filtered and dried. This product was then thoroughly washed with ether and dried again (0.390 g., m.p. ~200°).

The hydrochloride salt was treated with 10% ammonium hydroxide solution (25 ml.) and the resulting base was collected and dried (0.374 g., 85%), m.p. 126–128°. The amine was recrystallized twice from aqueous ethanol to afford an analytical sample: m.p. 126–128°; $\lambda_{max}^{CHCl_3}$ 2.87, 2.95, 6.26, 6.72 μ; λ_{max}^{EtOH} 258 mμ (ε 33,800), 333 mμ (ε 8100).

Anal. Calcd. for $C_{14}H_{10}BrN$: C, 61.79; H, 3.71; N, 5.15. Found: C, 61.66; H, 3.92; N, 5.24.

Lactam of 10-Amino-1-phenanthroic Acid (XI).—In a 20-ml. three-necked, round-bottom flask, fitted with a water condenser with gas inlet tube, a rubber stopper injection port, and a Teflon stirring bar, was placed a solution of 1-bromo-10-phenanthrylamine (Xa, 0.100 g., 0.00034 mole, m.p. 126–128°) in anhydrous ether (3 ml.). The system was flushed with nitrogen and kept under this atmosphere throughout the reaction. Freshly prepared *n*-butyllithium solution (0.5 ml.) (made according to the method of Gilman, *et al.*[13]) was added dropwise to the stirred mixture by means of a hypodermic syringe. After 15 min., the mixture was carbonated by pouring it over powdered Dry Ice. The lithium salts were then decomposed by the addition of 10% hydrochloric acid (15 ml.) and the product was extracted with ether. The ethereal extract was washed with water and dried over sodium sulfate. Evaporation of the ether afforded an oily brown product (0.081 g.) which was chromatographed on acid-washed alumina. Chloroform–Skellysolve B (1:9) eluted a colorless crystalline compound (0.023 g.): m.p. 139–140°; $\lambda_{max}^{CHCl_3}$ 2.92, 3.0 (N–H stretching), 6.27, 6.67 μ (aromatic). This compound gave a negative halogen test on sodium fusion. The ultraviolet spectrum of this product was found to be superimposable with that of 9-aminophenanthrene (lit.[14] m.p. 137–138°).

Chloroform–Skellysolve B (1:3) eluent yielded the desired lactam as a strongly fluorescent solid which was recrystallized from chloroform–Skellysolve B (12 mg., m.p. 235°) (15% yield): λ_{max}^{EtOH} 221.5 mμ (ε 51,000) 230 (28,000), 244 (27,500), 284 (21,000), 295 (22,000); λ_{max}^{KBr} 3.10 (N–H stretching), 6.00 μ (lactam carbonyl).

Anal. Calcd. for $C_{15}H_9NO$: C, 82.17; H, 4.14; N, 6.39. Found: C, 81.95; H, 4.33; N, 6.36.

N-Acetyl-1-bromo-10-phenanthrylamine (Xb).—Acetylation of Xa (50 mg., 0.00018 mole, m.p. 126–128°) with a tenfold excess of acetic anhydride yielded, after work-up, shiny colorless crystals (42 mg., 73%), m.p. 208–209.5°. Recrystallization from aqueous ethanol gave an analytical sample: m.p. 210–210.5°; λ_{max} 2.91 (N–H stretching), 5.95 μ (amide carbonyl).

Anal. Calcd. for $C_{16}H_{12}BrNO$: C, 61.16; H, 3.85; N, 4.46. Found: C, 61.01; H, 3.85; N, 4.57.

10-Nitro-1-phenanthroic Acid (II).—A suspension of the lactam XI (0.022 g., 0.0001 mole, m.p. 235°) in 5% sodium hydroxide solution (2 ml.) was stirred and refluxed in an oil bath overnight. The yellow solution was cooled and sodium nitrite (0.069 g., 0.0010 mole) was added. This solution was added dropwise to 5% hydrochloric acid (10 ml.) cooled to 0°. A positive alkaline β-naphthol test was obtained. The diazonium solution was then added dropwise to a mixture of sodium nitrite (4.50 g.), copper sulfate pentahydrate (0.75 g.), sodium bicarbonate (3.5 g.), and cuprous oxide (0.5 g.) in water (100 ml.). The pH of the mixture remained at about 7.5 throughout a 12-hr. period. The mixture was filtered and the filtrate was acidified with hydrochloric acid to congo red. The small precipitate which had formed was filtered and dried (5 mg.), m.p. 240–246°. This product was recrystallized once from glacial acetic acid and once from ethanol to afford tan needles (2 mg.): m.p. 268–270°; λ_{max}^{EtOH} 256 mμ (ε 37,200); λ_{max}^{KBr} 6.60, 7.45 μ (nitro).

