673. *The Nitration of 5-Iodoveratraldehyde.*

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5-Iodoveratraldehyde gave 3,4,5-trinitroveratrole, 5-iodo-6-nitroveratraldehyde, 3-iodo-4,5-dinitroveratrole, 3-iodo-5-nitroveratrole, or mixtures of two or more of these compounds on nitration depending on the experimental conditions. 3-Iodo-4,5-dinitroveratrole and 3-iodo-5-nitroveratrole have been synthesised unambiguously. A paper-chromatographic system suitable for the resolution of compounds of this type is described.

It has been reported[1] that 5-iodoveratraldehyde (I) gave 5-iodo-6-nitroveratraldehyde (II) on nitration. However, no experimental details were given and the product described as (II) was not accurately characterised. Since the authors required reasonable quantities of the pure 6-nitro-derivative for further synthetic work the nitration of 5-iodoveratraldehyde (I) has been reinvestigated; it has been shown that even under relatively mild conditions mixtures were formed, including products which did not contain the aldehyde group. The replacement of formyl groups and halogen atoms during the nitration of aromatic compounds of this type has been reported before.[2]

It was possible to separate the nitro-aldehyde (II) from other products by forming its sodium bisulphite derivative. However, in order to ascertain the approximate percentage conversion (I) ⟶ (II) and to obtain some idea of the number and nature of the by-products, the crude nitration products were subjected to paper chromatography. The use of formamide-treated paper with non-polar developing solvents has recently been described for chromatography of aromatic nitro-compounds,[3] and proved satisfactory for separation of all the compounds encountered in the current investigation.

The nature of the products obtained under various conditions are given in Table 1.

Table 1.

The nitration of 5-iodoveratraldehyde.

Expt.	Reagent	Temp.	Time (min.)	Yield (%) of purified products (II)	(III)	(IV)	(V)
A	HNO_3 (*d* 1·5)–AcOH	55° *	25	24	—	—	50
B	HNO_3 (*d* 1·4)–Ac_2O	60 *	20	43·5	—	22	—
C	HNO_3 (*d* 1·4)	105	90	—	—	—	50
D	HNO_3 (*d* 1·4)–H_2SO_4	40	5	—	53·5	—	—

* The temperature was raised from 5° to the value indicated during the time specified.

The compounds (II), (IV), and (V) were proved to be 5-iodo-6-nitroveratraldehyde, 3-iodo-5-nitroveratrole, and 3-iodo-4,5-dinitroveratrole, respectively, in the following manner. On reduction and deiodination, compound (V) gave 4,5-diaminoveratrole which was characterised as its *NN'*-diacetyl derivative[4] and by conversion into 7,8-dimethoxydibenzo[*a*,*c*]phenazine[5] by condensation with phenanthraquinone. The controlled nitration of 3-iodo-5-nitroveratrole (IV) gave 3-iodo-4,5-dinitroveratrole (V) and further nitration of this gave 3,4,5-trinitroveratrole (III). Finally, the products (IV) and (V) have been prepared from 3-amino-5-nitroveratrole (VI) and 3-amino-4,5-dinitroveratrole (VII), respectively, by replacement of the amino-group by iodine *via* the diazonium salt. Both the amines (VI) and (VII) have been adequately described previously.

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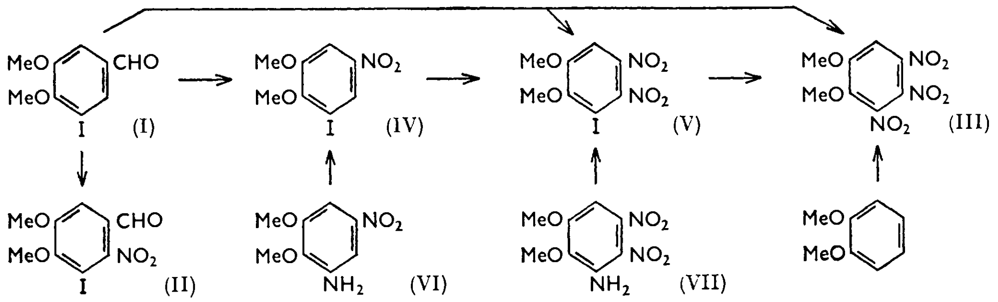
[1] Wittmer and Raiford, *J. Org. Chem.*, 1945, **10**, 527.

