[CONTRIBUTION FROM THE CHEMICAL SECTION, CULION LEPER COLONY, PHILIPPINE HEALTH SERVICE][1]

SYNTHESIS OF COMPOUNDS SIMILAR TO CHAULMOOGRIC ACID. II. *dl*-CHAULMOOGRIC ACID

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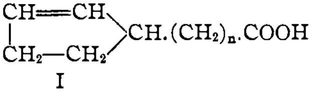
In a recent paper[2] we have mentioned the desirability, in connection with the study of the treatment of leprosy, of the preparation of compounds similar to chaulmoogric acid, especially those of somewhat lower molecular weights. The compounds described in that paper have the Δ^2-cyclopentenyl group in the alpha position.

In order to make an homologous series with Structure I strictly analogous to that of chaulmoogric acid, we have endeavored to find a general method for introducing the Δ^2-cyclopentenyl group in the omega position. The Wurtz synthesis was discarded because preliminary trials gave discouraging results and especially because of the difficulty involved in obtaining the various required omega-halogen substitution products of the fatty acids. Other applicable syntheses lead in general to dicarboxylic acids, keto acids, hydroxy acids[3] or similar derivatives. Of the sethe keto derivatives appear to offer the most favorable prospects for transformation into the desired series, thanks to Wolff's method for reducing the ketone group.

Methyl ketones have been prepared from aceto-acetic ester by two methods, alkylation and acylation, each followed by hydrolysis. Since these two methods, in effect, introduce radicals on opposite sides of the ketone group, it occurred to us that a combination of the two might lead to a series of keto derivatives from which the desired series of acids could be obtained.

An appropriate alkyl halide is Δ^2-chlorocyclopentene. The acyl chlorides required for the desired series (I) are derivatives of the normal dicarboxylic acids in which one carboxyl group has been converted into the acid chloride group and the other carboxyl has been protected, as, for example, by ester formation (II).



$$\left.\begin{array}{l}\mathrm{CH{=\!=}CH}\\ \mathrm{CH_2{-}CH_2}\end{array}\right\rangle\mathrm{CH.(CH_2)_n.COOH}$$

I

$\mathrm{Cl.CO.(CH_2)_{n-2}.COOR}$

II

In the present instance, the preparation of *dl*-chaulmoogric acid, the required dicarboxylic acid was not immediately available, and our starting

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[1] Published with the permission of the Director of Health upon recommendation of the Philippine Leprosy Research Board.

[2] Perkins and Cruz, THIS JOURNAL, **49**, 517 (1927).

[3] Noller and Adams [*ibid.*, **48**, 2445 (1926)] have recently reported progress on a method of synthesis through the hydroxy acids.

material was undecylenic acid, $CH_2{=}CH.(CH_2)_8.COOH$, obtained from the destructive distillation of castor oil. This acid reacts with hydrobromic acid giving, under certain conditions, a product melting at 51° which has been definitely shown[4] to be ω-bromo-undecylic acid, $Br.(CH_2)_{10}COOH$. In working with undecylenic acid which had been purified only as much as seemed practical from a preparative point of view we encountered a most interesting situation, evidently complicated by catalysts, when we added hydrobromic acid. We were unable to undertake an investigation of the catalysts or of the side reactions involved, but established empirically a method (see Experimental Part) for the practical preparation of the omega bromide.

From the omega bromide the previous investigators[4] obtained an impure, semi-solid cyanide. By a modified process we obtained good yields of ω-cyano-undecylic acid, $CN.(CH_2)_{10}.COOH$, as colorless crystals; m. p., 57°.

The cyano acid was converted into the cyano acid chloride (III) and condensed with the sodium salt of aceto-acetic ester, giving presumably the diketo ester (IV). By treatment with sodium and then with Δ^2-chlorocyclopentene, the Δ^2-cyclopentenyl group was introduced (V).

So far as we know, no β,β-diketo ester has been alkylated previously to the present work. James[5] made an unsuccessful attempt to alkylate diaceto-acetic ester in alcohol solution. He was successful in using the reverse order, acylating after alkylating. We tried this order, but obtained a product apparently acylated almost exclusively on the enol oxygen atom, and giving mere traces of the desired ketone on hydrolysis. We also tried splitting off the acetyl group from the diketo ester (IV) before alkylation, obtaining results somewhat inferior to those from the simpler process of alkylating the diketo ester. Since James' difficulty was apparently due to the use of alcohol as a solvent, we used benzene, in which we obtained fair yields.