Anal. Calcd. for $C_{15}H_9NO_4$: C, 67.41; H, 3.39; N, 5.24. Found: C, 67.57; H, 3.62; N, 5.34.

The melting point was undepressed by admixture with a sample (m.p. 268–270°) prepared by an alternate route[6] and the infrared spectrum (KBr) was superimposable upon that of the comparison sample.

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[13] H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949).

[14] M. A. Goldberg, E. P. Ordas, and G. Carsch, *ibid.*, **69**, 260 (1947).

Tumor Inhibitors. XI.[1] Proof of Structure of Aristolochic Acid-C by Total Synthesis of Its Methyl Ester Methyl Ether[2,3]

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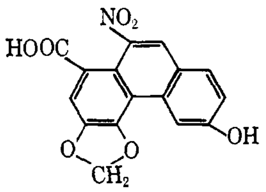
Following the discovery of a water-soluble quaternary base, magnafluorine, in the basic component of the Chinese drug "Fang Chi," the acid and neutral components were examined by Tomita and co-workers.[5] The acid fraction yielded aristolochic acid-I[1] and two nitrophenanthroic acids, aristolochic acid-B and aristolochic acid-C. Crystalline neutral substances isolated were aristololactam, allantoin, and β-sitosterol. The identical acid components were later found in *Aristolochia debilis.*[6] The new acid-C was converted to various derivatives and structure I was tentatively proposed by the Japanese workers from the results of elemental analysis, infrared spectrum, and various chemical properties.



I

The total synthesis of the methyl ester methyl ether of I was undertaken to provide unequivocal proof for the postulated structure (see Chart I). We have recently reported the synthesis of several substituted phenanthrenes, including aristolochic acids I and II, by photocyclization of substituted 2-iodostilbenes.[1,7] This general reaction has been used in the present synthesis. The synthetic precursor of ring A of the desired phenanthrene derivative, namely, 2-carbomethoxy-4,5-methylenedioxyphenylnitromethane (XIV) was available from our earlier work.[1] The synthetic precursor of ring C, 2-iodo-4-methoxybenzaldehyde (VI), had been prepared by Hodgson[8] by Reimer–Tiemann reaction on *m*-iodophenol, followed by dimethyl sulfate methylation. These reactions proved unsuitable since the yields obtained seldom exceeded 10%. Our subsequent approach was very

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[1] Part X: S. M. Kupchan and H. C. Wormser, *J. Org. Chem.*, **30**, 3792 (1965).

[2] Abstracted from a part of the dissertation submitted by H. C. Wormser to the University of Wisconsin Graduate School, June 1965, in pa l fulfillment of the requirements of the Ph.D. degree.

[3] This investigation was supported in part by research grants m the National Cancer Institute (CA-04500) and the American Cance ociety (T-275).

[4] American Foundation for Pharmaceutical Education Fello 1961–1963; National Institutes of Health Predoctoral Fellow, 1963–19

[5] M. Tomita and S. Sasagawa, *J. Pharm. Soc. Japan*, **79**, 973 959).