[2] (*a*) Parijs, *Rec. Trav. chim.*, 1930, **49**, 17; (*b*) Frisch and Bogert, *J. Org. Chem.*, 1943, **8**, 331; (*c*) Nightingale, *Chem. Rev.*, 1947, **40**, 117.

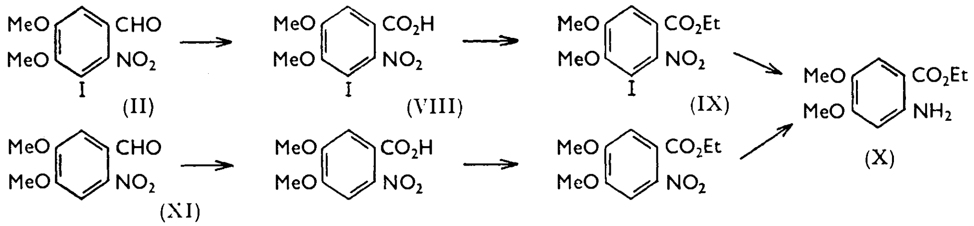
[3] Ettel, Pospisil, and Deyl, *Chem. listy*, 1958, **52**, 623; Colman, *J. Chromatog.*, 1962, **8**, 399.

[4] Frisch, Silverman, and Bogert, *J. Amer. Chem. Soc.*, 1943, **65**, 2432.

[5] Jones and Robinson, *J.*, 1917, **111**, 903.



The nitro-group in the nitro-aldehyde (II) was proved to be in the 6-position and not the alternative 2-position by oxidising it to the corresponding nitro-acid (VIII), which was esterified, reduced, and deiodinated to give ethyl 6-aminoveratrate (X), an authentic sample of which, for comparison, was prepared by a similar route from authentic 6-nitroveratraldehyde (XI).[6]



Jones and Robinson[5] reported that nitration of 5-bromo-6-nitroveratric acid with boiling fuming nitric acid gave 3-bromo-4,5-dinitroveratrole. However, it appears that the iodine atom in the analogous 5-iodo-6-nitroveratric acid (VIII) is more labile since treatment of this acid with boiling fuming nitric acid invariably gave 3,4,5-trinitroveratrole (III), and the dinitro-derivative (V) was never formed.

EXPERIMENTAL

Nitration of 5-Iodoveratraldehyde (I).—(*A*) A solution of 5-iodoveratraldehyde (I) (2·0 g.; prepared from 5-iodovanillin by the method of Domínguez *et al.*[7]) in acetic acid (30 ml.) was added dropwise with stirring to fuming nitric acid (40 ml.) maintained at 5—10° during the addition and then raised to 55° during 25 min. The product was poured into ice-water; the solid obtained was removed and dissolved in dioxan (30 ml.) (this was essential to ensure complete formation of the sodium bisulphite addition product); saturated aqueous sodium hydrogen sulphite (10 ml.) was added to the dioxan solution. After being stirred for 10 min. the mixture was diluted with water (120 ml.), set aside at 4° for 30 min., and filtered. On recrystallisation from ethanol the solid product afforded 3-*iodo*-4,5-*dinitroveratrole* (V) in pale yellow needles (1·2 g.), m. p. 156—157°, raised to 158° by a second treatment with sodium hydrogen sulphite and recrystallisation from benzene-light petroleum (b. p. 80—100°) and chloroform-carbon tetrachloride (Found: C, 27·2; H, 2·1; N, 7·8; I, 35·9. $C_8H_7IN_2O_6$ requires C, 27·2; H, 2·0; N, 7·9; I, 35·8%). Acidification of the filtrate, containing the material soluble in dioxan-aqueous sodium hydrogen sulphite, with concentrated hydrochloric acid gave a precipitate, which afforded very pale yellow needles of 5-*iodo*-6-*nitroveratraldehyde* (II) (0·55 g.), m. p. 153—154° (from ethanol). A sample, m. p. 154—155°, was obtained *via* the sodium bisulphite derivative and recrystallisation from ethanol (Found: C, 32·4; H, 2·4; N, 4·1; I, 37·4. $C_9H_8INO_5$ requires C, 32·1; H, 2·4; N, 4·2; I, 37·65%).

(*B*) A solution of 5-iodoveratraldehyde (I) (3·0 g.) in acetic anhydride (40 ml.) was added dropwise, with stirring, to nitric acid (60 ml.; *d* 1·4) kept at 0—10° during the addition and

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[6] Fetscher and Bogert, *J. Org. Chem.*, 1939, **4**, 71.