Malonic ester syntheses corresponding to the three methods mentioned above were tried. Acylation and alkylation occurred smoothly, but hydrolysis gave acids rather than the desired ketone.

As might be expected, the crude, alkylated diketo ester (V) gave on hydrolysis a mixture of products. The desired ketone, *dl*-λ-ketochaulmoogronitrile (VI), appeared to be a low-melting substance not readily separable from the mixture, but on further hydrolysis of the whole a yield of *dl*-λ-ketochaulmoogric acid (VII) was obtained, accounting for about one third of the cyano-undecylic acid used. Another third of the cyano acid was recovered, partly in hydrolyzed form, and the remaining third was lost in the process.

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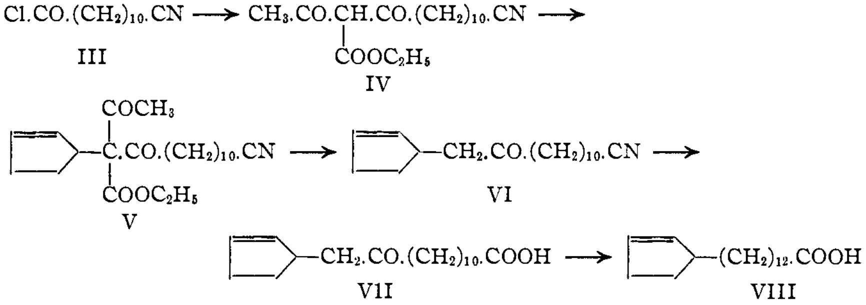
[4] Walker and Lumsden, *J. Chem. Soc.*, **79**, 1191 (1901).

[5] James, *Ann.*, **226**, 211 (1884).

The ketochaulmoogric acid was reduced to *dl*-chaulmoogric acid (VIII) by heating under pressure with anhydrous hydrazine and sodium ethylate.[6]



The method of preparation leaves perhaps some room for doubt as to whether the acids in hand have actually the structure of *dl*-ketochaulmoogric and *dl*-chaulmoogric, in that the position of the double bond in chlorocyclopentene has never been absolutely established. Comparisons of the synthetic chaulmoogric acid with the natural dextrorotatory substance, however, reveal a close similarity. The melting points of the two and of their mixtures were found to be practically identical. We conclude not only that the synthetic product is *dl*-chaulmoogric acid, but also that it is in that class of mixtures known as pseudo-racemic mixed crystals. The remotely possible alternative that spontaneous resolution of the synthetic product had occurred was eliminated by a polariscopic test, which showed the substance to be optically inactive. Further evidence of the structure of the synthetic acid was obtained by oxidizing it and identifying the resulting product with the characteristic γ-keto-*n*-pentadecane-α,α'-dicarboxylic acid obtained by the oxidation of natural chaulmoogric acid. These results confirm the Δ^2 position proposed by Eykman[7] for the double bond in chlorocyclopentene and its derivatives.

It is not expected that the synthetic chaulmoogric acid will have any therapeutic advantages over the natural product; certainly it cannot compete economically. We are applying practically the same method of synthesis, however, to the preparation of some lower homologs, not available from natural sources, which were the main objectives of the present preliminary investigation. It is hoped that not only these homologs, but also the intermediate keto acids and products obtainable from them will be valuable in the study of the treatment of leprosy.

Experimental Part

ω-Bromo-undecylic Acid.—Undecylenic acid was prepared[8] from castor oil by

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[6] This simplification of Wolff's procedure is similar to that employed by Stoermer and Foerster [*Ber.*, **52,** 1255 (1919)], but our mixture contained practically no water.

[7] Eykman, *Chem. Weekblad,* **6,** 703 (1909).

[8] Krafft, *Ber.*, **10,** 2034 (1877).

destructive distillation in a vacuum. When 1 liter of the oil in a 3-liter, long-necked flask, at about 50 mm., was heated with a powerful burner, the distillation required only 20–30 minutes, the still-head temperature rose to about 400°, and 580 cc. of distillate was collected before the residue changed to a foamy mass. The distillate yielded, on fractionation, about 250 cc. of heptaldehyde and 120 cc. of undecylenic acid. Slower distillation of the oil resulted in lower yields of both products.

