formed in boiling pyridine-acetic anhydride, 1:1, gave products of the same acetyl content.

Summary

1. Two independent methods, one employing the use of *p*-toluenesulfonyl chloride and a second using triphenylchloromethane, have been employed successfully to confirm primary hydroxylation in the previously reported structure for arabogalactan.

2. It is suggested that both *p*-toluenesulfonyl chloride and triphenylchloromethane can be more generally applied in the study of polysaccharide hydroxylation.

MOSCOW, IDAHO RECEIVED AUGUST 18, 1943

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

An Unexpected Rearrangement in the Application of the Skraup Reaction to 3-Nitro-4-aminoveratrole

BY KURT C. FRISCH,[1a] MILTON SILVERMAN AND MARSTON TAYLOR BOGERT

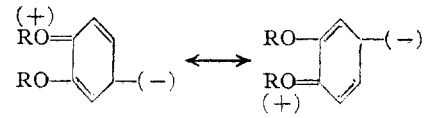
In the course of one of our antimalarial research projects, it became necessary to prepare 8-nitro-6,7-dimethoxyquinoline, and the synthesis which quite naturally suggested itself was the application of the Skraup reaction to 3-nitro-4-aminoveratrole, just as 8-nitro-6-methoxyquinoline is obtained from 3-nitro-4-aminoanisole in the manufacture of Plasmochin.

The preparation of the requisite 3-nitro-4-aminoveratrole from vanillin has been described by Pisovschi,[1b] and we had no difficulty in duplicating his results.

No complications were expected in subjecting this amine to the Skraup reaction, for this reaction has failed very rarely with primary aromatic amines. It is true, that, in the case of some nitroanilines, even when arsenic pentoxide is used as oxidizing agent, as recommended by Knueppel,[2] the yields are not infrequently quite unsatisfactory. In the manufacture of Plasmochin, the patents are significantly silent as to the yields in the Skraup step. Strukov,[3] who carried this out under special conditions, appears to have secured the best result (78%). So far as our own examination of the literature has shown, no molecular rearrangements have been observed in the application of this reaction.

In the veratrole series, 6,7-dimethoxyquinoline is readily synthesized from 4-aminoveratrole by this method.[4] The directive influence of the two methoxyl groups is shown by the formation of the 6,7- rather than 5,6-dimethoxyquinoline. The synthesis of this same quinoline from 6-aminoveratric acid by Goldschmidt,[5] involving simultaneous decarboxylation, is further evidence of this strong orienting property.

Arnold and Bordwell,[6] as a theoretical explanation of this directive influence, have postulated the existence of the following resonance forms for the veratrole molecule



In the experiments recorded beyond, when we subjected 3-nitro-4-aminoveratrole to standard Skraup reactions, using either nitrobenzene or arsenic pentoxide as oxidizing agent, strong or dilute sulfuric acid, and varying the temperature and length of heating, with the free amine or its acetyl derivative, no quinoline compound could be isolated.

When phosphoric (85%) was substituted for the sulfuric acid in the reaction mixture, an orange product was isolated which, crystallized from alcohol, melted at 172–174°, and on analysis gave figures for carbon, hydrogen and nitrogen, agreeing with those calculated for the initial nitro amine.

That these orange crystals were not identical with the brilliant red 3-nitro-4-aminoveratrole (m. p. 74°) was obvious from the m. p.'s of the two and of a number of their derivatives, and that the product actually separated (m. p. 172–174°) was the 5-nitro-4-aminoveratrole, and mixtures of this product with authentic samples of 5-nitro-4-aminoveratrole showed no change in the melting point.

To ascertain what conditions were requisite for this rearrangement, the arsenic pentoxide and the glycerol were omitted successively, and it was found that it could not be accomplished by heat alone (in tetralin solution), but that the best yield (30%) was obtained by digesting the 3-nitro isomer in a mixture of phosphoric (85%) and glacial acetic acids for one and one-half hours at 140–160°. There was always a great deal of carbonization in all of these experiments.

Superficially, this rearrangement can be explained by the migration either of the nitro group or of one of the methoxyls, but the mechanism of the change is obscure.

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(1a) Hopkinson Fellow, Columbia University.
(1b) Pisovschi, *Ber.*, **43**, 2137 (1910).
(2) Knueppel, *ibid.*, **29**, 703 (1896).
(3) Strukov, *Org. Chem. Ind.* (U. S. S. R.), **4**, 523 (1937).
(4) Frisch and Bogert, *J. Org. Chem.*, **8**, 331 (1943).
(5) Goldschmidt, *Monatsh.*, **8**, 343 (1887).
(6) Arnold and Bordwell, THIS JOURNAL, **64**, 2983 (1942).