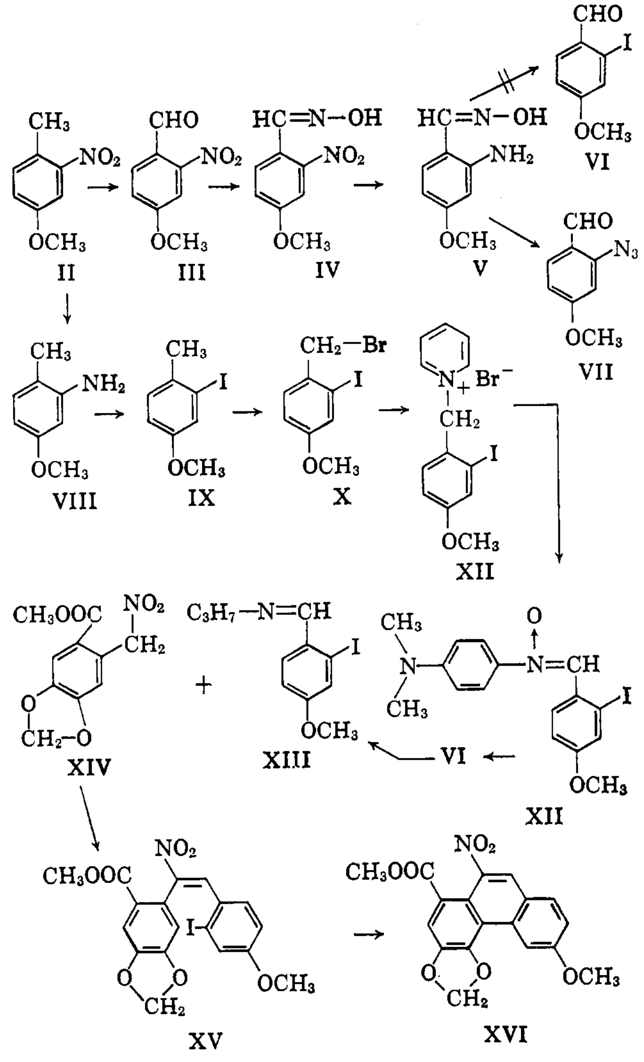
[6] S. Sasagawa, *J. Pharm. Soc. Japan*, **82**, 921 (1962).

[7] S. M. Kupchan and H. C. Wormser, *Tetrahedron Letters*, 3 (1965).

[8] H. H. Hodgson and T. A. Jenkinson, *J. Chem. Soc.*, 3041 (27).

similar to that used for the synthesis of ring C of aristolochic acid-I.[1] 2-Nitro-4-methoxybenzaldehyde (III) was prepared essentially by the method of Suvorov.[9] III was converted to 2-amino-4-methoxybenzaldoxime (V) by an already well-established synthesis.[1,10] Sandmeyer conversion of this product to the corresponding iodo compound failed to give the desired product VI and afforded instead, in 93% yield, 2-azido-4-methoxybenzaldehyde (VII). The next approach made use of 2-iodo-4-methoxytoluene (IX) prepared by the method of Roberts and Smiles.[11]

CHART I



This compound was converted to the unstable 2-iodo-4-methoxybenzyl bromide (X) by the use of N-bromosuccinimide (96%). Conversion of the benzyl bromide into 1-(2-iodo-4-methoxybenzyl)pyridinium bromide (XI) was affected in 87% yield. 2-Iodo-4-methoxyphenyl-N-*p*-dimethylaminophenylnitrone (XII) was prepared in 43% yield as yellow-green crystals. Hydrolysis of this product in 6 *N* sulfuric acid afforded an 82% yield of 2-iodo-4-methoxybenzaldehyde (VI). The condensation reaction of 2-carbomethoxy-4,5-methylenedioxyphenylnitromethane (XIV) with the *n*-propylidene base of 2-iodo-4-methoxybenzaldehyde (XIII) was effected in glacial acetic acid and a 57% yield of 2-carbomethoxy-4,5-methylenedioxy-2′-iodo-4′-methoxy-α-nitro-*cis*-stilbene (XV) was obtained. Photolysis of this product afforded, in 45% yield, aristolochic acid-C methyl ester methyl ether (XVI), which was identical in all respects with an authentic sample.[12]

Experimental Section[13]

2-Nitro-4-hydroxytoluene was prepared by the method of Suvorov, *et al.*,[9] m.p. 74–75°, in 65% yield (lit.[9] m.p. 77–78°).

2-Nitro-4-methoxytoluene (II) was prepared by the method of Suvorov, *et al.*,[9] b.p. 108–115° at water pump pressure (~25 mm.), in 66% yield (lit.[9] b.p. 138° at 11–14 mm.).

2-Nitro-4-methoxybenzaldehyde (III) was prepared by the method of Suvorov, *et al.*,[9] m.p. 93–94° (lit.[9] m.p. 95–96°).

2-Nitro-4-methoxybenzaldoxime (IV) was prepared by the method of Boon,[10] m.p. 124–125°, in 96% yield (lit.[10] m.p. 123°).