The undecylenic acid melted at 20–21°. This product did not give good yields of ω-bromo-undecylic acid upon treatment with hydrobromic acid in toluene solution,[4] probably because it was not sufficiently pure. Further fractionation did not noticeably raise the melting point; repeated freezing and draining involved considerable loss of material, and crystallization of the barium salt required excessive volumes of solvent for the quantities required. By the following methods, however, yields of ω-bromo-undecylic acid somewhat greater than the weight of undecylenic acid used were readily obtained.

METHOD 1.—A fraction of undecylenic acid was collected twice within fairly narrow limits (for example, 175–182°, at 20 mm.). Two hundred cc. of such a fraction was mixed with 100 cc. of 90% (aqueous) acetic acid and 400 cc. of petroleum ether. Through this solution, cooled to —10°, hydrobromic acid gas was bubbled. When crystals appeared, the solution was allowed to warm slowly to room temperature, the current of gas being continued until absorption ceased. The solution was washed with water and cooled to 10°. Nearly pure β-bromo-undecylic acid was deposited, in colorless leaflets, and a further quantity was obtained by concentration of the mother liquor.

METHOD 2.—Another procedure consisted in bubbling hydrobromic acid gas through undecylenic acid dissolved in 8 volumes of cold, dry petroleum ether. This method required undecylenic acid produced by the slow distillation (1 or 2 hours) of castor oil, and was less desirable than Method 1 because, although the yields based on undecylenic acid were even greater, the yields from the original castor oil were considerably less than those obtained by Method 1. Repeated fractionation of the undecylenic acid did not noticeably affect the yield by this method. Thus, some samples of undecylenic acid (rapidly distilled originally and fractionated twice or thrice) gave good yields by Method 1 and practically no yield by Method 2; other samples (slowly distilled and fractionated only once) gave no yield by Method 1 but good yields by Method 2; other samples (slowly distilled and fractionated twice or thrice) gave good yields by both methods.

The above-mentioned *leaflets* of ω-bromo-undecylic acid (m. p., about 50.5°) gave needles on recrystallization from petroleum ether; m. p., 51°. The material in the mother liquors was found to be resolvable, by repeated concentration, cooling, filtration and recrystallization, into pure ω-bromo-undecylic acid and a portion, obviously impure, very soluble in petroleum ether, and melting below 10°. In unfavorable cases this low-melting fraction formed the main portion or even the whole of the reaction product.

ω-Cyano-undecylic Acid.—Two hundred g. of bromo-undecylic acid was melted and mixed with 1200 cc. of methanol. Thirty g. of sodium carbonate was dissolved in 100 cc. of water and added. The mixture was boiled until the precipitate dissolved. Two hundred g. of sodium cyanide ("cyanegg") was dissolved in 300 cc. of water and added. The mixture was gently boiled for one hour in a flask containing pieces of porous porcelain and provided with a reflux condenser.

A test for completeness of the reaction was made by acidifying a small sample. The resulting crystals were melted in warm water. If the melted product sank, boiling of the reaction mixture was continued until a product was obtained which, when melted, was lighter than water.

Four liters of water and 800 cc. of hydrochloric acid were added to the reaction mixture and the product was extracted with benzene. The benzene extract was treated with decolorizing carbon, filtered, and evaporated in the hood. The product weighed about 155 g.; m. p., varying from 45° to 52° in different runs.

The crude cyano acid was purified by several crystallizations from small amounts of carbon tetrachloride, or by crystallization of the barium salt or (for titration) by both methods. Purification through the barium salt, which was especially applicable to the working of impure residues, was conducted as follows. One hundred g. of crude acid was melted in 500 cc. of water and converted to the sodium salt by just sufficient sodium hydroxide to color phenolphthalein. This solution was poured into a boiling solution of 60 g. of crystallized barium chloride in 6 liters of water. If the precipitate was oily, fuller's earth was added. The solution was filtered while hot, bromo-undecylic acid, if present, and other impurities being thus eliminated. On cooling, crystals of the barium salt were deposited, and a further yield was obtained by evaporation of the mother liquor to 2 liters, filtering and cooling. The barium salt was recrystallized, if necessary, from dil. alcohol or water, and then treated with dil. hydrochloric acid.