N. Y., in establishing the Hopkinson Research Fellowship at Columbia University. The vanillin necessary for the synthesis of the 3-nitro-4-aminoveratrole was provided by Fritzsche Bros., Inc., 76 Ninth Avenue, New York, N. Y., through the courtesy of Mr. John H. Montgomery, Secretary. For the analytical work, we are indebted to Mr. Saul Gottlieb and Miss Frances E. Marx. To all of these we are most grateful.

Experimental

All temperatures reported, unless otherwise stated, have been corrected for thermometer stem exposure.

3-Nitro-4-aminoveratrole.—The procedure worked out by Pisovschi[1] for the synthesis of this compound from vanillin, was repeated, with the following modifications and in general with similar yields. The final product crystallized from dilute alcohol in beautiful dark red needles, m. p. 74°, as found by Pisovschi.

The nitration of the acetylvanillin was carried out with red fuming nitric acid, according to the method of Pschorr and Sumuleanu,[7] but with only 2.5 parts of the acid instead of the four parts recommended by Pisovschi, and the product was deacetylated by a 33% sodium hydroxide solution, as Pschorr and Sumuleanu had done.

After methylation of the nitrovanillin in sodium hydroxide solution by methyl sulfate, as Buck[8] methylated vanillin to veratraldehyde, and oxidation of the aldehyde by permanganate in acetone solution, the nitroveratric acid so obtained was dissolved in thionyl chloride, by refluxing for an hour at 100°. Excess of thionyl chloride was removed by distillation under diminished pressure, followed by the addition of benzene and repetition of the vacuum distillation. The residual red-brown oily crude acid chloride, without further purification, was added very slowly to a concentrated ammonium hydroxide solution, keeping the temperature below 25°. The precipitated white amide was removed, washed, and crystallized from dilute alcohol. In the degradation of this amide to the amine sought, by the usual Hofmann reaction, it was found better to add the amide to the hypobromite, rather than to follow the reverse order.

Acetyl Derivative.—From 3-nitro-4-aminoveratrole and acetic anhydride: white needles, from water, m. p. 150.5°; yield, 83%.

Anal. Calcd. for $C_{10}H_{12}O_5N_2$: C, 50.0; H, 5.0. Found: C, 50.3; H, 5.1.

Application of the Skraup Reaction to 3-Nitro-4-aminoveratrole.—As noted in the foregoing, attempts to convert this nitro amine into the desired 8-nitro-6,7-dimethoxyquinoline by the standard Skraup reaction, or various modifications thereof, were uniformly unsuccessful, but a 30% yield of the isomeric 5-nitro-4-aminoveratrole was isolated, m. p. 172–174°. Mixed with an authentic sample, in 50:50 and 70:30 weight per cent., no change in melting point occurred.

Anal. Calcd. for $C_8H_{10}O_4N_2$: C, 48.5; H, 5.0; N, 14.1. Found: C, 48.8; H, 5.2; N, 14.1.

To throw some light upon this rearrangement, the following experiments were carried out, using in all cases 1 g. of the 3-nitro-4-aminoveratrole, represented by "V," except in (e) (where 3 g. was used), and (h) (where 5 g. was used), heating the mixtures for one and one-half hours at 140–160° adding a few drops of concentrated hydrochloric acid, diluting and filtering out carbonaceous material, making the filtrate alkaline and extracting it with ether. The ether extracts were washed, dried with sodium sulfate and the solvent evaporated.

(a) = V + tetralin (5 cc.)
(b) = V + concentrated sulfuric acid (5 cc.)
(c) = V + phosphoric acid (85%) (5 cc.)
(d) = V + acetic acid (5 cc.)
(e) = V (3 g.) + arsenic pentoxide (2.2 g.) + glycerol (4.2 g.) + phosphoric acid (85%) (3 cc.) + acetic acid (6 cc.).
(f) = V + arsenic pentoxide (0.8 g.) + phosphoric acid (85%) (1 cc.) + acetic acid (3 cc.)
(g) = V + phosphoric acid (85%) (1 cc.) + acetic acid (3 cc.)
(h) = V (5 g.) + phosphoric acid (85%) (6 cc.) + arsenic pentoxide (3.6 g.) + glycerol (6 g.)