2-Amino-4-methoxybenzaldoxime (V) was prepared by the method outlined in a previous report,[1] m.p. 144–145°, in 30% yield (lit.[10] m.p. 145°).

Sandmeyer Reaction on 2-Amino-4-methoxybenzaldoxime.—2-Amino-4-methoxybenzaldoxime (V, 0.200 g., 0.0012 mole, m.p. 144–145°) dissolved in dioxane (3 ml.) was added dropwise to a frozen paste of hydrochloric acid in an acetone–Dry Ice bath. When all the oxime had been added, a salt–ice bath was substituted, and the tan paste was diazotized by the addition of sodium nitrite (0.150 g., 0.0022 mole) in a small volume of water. The reaction mixture turned yellow but did not give a strongly positive test with alkaline β-naphthol. Potassium iodide (0.50 g., 0.030 mole) in water (5 ml.) was added to the diazotized mixture and the dark brown oily product was heated on a water bath for 30 min. The reaction mixture was extracted with three 50-ml. portions of chloroform; the extract was washed with 10% sodium hydroxide solution and water and dried over magnesium sulfate. Evaporation of the solvent afforded a semicrystalline product (0.195 g., m.p. 64–66°). T.l.c. showed that this material was not the expected 2-iodo-4-methoxybenzaldehyde (VI). The infrared spectrum indicated that the compound was azide VII: $\lambda_{\max}^{\mathrm{CHCl_3}}$ 4.72, 5.95 μ. An analytical sample was obtained by crystallization from benzene–Skellysolve B: m.p. 72.5–73°.

Anal. Calcd. for $C_8H_7N_3O_2$: C, 53.92; H, 3.96; N, 23.60. Found: C, 54.06; H, 3.81; N, 23.88.

2-Amino-4-methoxytoluene (VIII).—A solution of 2-nitro-4-methoxytoluene (II, 5.0 g., 0.030 mole) in ethyl acetate (200 ml.), containing platinum oxide (82.34%, 0.150 g.), was submitted to Parr pressure hydrogenation (40 p.s.i.) for a period of 20 min. Approximately 6 lb. of hydrogen was absorbed and the yellow solution became colorless toward the end of the reaction. After filtration of the platinum catalyst, followed by evaporation of the solvent, a yellow oil resulted, which on cooling gave a yellow solid product. This material was washed with cold Skellysolve B, affording an off-white crystalline material (3.80 g., 92%), m.p. 41–43° (lit.[11] m.p. 47°).

2-Iodo-4-methoxytoluene (IX) was prepared by the method of Roberts and Smiles,[11] giving oily material in 85% yield (lit.[11] b.p. 252–253° at atmospheric pressure).

2-Iodo-4-methoxybenzyl Bromide (X).—A solution of 2-iodo-4-methoxytoluene (IX, 0.552 g., 0.0022 mole) in carbon tetra-

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[9] N. N. Suvorov, M. V. Fedotava, O. B. Ogareva, and E. G. Balasheva, *J. Gen. Chem. USSR*, **30**, 3091 (1960).

[10] W. R. Boon, *J. Chem. Soc.*, S230 (1949).

[11] K. C. Roberts and S. Smiles, *ibid.*, 863 (1929).

[12] Appreciation is expressed to Professor M. Tomita (Kyoto University) for supplying us with a sample of aristolochic acid-C methyl ester methyl ether.

[13] Melting points were determined on a Fisher-Johns melting point stage which had been calibrated with standard samples. Ultraviolet absorption spectra were determined in 95% ethanol on a Beckman (Model DK2A) recording spectrophotometer. Infrared absorption spectra were recorded in chloroform (unless otherwise specified) on a Beckman (Model 5A) double-beam infrared recording spectrophotometer. Microanalyses were by J. F. Alicino, Metuchen, N. J., and Spang Microanalytical Laboratory, Ann Arbor, Mich. Skellysolve B refers to petroleum ether, fraction boiling at 60–80°.

chloride (5 ml.) was placed in a 20-ml. round-bottom flask along with freshly recrystallized N-bromosuccinimide (0.391 g., 0.0022 mole, m.p. 173°). The mixture was stirred and irradiated during 45 min. by means of two 200-w. tungsten lamps. At the end of the reaction, when all the succinimide floated at the surface of the mixture, the flask was cooled and the content was filtered. Succinimide was obtained (0.214 g., m.p. 122–125°), and the filtrate, after evaporation, afforded a brown oil (0.692 g., 96%). Because of the instability of this compound, it was utilized immediately without further purification (on standing, a darkening occurred accompanied by hydrogen bromide evolution).