[7] Domínguez, Díaz, and González, *Ciencia*, 1955, **15**, 208; *Chem. Abs.*, 1956, **50**, 12,886.

then raised to 60° during 20 min. The mixture was poured into ice–water, and the insoluble products were separated as described in paragraph (*A*). Material insoluble in dioxan–aqueous sodium hydrogen sulphite afforded colourless needles of 3-*iodo*-5-*nitroveratrole* (IV) (0·7 g.), m. p. 116° (from ethanol), raised to 117—118° by further treatment with sodium hydrogen sulphite and recrystallisation from ethanol and carbon tetrachloride–light petroleum (b. p. 80—100°) (Found: C, 30·9; H, 2·7; N, 4·5; I, 40·9. $C_8H_8INO_4$ requires C, 31·1; H, 2·6; N, 4·6; I, 41·1%). 5-Iodo-6-nitroveratraldehyde (II) (1·5 g.), m. p. 154—155°, was obtained from the aqueous-dioxan filtrate by the method described above.

(*C*) A suspension of compound (I) (2·0 g.) in nitric acid (80 ml.; *d* 1·4) (prepared below 10°) was boiled for 1¼ hr., during which the solid dissolved. The crude product, obtained when the mixture was poured into ice–water, was worked up as described in paragraph (*A*). The material which did not form a bisulphite derivative gave 3-iodo-4,5-dinitroveratrole (V) (1·2 g.) in pale yellow needles, m. p. 154° (from ethanol). No 5-iodo-6-nitroveratraldehyde (II) could be isolated from the filtrate by the method described above.

(*D*) 5-Iodoveratraldehyde (I) (0·5 g.) was dissolved in a mixture of nitric acid (10 ml.; *d* 1·4) and concentrated sulphuric acid (10 ml.) at $<10°$. The solution was cautiously heated to 40° and after being kept at 40° for 5 min. was poured into ice–water. Recrystallisation of the solid so obtained from 95% ethanol gave 3,4,5-trinitroveratrole (III) (0·25 g.) in colourless needles (becoming yellow on storage), m. p. 147·5° (undepressed on admixture with a specimen prepared by nitration of veratrole [2b]).

(*E*) Paper chromatography of the crude products obtained when the nitration was carried out with some variations of the conditions specified in Table 1 indicated that : (i) with system A at 80° for 30 min. compound (III) was the major product, contaminated with some (V); (ii) with system B at 80° for 30 min. compounds (II) and (IV) were the main products, together with a small quantity of (V); (iii) with system C, boiling for 1 hr. gave some (II), but (V) was the main product; however, boiling for 2 hr. gave (V) as the main product contaminated with a little (III); with concentrated nitric acid at lower temperatures (35° or 65°) and with reaction times of up to 15 min., the main product was (IV) together with much unchanged starting material; and (iv) fuming nitric acid alone gave mainly product (V) at 5° and (III) at 45°.

Nitration of 3-*Iodo*-5-*nitroveratrole* (IV).—A suspension of 3-iodo-5-nitroveratrole (IV) (60 mg.) in nitric acid (20 ml.; *d* 1·4) was boiled for 15 min. Recrystallisation of the product (obtained by pouring the mixture into ice–water) from 95% ethanol gave 3-iodo-4,5-dinitroveratrole (V) (30 mg.), m. p. and mixed m. p. 152°.

Nitration of 3-*Iodo*-4,5-*dinitroveratrole* (V).—A suspension of 3-iodo-4,5-dinitroveratrole (V) (0·25 g.) in nitric acid (10 ml.; *d* 1·4) and concentrated sulphuric acid (10 ml.), prepared at 10°, was heated to 55° during 15 min., by which time dissolution was complete. The mixture was poured into ice–water; the solid was recrystallised from 95% ethanol and gave 3,4,5-trinitroveratrole (III) (0·12 g.), m. p. 145°, undepressed on admixture with an authentic specimen.[2b]