In experiments (a), (b) and (d), only the initial compound was recovered. In experiment (c), carbonization was so extensive that no pure organic product could be separated. In experiments (e), (f) and (h), yields averaging 30% of the 5-nitro isomer were obtained consistently. In experiment (g), a 25% yield of the 5-nitro compound was secured, plus 5–10% of its acetyl derivative (m. p. 199°). In a later run, using 0.7 g. of the 3-nitro amine, 0.7 cc. of 85% phosphoric acid, and 2.6 cc. of glacial acetic acid, the chief product was this acetyl derivative of the 5-nitro isomer. When concentrated sulfuric was substituted for the 85% phosphoric acid in this experiment, small amounts of the rearranged product were isolated.

In identifying the product of this rearrangement, it became necessary to prepare additional quantities of the **5-nitro-4-aminoveratrole.** In a previous article,[4] we have described its preparation by catalytic reduction of 4,5-dinitroveratrole in the presence of palladium. Our catalytic hydrogenation equipment being temporarily out of order, the desired compound was synthesized as follows.

4-Acetaminoveratrole (m. p. 133°)[9] was nitrated by adding the dry powdered material, in small portions, to concentrated nitric acid at 0°, and purifying the crude product by crystallization from alcohol.[10] Yellow needles were obtained, m. p. 199° (literature, 196° and 199°); yield, 60%. Deacetylation of this product was effected by digestion with either concentrated hydrochloric acid,[11] 90% sulfuric acid, or concentrated sodium hydroxide solution. The purified compound melted at 172–174°, as noted above.

3,4-Diaminoveratrole.—A mixture of 1 g. of 3-nitro-4-aminoveratrole, 3 g. of mossy tin, and 40 cc. of 50% hydrochloric acid was heated for an hour at 100°, filtered, the filtrate made alkaline with sodium hydroxide solution, and the mixture extracted with chloroform. These extracts were dried with anhydrous sodium sulfate and the solvent driven off. White plates with a pale violet tinge remained, m. p. 96° (literature,[1] 97°); yield, 60%.

4,5-Diaminoveratrole was secured by reduction of the 5-nitro-4-aminoveratrole with stannous chloride and concentrated hydrochloric acid. It formed white prisms, m. p. 131°, which darkened rapidly in the air, identical with the product obtained by reduction of 4,5-dinitroveratrole.[4]

Picrate.—Yellow needles, from ethyl acetate, m. p. 192°.

Anal. Calcd. for $C_{14}H_{15}O_9N_5$: C, 42.3; H, 3.8; N, 17.6. Found: C, 42.5; H, 4.0; N, 17.7.

Diacetyl Derivative.—White needles, from alcohol or ethyl acetate, m. p. 204–205°.

Anal. Calcd. for $C_{12}H_{16}O_4N_2$: C, 57.1; H, 6.4. Found: C, 57.2; H, 6.5.

Two hours of refluxing of an acetic anhydride solution of this diamine, failed to convert it into the corresponding benzimidazole derivative, the initial compound being recovered unchanged.

2,3-Diphenyl-5,6-dimethoxyquinoxaline, prepared from 3,4-diaminoveratrole and benzil as described below for the preparation of its 6,7-dimethoxy isomer from 4,5-diaminoveratrole; yellow needles, m. p. 139–140°; yield, over 50%.

Anal. Calcd. for $C_{22}H_{18}O_2N_2$: C, 77.2; H. 5.3. Found: C, 77.4; H, 5.4.

(7) Pschorr and Sumuleanu, *Ber.*, **32**, 3407 (1899).
(8) Buck, "Organic Syntheses," **13**, 102 (1933).
(9) Fetscher and Bogert, *J. Org. Chem.*, **4**, 71 (1939).
(10) Simonsen and Rau, *J. Chem. Soc.*, **113**, 27 (1918).
(11) Jones and Robinson, *ibid.*, **111**, 914 (1917).

2,3-Diphenyl-6,7-dimethoxyquinoxaline.—A mixture of equimolecular quantities of 4,5-diaminoveratrole and benzil, dissolved in alcohol, was warmed for ten minutes. Lustrous plates promptly separated. The mixture when cold was further cooled in an ice-pack and filtered. The crude product was crystallized from dilute acetic acid and washed with a small amount of Skellysolve D. Pale yellow plates were thus obtained, m. p. 251–252°; yield, over 50%.

Anal. Calcd. for $C_{22}H_{18}O_2N_2$: C, 77.2; H, 5.3. Found: C, 77.3; H, 5.3.

Summary

1. 3-Nitro-4-aminoveratrole, when subjected to an ordinary Skraup reaction, yields no quinoline derivative, but rearranges to 5-nitro-4-aminoveratrole.

2. The same change can be brought about by digestion of the 3-nitro compound for one and one-half hours at 140–160° with a mixture of phosphoric and glacial acetic acids.