ω-Cyano-undecylic acid is nearly insoluble in water and petroleum ether, but readily soluble in most organic solvents. It crystallizes from cold carbon tetrachloride in hard rosets; m. p., 57°.

Anal. Subs., 0.4838: 22.83 cc. of 0.1 *N* NaOH. Calcd. for $C_{12}H_{21}O_2N$: equiv. wt., 211.2. Found: 211.9.

dl-λ-**Ketochaulmoogric Acid.**—ω-Cyano-undecanoyl chloride was prepared from 211 g. of cyano-undecylic acid and 60 cc. of phosphorus trichloride, with 200 cc. of toluene as diluent. The mixture was warmed for about two hours somewhat below the boiling point, with occasional agitation. The solution was decanted, boiled for half an hour, filtered, and the residue thoroughly washed with boiling toluene. The filtrate and washings were distilled until the liquid reached 150°, and 200 cc. of toluene was twice added and distilled off, to the same temperature, in order to remove volatile phosphorus compounds. The clear, amber, liquid residue was cooled to room temperature and used without further purification.

To facilitate manipulation and avoid danger of breakage it was found advisable to use heavy-walled Pyrex Erlenmeyer flasks ("filter flasks without tubulation") for the heating with phosphorus chloride, for the powdering of sodium and for the aceto-acetic ester condensation.

Twenty-three g. of sodium was melted in 100 cc. of toluene and powdered by violent shaking. The process was repeated if necessary until none of the particles exceeded 0.5 mm. in diameter. The mixture was transferred to a 2-liter flask and 800 cc. of benzene was added. One hundred and thirty g. of ethyl aceto-acetate was then slowly added, with agitation. Vigorous and complete reaction took place, with spontaneous heating. The product, a light yellow, curdy mass, was allowed to cool.

The cyano-undecanoyl chloride was added, with agitation. The mixture became warm; it liquefied and then very slowly thickened as the colloidal sodium chloride formed a gel. The mixture was allowed to stand for one hour. It usually remained slightly alkaline (to aqueous phenolphthalein).

Twenty-three g. of powdered sodium in 100 cc. of toluene was added, with agitation. The mixture became hot and liquefied, forming two layers. The evolution of hydrogen soon slackened, and the sodium began to settle in the lower, turbid and somewhat viscous layer. The sodium was kept in action by mechanical stirring, and heat was finally applied to keep the mixture gently boiling. When the boiling mixture had been stirred for about one hour, it was allowed to cool to 50°. It remained liquid, with only a few lumps of insoluble material, and a very small amount of free sodium.

Slightly more than one mole of Δ^2-chlorocyclopentene (prepared as described in our earlier paper[2]) was stirred in. The reaction kept the mixture warm for about an hour, after which gentle heat was applied, or the mixture was allowed to stand overnight. Lumps of insoluble matter, if any remained, were mechanically disintegrated. Tests were made by adding a drop of the solution to a few drops of aqueous phenolphthalein. The color should rapidly disappear, showing an excess of chloride to be present. When momentary color was no longer produced by either the solution or the sediment, the reaction was shown to be complete.

The reaction mixture was boiled with 2 liters of an aqueous solution of 30 g. of sodium carbonate until benzene and toluene ceased to distil with the steam. Removal of the excess of chlorocyclopentene was thus insured. The ester was separated from the aqueous solution with the aid of a little benzene, which was subsequently evaporated. The product, a clear, brown oil which remained liquid at —15°, weighed 350 g. From the clear, alkaline solution 13 g. of cyano-undecylic acid was recovered, by acidification with hydrochloric acid.

The crude diketo ester was dissolved in 1.5 liters of alcohol. A solution of 140 g. of sodium hydroxide in 200 cc. of water was added in small portions during an hour, and the mixture was allowed to stand for 18 hours at about 27°. The deposition of sodium carbonate was then almost complete, as shown by the fact that a small filtered portion gave only a very slight precipitate on boiling and cooling. The hydrolysis was halted at this state to facilitate separation of by-products, especially cyano-undecylic acid.