Reduction and Deiodination of 3-*Iodo*-4,5-*dinitroveratrole* (V).—A solution of the dinitro-derivative (V) (0·4 g.) in ethanol (5 ml.) and acetic acid (10 ml.) was heated to the b. p. and zinc dust (2·0 g.) was cautiously added to the stirred, boiling solution. After boiling for 30 min., the mixture was filtered and water (20 ml.) and ether (50 ml.) were added to the filtrate which was then made strongly alkaline with 40% sodium hydroxide solution with stirring under nitrogen. The ether layer was removed, dried (K_2CO_3), and divided into two portions. The larger portion (about ⅔ of the total) gave, on evaporation to dryness under nitrogen, a brown solid, which was dissolved in acetic anhydride (5 ml.). This solution was boiled for 5 min. and poured into water; the aqueous product was neutralised with solid sodium hydrogen carbonate and extracted with ether. Recrystallisation of the product [obtained by evaporation of the dried (Na_2SO_4) ethereal extract] from ethanol gave colourless needles of 4,5-diacetamido-veratrole (0·15 g.), m. p. 203—204° (Found: C, 57·1; H, 6·4. Calc. for $C_{12}H_{16}N_2O_4$: C, 57·1; H, 6·4%). Frisch *et al.*[4] report m. p. 204—205°. A saturated solution of phenanthraquinone in ethanol was added to the smaller portion of the ethereal solution of the zinc–acetic acid reduction product. The yellow solid that was produced after the mixture had been left at room temperature for several hours was recrystallised from ethanol, to give 7,8-dimethoxy-dibenzo[*a,c*]phenazine in bright yellow needles, m. p. 262° (Found: C, 77·3; H, 5·1. Calc. for $C_{22}H_{16}N_2O_2$: C, 77·6; H, 4·75%). Jones and Robinson report 260° as the m. p. of this compound prepared by a somewhat different route.[5]

3-*Iodo*-5-*nitroveratrole* (IV).—A suspension of 3-amino-5-nitroveratrole (VI)[8] (0·4 g.) in concentrated sulphuric acid (0·6 g.) and water (10 ml.) was diazotised below 5° with sodium nitrite (0·154 g.) in water (3 ml.). After being stirred at 5° for 10 min. the solution was filtered and potassium iodide (0·36 g.) in water (3 ml.) was added with stirring at this temperature. The mixture was stirred at room temperature for 2 hr. during which a brown flocculent precipitate settled; the precipitate was removed and gave 3-iodo-5-nitroveratrole (IV) (0·32 g.) in colourless needles, m. p. 117° after repeated recrystallisation from ethanol. This product was identical with that obtained by nitration of 5-iodoveratraldehyde (I).

3-*Iodo*-4,5-*dinitroveratrole* (V).—A solution of 3-amino-4,5-dinitroveratrole (VII)[8] (0·065 g.) in warm glacial acetic acid (8 ml.) was added dropwise, with stirring, to a mixture of water (3 ml.) and concentrated sulphuric acid (0·08 g.). The resulting suspension of the amine sulphate was diazotised below 10° with sodium nitrite (0·019 g.) in water (2 ml.). After being stirred for 10 min. at 5° the solution was filtered and potassium iodide (0·045 g.) in water (3 ml.) added, with stirring at 5°. The mixture was stirred at room temperature for 45 min.; water (5 ml.) was added and, after cooling to 5°, the suspension was filtered. The product, a brown solid, gave, on recrystallisation from ethanol, colourless needles of 3-iodo-4,5-dinitroveratrole (V) (0·03 g), m. p. 151°, identical with that obtained by nitration of 5-iodoveratraldehyde (I).

Proof of Structure of 5-*Iodo*-6-*nitroveratraldehyde.*—5-*Iodo*-6-*nitroveratric acid* (VIII). A solution of 5-iodo-6-nitroveratraldehyde (II) (0·4 g.) in 0·5N-sodium hydroxide (25 ml.) was oxidised with potassium permanganate (1·5 g.) near the b. p. for 40 min. The mixture was filtered, cooled, and acidified with sulphuric acid. The crude acid which separated was recrystallised from aqueous ethanol and gave 5-*iodo*-6-*nitroveratric acid* (VIII) (0·31 g.) in colourless needles, m. p. 223° (Found: C, 30·8; H, 2·3; N, 4·2; I, 35·8. $C_9H_8INO_6$ requires C, 30·6; H, 2·3; N, 4·0; I, 35·95%). Wittmer and Raiford[1] described this acid as crystallising from acetic acid in brown plates and needles, m. p. 205—206°.