1-(2-Iodo-4-methoxybenzyl)pyridinium Bromide (XI).—A solution of 2-iodo-4-methoxybenzyl bromide (X, 2.20 g., 0.0067 mole), dissolved in dry benzene (50 ml.) containing pyridine (5 ml.), was refluxed for 30 min. After cooling, the light brown pyridinium salt was filtered, washed with anhydrous ether, and dried (2.37 g., 87%). Recrystallization from an ethanol–ether mixture afforded an analytical sample as a tan crystalline material, m.p. 200–201°.

Anal. Calcd. for $C_{13}H_{13}BrINO$: C, 38.44; H, 3.22; N, 3.45. Found: C, 38.60; H, 3.22; N, 3.33.

2-Iodo-4-methoxyphenyl-N-*p*-dimethylaminophenylnitrone (XII).—A cold solution of 5% sodium hydroxide (5 ml.) was added dropwise at 0° to a stirred suspension of 1-(2-iodo-4-methoxybenzyl)pyridinium bromide (XI, 0.990 g., 0.00245 mole, m.p. 200–201°) and N,N-dimethylnitrosoaniline (0.365 g., 0.00245 mole, m.p. 85°) in ethanol (7.8 ml.). Stirring in the cold was allowed to proceed for 5 hr. During this period a reddish brown precipitate occurred; this material was filtered and dried (0.412 g., 43%). An analytical sample was obtained by preparative t.l.c. on silica gel $HF_{254+366}$ (2% methanol in chloroform elution), followed by recrystallization from benzene–Skellysolve B, m.p. 154–155° (yellow-green crystals).

Anal. Calcd. for $C_{16}H_{17}IN_2O_2$: C, 48.48; H, 4.32; N, 7.07. Found: C, 48.30; H, 4.20; N, 7.13.

2-Iodo-4-methoxybenzaldehyde (VI).—The nitrone XII (0.165 g., 0.00042 mole, m.p. 154–155°) was stirred vigorously into cold 6 *N* sulfuric acid to effect hydrolysis. The yellow product formed was filtered, washed with water, and dried (0.090 g., 82%). Recrystallization from Skellysolve B afforded light yellow crystals (0.073 g.), m.p. 112–113°, $\lambda_{max}^{CHCl_3}$ 5.95 μ (lit.[8] m.p. 115°).

2-Carbomethoxy-4,5-methylenedioxy-2′-iodo-4′-methoxy-*α*-nitro-*cis*-stilbene (XV).—In a 5-ml. erlenmeyer flask was placed a mixture of 2-carbomethoxy-4,5-methylenedioxyphenylnitromethane (XIV, 0.075 g., 0.000314 mole, m.p. 130–130.5°), *n*-propylidene base of 2-iodo-4-methoxybenzaldehyde (XIII, 0.104 g., 0.000343 mole), and glacial acetic acid (5 ml.). This mixture was heated to boiling on a hot plate and the acetic acid was allowed to evaporate almost to dryness. The resulting dark brown oil was subjected to preparative t.l.c. on silica gel $HF_{254+366}$ (chloroform elution) and the major yellow band afforded a viscous yellow oil. Crystallization was accomplished by the addition of a few drops of ethanol (0.087 g., 57%). The yellow product was recrystallized from ethanol and gave shiny yellow prisms (0.076 g.): m.p. 172–173°; $\lambda_{max}^{CHCl_3}$ 5.85, 6.60, 7.55, 8.0 μ; λ_{max}^{EtOH} 260 mμ (ϵ 12,950) (plateau), 308 (9600), 345 (12,000).

Anal. Calcd. for $C_{18}H_{14}INO_7$: C, 44.74; H, 2.92; N, 2.90. Found: C, 44.60; H, 2.87; N, 2.94.