Four liters of water was added and the solution was extracted twice with benzene. The completion of the extraction was insured by acidifying with hydrochloric acid, and again extracting with several portions of benzene, each of which was subsequently washed with dil. aqueous potassium hydroxide to remove the acids present. The potassium hydroxide solution gave, on acidification, 75 g. of a viscous liquid containing cyano-undecylic acid. The combined benzene solutions, on distillation of the solvent, yielded a brown oil weighing 203 g., believed to contain about 50% of *dl*-λ-ketochaulmoogronitrile.

In preliminary experiments an examination of the crude nitrile was made. On standing, the oil deposited a small amount of solid, difficultly soluble in ether and soluble in hot dil. potassium hydroxide solution. This and other impurities could be precipitated by the addition of petroleum ether. A portion so treated was filtered, and the solvent and an odorous substance (cyclopentene-acetone is to be expected) evaporated from the filtrate. The residue, when cooled, froze to a crystalline solid, melting at 6–9°, still evidently impure. In the preparation of *dl*-ketochaulmoogric acid it was found advantageous to hydrolyze the crude nitrile before attempting any removal of impurities.

The 203 g. of crude nitrile was refluxed for 24 hours with 1200 cc. of alcohol, 600 cc. of water and 120 g. of potassium hydroxide. The volume was then reduced by distillation to 800 cc. Hydrochloric acid was added in excess, and the mixture allowed to cool. The fatty acid was separated (practically all solidified as a cake above the aqueous liquid) and extracted thrice with 500 cc. of boiling petroleum ether at about 40°. The residue was extracted with hot benzene, and the benzene extract, after evaporation of the solvent, was again extracted with small portions of petroleum ether.

The combined petroleum ether solution was shaken with decolorizing carbon as it cooled, and was again boiled and filtered. The nearly colorless filtrate, cooled to 10°, deposited 93 g. of fine crystals; m. p., 72°. The product was crystallized several times from acetone, melting then at 76°.

Anal. Subs., 0.5466: 18.50 cc. of 0.1 *N* NaOH. Calcd. for $C_{18}H_{30}O_3$: equiv. wt., 294.2. Found: 295.5.

dl-λ-**Ketochaulmoogric acid is readily** soluble in benzene, alcohol, ethyl acetate and acetone, and moderately soluble in petroleum ether. It crystallizes from acetone in blades, and from petroleum ether in minute plates. The barium salt is not appreciably dissolved by hot water.

The portions (13 g. + 75 g.) of impure cyano-undecylic acid were purified through the barium salt. Forty-six g. of cyano-undecylic acid was thus recovered. The residues from this purification and the other products from which the 93 g. of ketochaulmoogric acid was separated were eventually boiled with alcoholic alkali. A further yield of 11 g. of ketochaulmoogric acid was thus obtained, in small amount from each portion. The final residues were tarry, containing some decane-dicarboxylic and other high-melting acids.

SEMICARBAZONE.—Eight g. of ketochaulmoogric acid and 6 g. of potassium acetate in 80 cc. of warm alcohol were mixed with 4 g. of semicarbazide hydrochloride in 20 cc. of water, and allowed to stand for 24 hours. The semicarbazone separated in short crystals, sparingly soluble in ether and benzene and insoluble in petroleum ether. After recrystallization from alcohol, methanol and ethyl acetate, the substance melted at 123°.

Anal. Subs., 0.2900: 8.24 cc. of 0.1 *N* NaOH. Calcd. for $C_{19}H_{33}O_3N_3$: equiv. wt., 351. Found: 352.

dl-λ-**Ketochaulmoogramide.**—In the process described above, ketochaulmoogramide was not found in appreciable quantities, either before or after the final hydrolysis. In preliminary experiments, however, in which the final hydrolysis was continued for only two or three hours, small yields of amide were obtained. The accompanying acids were removed by thorough extraction with hot, dil. potassium hydroxide solution and the unchanged nitrile by crystallization from benzene. The crystalline product was recrystallized several times from alcohol.

Anal. Subs., 0.2104: 6.85 cc. of 0.1 *N* H_2SO_4 (Kjeldahl). Calcd. for $C_{18}H_{31}O_2N$: N, 4.78. Found: 4.56.

Ketochaulmoogramide is sparingly soluble in ether and cold benzene, soluble in hot benzene and alcohol. It crystallizes in blades; m. p., 108°.

dl-**Chaulmoogric Acid.**—Seven g. of sodium was dissolved in absolute alcohol and the solution was boiled until the solid began to separate. Fifteen g. of ketochaulmoogric acid was dissolved in a little absolute alcohol and mixed with the ethylate solution in a tared beaker. Alcohol was evaporated until the mixture weighed 90 g.