3. It may be explained by the migration of the nitro group, or of one of the methoxyls.

4. A number of veratrole derivatives are described, some new, others old but prepared by new methods.

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Polyisopropylbenzenes. II.[1a] Nitro and Amino Derivatives[1b]

BY A. NEWTON

The nitration of an isopropyl substituted aromatic hydrocarbon has been studied extensively only in the case of *p*-cymene,[2,3] where it was found that, in addition to the main product, 2-nitrocymene, *p*-nitrotoluene was formed in about 8% yield. Many other cases have been reported in which an alkyl group in a polymethylbenzene,[4,5,6] polyethylbenzene,[7] polychlorocymene[8,9] or polychlorocumene[8,9] is replaced by an entering substituent, usually a nitro group. In almost all these cases, however, the replacement was effected by the use of rather severe conditions and led to the formation of a penta- or hexa-substituted benzene. The present study of the nitration of five polyisopropylbenzenes has provided three cases in which, under relatively mild conditions, the main product of mononitration is formed by replacement of an isopropyl group.

The nitrations described in the experimental part may be divided into three types.

Type 1.—Reactions in which the main product was formed by replacement of an isopropyl group by the entering nitro group. Mononitro derivatives from 1,4-diisopropylbenzene with acetyl nitrate contained the replacement product—4-nitroisopropylbenzene (X)—and the normal product—2-nitro-1,4-diisopropylbenzene (XI)—in the mole ratio 1.44 to 1. With mixed acids at 0–6° the ratio was 4.78 to 1. Tetraisopropylbenzene gave only 15% of the normal products—3-nitro-1,2,4,5-tetraisopropylbenzene (XXVII)—and 83% of 5-nitro-1,2,4-triisopropylbenzene at 45°, while at 80° the latter was the sole product. Nitration of 5-amino-1,2,4-triisopropylbenzene (XVIII) gave only 6-nitro-4-amino-1,3-diisopropylbenzene (VIB). In all three cases the condition obtained that a pair of para isopropyl groups was present, one of which occupied a position favorable, with respect to the directing effect of all other groups present, for the entry of the nitro group.

Type 2.—Reactions in which no replacement was observed though the above condition was fulfilled. This type comprises the nitration of 1,2,4-triisopropylbenzene which gave 5-nitro-1,2,4-triisopropylbenzene (XVIIIA) and of 2-amino-1,4-diisopropylbenzene which gave a nitroaminodiisopropylbenzene (XVI). The condition, while probably necessary, is evidently not sufficient.

Type 3.—Reactions in which the condition was not fulfilled and in which no replacement was observed. The reactions were the mononitration of 1,3-di- and 1,3,5-triisopropylbenzenes, the dinitration of the former and the trinitration of the latter and the nitration of 4-amino-1,3-diisopropylbenzene (V) and of 2-amino-1,3,5-triisopropylbenzene (XXIV).

The main relationships among these substances are summarized in Chart I. The constitutions of the derivatives are those that would be expected on the basis of known orientating effects and are confirmed or supported by the following additional evidence. The acetyl and benzoyl derivatives of 4-aminoisopropylbenzene (XII) have melting points corresponding with the known products. Tetraisopropylbenzoquinone (XXIX) was obtained by oxidation of 3-amino-1,2,4,5-tetraisopropylbenzene (XXVIII). Oxidation of 2-nitro- (I), 4-nitro- (II) and 4,6-dinitro-1,3-diisopropylbenzene (III) and of 2-nitro-1,4-diisopropylbenzene gave acids that formed methyl or ethyl esters

(1a) Abstract from a thesis approved by the University of London for the degree of Ph.D.; Paper No. 1, THIS JOURNAL, **65**, 320 (1943).

(1b) Original manuscript received July 6, 1942.

(2) Mann, Montonna and Larian, *Ind. Eng. Chem.*, **28**, 598 (1936).

(3) Kobe and Doumani, *ibid.*, **31**, 257 (1939).

(4) Smith and Harris, THIS JOURNAL, **57**, 1289 (1935).

(5) Tohl and Tripke, *Ber.*, **28**, 2463 (1895).

(6) Smith and Kiess, THIS JOURNAL, **61**, 989 (1939).

(7) Smith and Guss, *ibid.*, **62**, 2635 (1940).

(8) Qvist and Holmberg, *Acta Acad. Aboensis, Math. et Phys.*, **6**, No. 14, 3 (1932); *C. A.*, **27**, 5726 (1933).

(9) Qvist and Salo, *ibid.*, **8**, No. 4, 310 (1934); *C. A.*, **29**, 6884 (1935).