling point, 147.5° at 0.08 mm., and a constant index of refraction, $n^{20}D$ 1.4813 ± 0.0001.

Anal. Calcd. for $C_{25}H_{44}$; C, 87.1; H, 12.9. Found: C, 87.1, 87.0, H, 12.6, 12.8.

4-Cyclohexyl-13-*n*-propylhexadecane.—Approximately 213 g. of combined rejected fractions of the foregoing hydrocarbon and material from preliminary experiments was treated with hydrogen and Raney nickel as described before, and 207 g. of the oily product was fractionated through the 20-plate column. Twenty-six fractions (202 g. total), including several obtained when the still pot and column were finally heated to dryness, were collected without any sign of decomposition. Thirteen central fractions (131 g.) comprising 65% of the total distillate had the same boiling point, 148° at 0.02 mm., and identical refractive indices, $n^{20}D$ 1.4654.

Anal. Calcd. for $C_{25}H_{50}$: C, 85.6; H, 14.4. Found: C, 85.8, 85.8; H, 13.8, 14.3

Summary

Five new high molecular weight hydrocarbons, *i.e.*, 1,14-diphenyltetradecane, 1-phenyl-12-*n*-propylpentadecane, 4-phenyl-13-*n*-propylhexadecane, and the cyclohexyl analogs of the latter two, have been prepared in a high state of purity.

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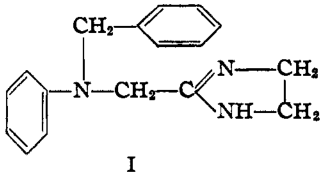
[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

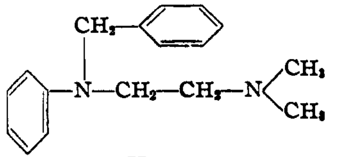
Aryloxyacetamidines and 2-(Aryloxymethyl)-imidazolines[1]

BY CARL DJERASSI AND CAESAR R. SCHOLZ

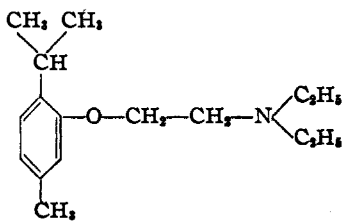
Recent reports have indicated that 2-(N-benzyl-N-phenylaminomethyl)-imidazoline (I), first prepared by Miescher, Urech and Klarer,[2] has strong histaminolytic properties and that this compound, known under the trade name Antistin, has found clinical application[3] against various allergic symptoms. Antistin differs from Antergan (II), a well-known antihistaminic[4] in the nature of the side chain, the 2-methylimidazoline group replacing the dimethylaminoethyl moiety. Since this change seemed to have enhanced the desirable antihistaminic activity, we have extended this observation to other series.



I



II



III

In this paper, we are reporting the results which we obtained in varying the side chain of ring-alkylated aryloxyethyldialkylamines, of which the histaminolytic F 929 (III)[5] is the best known example. Since imidazolines can be considered to be cyclized amidines, we have included aryloxyacetamidines in our investigation, in addition to 2-(aryloxymethyl)-imidazolines.

Of the many amidine syntheses reported in the literature,[6] that of Pinner[7] was most suited to our purpose. Ring-alkylated aryloxyacetonitriles, required as starting materials in our synthesis, have been prepared previously by dehydration of the corresponding amide[8] or aldoxime.[9] The patent literature[10,11,12] contains reports of the alkylation of phenols with chloroacetonitrile, but no details are given. In this work, it was found that the reaction could be carried out in good yields when a modification of the conventional Claisen O-alkylation of phenols[13] was employed.

Conversion of the nitriles into the imidic ester hydrochlorides (Table I) and thence to the amidines (Table II) was carried out by known methods.[6,7] With the exception of thymyloxyacetamidine and its N-dibutyl derivative,[14] all amidines reported in Table II are new compounds as far as we can determine.

The 2-(aryloxymethyl)-imidazolines (VI) (Table III) were synthesized by three different methods.

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[1] Presented on the program of the Division of Medicinal Chemistry at the Chicago meeting of the American Chemical Society, September 9–13, 1946.

[2] *Cf.* Meier and Bucher, *Schweiz. med. Wochschr.*, **76**, 294 (1946).

[3] Bourquin, *ibid.*, **76**, 296 (1946); Schindler, *ibid.*, **76**, 300 (1946); Brack, *ibid.*, **76**, 316 (1946).

[4] Halpern, *Arch. Internat. Pharmacodynamie*, **68**, 339 (1942).

[5] Staub, *Ann. Inst. Pasteur*, **63**, 400, 485 (1939).

[6] Shriner and Neumann, *Chem. Rev.*, **35**, 351 (1944).

[7] Pinner, "Die Imidoäther und ihre Derivate," Oppenheim, Berlin, 1892.

[8] *Cf.* (a) Powell and Adams, THIS JOURNAL, **42**, 646 (1920); (b) Higginbotham and Stephen, *J. Chem. Soc.*, 1534 (1920).

[9] Stoermer, *Ber.*, **30**, 1700 (1897).

[10] U. S. Patent 2,149,457; *C. A.*, **33**, 4379 (1939).

[11] U. S. Patent 2,149,473; *C. A.*, **33**, 4380 (1939).

[12] Swiss Patents 204,752–204,766; *C. A.*, **35**, 2280 (1941).

[13] *Cf.* Hurd and Perletz, THIS JOURNAL, **68**, 38 (1946).

[14] German Patent 684,945, *C. A.*, **34**, 2536 (1940).