Methyl Ester of Aristolochic Acid-C Methyl Ether (XVI).—A solution of XV (0.009 g., 0.00002 mole, m.p. 172–173°) in purified cyclohexane (75 ml.) was photolyzed in a Vycor tube utilizing a Rayonet photochemical reactor as the light source. The photolysis required 25 min. A noticeable color of iodine was observed as usual. Evaporation of the solvent afforded a yellow-orange oily solid (0.009 g.). This product was purified by preparative t.l.c. on silica gel $HF_{254+366}$ (chloroform elution). Starting material was isolated from a deep yellow band having a slightly higher R_f value than the desired product (2.3 mg.). The yellow band with the lower R_f value afforded shiny microcrystals (2.2 mg., 45% based on unrecovered starting material), m.p. 256–260°. Recrystallization from ethanol gave shiny yellow microcrystals (2.15 mg.), m.p. 258–260°, melting point undepressed upon admixture with an authentic sample.[12] The thin layer chromatographic behavior was identical with that of the reference sample in four different solvent systems (chloroform and 1, 2, and 3% methanol in chloroform). The infrared spectrum (KBr) was superimposable upon that of the authentic sample: λ_{max}^{EtOH} 255 mμ (ϵ 41,300), 281 (16,600), 302 (13,060).

An Improved Technique for the Hydroxylation of 4,5-Diphenyl-2-imidazolones

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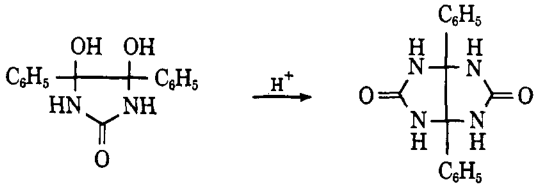
Biltz[2] has shown that 4,5-diphenyl-2-imidazolone can be hydroxylated to 4,5-dihydroxy-4,5-diphenyl-2-imidazolidinone (1) with concentrated nitric acid. His method omitted some critical experimental details and was later modified by Dunnavant.[3] The modified procedure still proved unsatisfactory in our hands, giving either benzil or N,N′-dibenzoylurea as the sole products.

It was shown that treatment of the imidazolone with bromine in acetic acid buffered with sodium acetate gave the glycol. This method was also used to prepare the glycol of 4,5-di(*p*-bromophenyl)-2-imidazolone. In both cases the glycols were quantitatively oxidized with periodate to the corresponding N,N′-dibenzoylurea.

In the presence of aqueous acid the glycol gave the benzil and the corresponding 3a,6a-diphenylglycoluril (2). These results are in conflict with those reported by Dunnavant and James[4] who claimed that the glycol rearranged to the 5,5′-diphenylhydantoin in acid solution; this rearrangement does occur, but only under alkaline conditions.[5] The glycols and urea in the presence of acid gave the corresponding glycolurils quantitatively.[6]



1 2

Experimental Section[7]

4,5-Dihydroxy-4,5-diphenyl-2-imidazolidinone.—4,5-Diphenyl-2-imidazolone[8] (2.36 g., 0.01 mole), glacial acetic acid (25 ml.), and anhydrous sodium acetate (3 g.) were heated to boiling. The external heating was removed and a solution of bromine in acetic acid (160 g. of Br_2/l. of acetic acid, 10 ml., 0.01 mole) was added rapidly. The reaction mixture was allowed to stand until all the bromine had been consumed (about 10 min.) and then ice–water (70 ml.) was added dropwise with stirring. The reaction mixture set to a jelly-like mass which on continued stirring became granular. The solid was removed by filtration and washed with saturated sodium bicarbonate solution with water, and finally twice with ethanol–ether (1:3, 20 ml.). After drying in a vacuum desiccator, the glycol was crystallized from methanol, yielding 1.99 g. (74%), m.p. 153–155° (lit.[3] m.p. 158–161°).

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(1) To whom correspondence should be addressed.

(2) H. Biltz, *Ann.*, **368**, 173 (1909).

(3) W. R. Dunnavant, *J. Org. Chem.*, **21**, 1513 (1956).

(4) W. R. Dunnavant and F. L. James, *J. Am. Chem. Soc.*, **78**, 2740 (1956).

(5) H. Biltz, *Ber.*, **41**, 1379 (1908).

(6) H. Biltz, *Ann.*, **368**, 250 (1909).

(7) All melting points are uncorrected and were determined in an electrically heated copper block.

(8) F. D. Chattaway and E. A. Coulson, *J. Chem. Soc.*, 1361 (1928).