Ethyl 5-*iodo*-6-*nitroveratrate* (IX). Thionyl chloride (15 ml.) was added to a solution of the acid (VIII) (0·31 g.) in chloroform (10 ml.), and the mixture was boiled for 5 min. The crude acid chloride obtained on evaporation to dryness *in vacuo* was dissolved in ethanol (*ca.* 10 ml.). After 5 min. refluxing the excess of ethanol was removed by evaporation and the yellow crystalline residue recrystallised from aqueous ethanol, affording *ethyl* 5-*iodo*-6-*nitroveratrate* (IX) (0·3 g.) in very pale yellow needles, m. p. 112—113° (Found: C, 34·7; H, 3·3; N, 3·6; I, 33·4. $C_{11}H_{12}INO_6$ requires C, 34·7; H, 3·2; N, 3·7; I, 33·3%).

Ethyl 6-*Aminoveratrate* (X). Zinc dust (1·2 g.) was added portionwise during 30 min. to a stirred solution of ethyl 5-iodo-6-nitroveratrate (IX) (0·3 g.) in boiling acetic acid (10 ml.). The mixture was filtered hot and the residual zinc washed with hot water (5 ml.). The filtrate was cooled; water (30 ml.) and ether (100 ml.) were added and the aqueous layer was made stongly alkaline with 40% aqueous sodium hydroxide. The residue obtained on concentration of the dried (Na_2SO_4) ethereal layer was recrystallised from light petroleum (b. p. 80—100°), to give colourless prisms of ethyl 6-aminoveratrate (X) (0·11 g.), m. p. 87—88°. This substance was identical with a specimen (m. p. 87—88°) prepared from 6-nitroveratraldehyde (XI) by the method of Fetscher and Bogert.[6]

Nitration of 5-*Iodo*-6-*nitroveratric Acid* (VIII).—5-Iodo-6-nitroveratric acid (VIII) (0·2 g.) was added to fuming nitric acid (20 ml.) at 5° and the suspension slowly heated to the b. p. After being boiled for 5 min. the solution was poured into ice–water. The solid product gave colourless needles (0·08 g.), m. p. and mixed m. p. 146° (from ethanol), of 3,4,5-trinitroveratrole (III).

TABLE 2.

R_F values of some nitro- and iodo-derivatives of veratrole.

I	II	III	IV	V	XI	4,5-Dinitroveratrole	5-Nitroveratraldehyde
0·80	0·45	0·25	0·85	0·42	0·22	0·15	0·35

Paper Chromatography. The R_F values of a number of nitro- and iodo-derivatives of veratrole and veratraldehyde are given in Table 2. The following notes apply.

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[8] Slotta and Lauersen, *J. prakt. Chem.*, 1934, **139**, 220; Pschorr and Sumuleanu, *Ber.*, 1899, **32**, 3405; Kühn, *Ber.*, 1895, **28**, 809; Gibson, Simonsen, and Rau, *J.*, 1917, **111**, 69.

Radial development with light petroleum (B.D.H. " AnalaR," b. p. 80—100°) on formamide-treated paper was used, the general procedure being as described for indole derivatives by Heacock *et al.*[9] (time for development ~30 min.).

If the chromatographic paper was impregnated with formamide containing sodium hydrogen sulphite, the rate of migration of the aldehydes (I), (II), and (XI), and 5-nitroveratraldehyde was considerably arrested, and only streaky zones in the R_F range 0·0—~0·1 were observed on the developed chromatograms; this was presumably due to formation of the bisulphite derivative of the aldehyde. The R_F values of the other nitro-compounds were not affected by the presence of sodium hydrogen sulphite in the formamide.

All the compounds could be located on the developed chromatograms by viewing them in short-wave ultraviolet light. The nitro-aldehyde (XI) was coloured and was therefore self-indicating; the aldehydes (I), (II), and (XI), and 5-nitroveratraldehyde gave yellow to red-brown colours with 2,4-dinitrophenylhydrazine. In order to locate these four with the 2,4-dinitrophenylhydrazine reagent on the papers impregnated with sodium hydrogen sulphite, it was necessary to expose the developed chromatograms to hydrogen chloride fumes for 5 min. before spraying, in order to decompose the addition products.

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[9] Heacock and Mahon, *Canad. J. Biochem. Physiol.*, 1960, **38**, 1500; Heacock, Mahon, and Scott, *Canad. J. Chem.*, 1961, **39**, 231.