The mixture was heated with 7 g. of dry hydrazine hydrochloride ($N_2H_4.HCl$) in an iron bomb (170 cc. capacity) for 40 hours at 195–205°. The product was dissolved in hot water, acidified with hydrochloric acid and extracted with benzene. The benzene was evaporated and the residue stirred with 200 cc. of petroleum ether (d., 0.650–0.660) at 20–25°. The undissolved portion was separated by filtration and further extracted with petroleum ether, with heating and subsequent cooling to 20–25°, until no more was dissolved. The petroleum ether filtrates (total about 500 cc.) gave, on evaporation, 10 g. of a crystalline solid; m. p., about 63°. This was crystallized several times from ethyl acetate and finally from petroleum ether; m. p., 68.5°.

Anal. Subs., 0.2639: CO_2, 0.7470; H_2O, 0.2742. Calcd. for $C_{18}H_{32}O_2$: C, 77.1; H, 11.5. Found: C, 77.2; H, 11.6.

Subs., 0.2926: 10.48 cc. of 0.1 *N* NaOH. Calcd. for $C_{18}H_{32}O_2$: equiv. wt., 280.3. Found: 279.2.

dl-Chaulmoogric acid is very similar to the natural dextrorotatory acid in its appearance and solubilities. In order to compare the melting points, a sample of nearly pure chaulmoogric acid from *Hydnocarpus alcalae* oil was recrystallized from petroleum ether and then several times from ethyl acetate. After drying at a low temperature, this melted at 69°. Mixtures of approximately equal amounts of the natural and the synthetic acids melted at 68.5°. Repeated simultaneous determinations showed that such mixtures melted possibly a trifle higher, certainly no lower, than the unmixed synthetic acid. The absence of a marked melting-point depression, characteristic of conglomerates, shows that the *dextro* and *levo* substances form mixed crystals.

dl-Chaulmoogric acid has the same peculiar odor as the natural substance. This is more readily perceptible when the substances are stored in closed containers.

Five g. of *dl*-chaulmoogric acid was oxidized with potassium permanganate in acetic acid as described in an earlier paper.[9] A product sparingly soluble in ether was obtained, the melting point (125°) of which was not depressed by admixture with γ-keto-*n*-pentadecane-α,α'-dicarboxylic acid (m p., 126°) from natural chaulmoogric acid.

Summary

In studies aiming to produce anti-leprosy drugs superior to those obtainable from chaulmoogra-group oils, various lower homologs of chaulmoogric acid were required. A method of synthesis was developed for the preparation of these. Aceto-acetic ester was condensed with ω-cyanoundecanoyl chloride and then with Δ^2-chlorocyclopentene. The resulting diketo ester gave, on hydrolysis, *dl*-λ-ketochaulmoogric acid.

The keto acid, on reduction with hydrazine and sodium ethylate, yielded *dl*-chaulmoogric acid.

The synthetic chaulmoogric acid is very similar to the natural dextrorotatory substance and, judging from melting-point determinations, isomorphous with it. The structural identity of the two was confirmed by oxidation of the new product to γ-keto-*n*-pentadecane-α,α'-dicarboxylic acid.

CULION, PHILIPPINE ISLANDS

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

NEW MONOBROMO DERIVATIVES OF VANILLIN

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Hitherto, the only known bromine derivative of vanillin is that melting at 164°[1] and having the halogen in Position 5 (CHO = 1). In the work reported here two other derivatives have been obtained, melting at 154–155° and 178°, respectively.

The first of these was prepared from an aminovanillin,[2] m. p. 127°, by the Sandmeyer reaction. The structure of the amine has been fixed in the following way: Pschorr and Sumuleanu[3] obtained a nitrovanillin

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[9] Perkins, THIS JOURNAL, **48**, 1723 (1926).

[1] Tiemann and Haarmann [*Ber.*, **7**, 615 (1874)], who first prepared it, recorded 160–161°.

[2] Sumuleanu [*Ann. Sci. Univ. Jassy*, **2**, 131 (1902–1903)] found 128–129°.

[3] Pschorr and Sumuleanu, *Ber.*, **32**, 3408 (1899).