768. *Nitration of 2-Acetamido-5-methoxytoluene.*

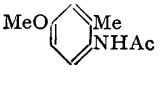
By J. MacMillan.

The preparation is described of the 3- and 4-nitro-derivatives of 2-acetamido-5-methoxytoluene. The corresponding amines, *N*-acetylanthranilic acids, and anthranilic acids have also been prepared.

Although direct comparison has confirmed the 3-nitro-structure of the nitroamine described by Dewar (*J.*, 1944, 619), the acetamido-compound, acetylanthranilic acid, and anthranilic acid to which he assigned the 3-nitro-structures have been shown to be the 4-nitro-isomers. The structures of an identical series of compounds described by Elderfield *et al.* (*J. Org. Chem.*, 1947, **12**, 405) must be similarly modified.

Mononitration of 2-acetamido-5-methoxytoluene (I) was first described by Dewar (*J.*, 1944, 619). Using nitric acid (*d* 1·5) in acetic acid below 0°, he obtained, in 70% yield, a mononitro-derivative, $C_{10}H_{12}O_4N_2$, m. p. 173—176°, raised to 187° by repeated crystallisation. The 3-nitro-structure (II; R = Ac) was assigned to this compound since hydrolysis with hydrochloric acid afforded an amine, $C_8H_{10}O_3N_2$, m. p. 134°, characterised as the *o*-nitro-amine (II; R = H) by reduction and phenanthrazine formation. Subsequently, Elderfield, Williamson, Gensler, and Kremer (*J. Org. Chem.*, 1947, **12**, 405) reported that they were unable to reproduce the high yield of (II; R = Ac) under Dewar's conditions. However, by lowering the temperature of nitration to −5°, they obtained a 65% yield of the pure mononitro-derivative, m. p. 187°, which they assumed was the 3-nitro-compound (II; R = Ac) apparently on the basis of Dewar's orientation. There

can be little doubt that the mononitro-2-acetamido-5-methoxytoluenes, described by Dewar and by Elderfield *et al.*, are identical since the series of compounds independently prepared from them possessed melting points in very close agreement.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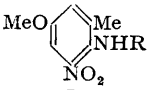
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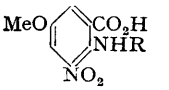
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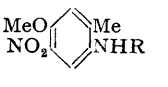
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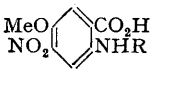
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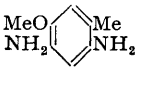
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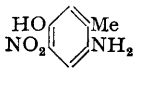
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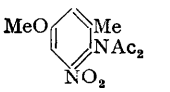
(VIII)

On repetition of the nitration of 2-acetamido-5-methoxytoluene using the method of Elderfield *et al.*, the expected mononitro-derivative (A), $C_{10}H_{12}O_4N_2$, m. p. 187°, was obtained in consistently high yield. However, hydrolysis with hydrochloric acid gave an amine (B), $C_8H_{10}O_3N_2$, m. p. 77—78°, and not the amine, m. p. 134°, described by Dewar. The amine (B) was readily re-acetylated to (A) and, on reduction, furnished a diamine (C), $C_8H_{12}ON_2$, m. p. 100°, which was not an *o*-diamine since it failed to give quinoxaline derivatives or yield a triazole on diazotisation. The close agreement in melting point between (C) and a diamine, m. p. 101°, described as 2 : 4-diamino-5-methoxytoluene (VI) by Bogacheva (*J. Appl. Chem. U.S.S.R.*, 1940, **13**, 1606) suggested that the compounds (A) and (B) were the 4-nitro-isomers (IV; R = Ac and R = H respectively). This was supported by the ease with which the methoxyl group in (A) was hydrolysed by 70% sulphuric acid, to yield an aminophenol (D), $C_7H_8O_3N_2$ (cf. Haworth and Lapworth, *J.*, 1923, **123**, 2982). Finally, the orientation of this series was firmly established by deamination of amine (B), *via* the diazonium salt, to 3-methoxy-4-nitrotoluene, identical with an authentic specimen. Compounds (A), (B), (C), and (D) therefore possess the structures (IV; R = Ac), (IV; R = H), (VI), and (VII) respectively. Accordingly, it is concluded that nitration of 2-acetamido-5-methoxytoluene, under the conditions specified by Elderfield *et al.*, affords the 4-nitro-derivative (IV; R = Ac) and not the 3-nitro-isomer (II; R = Ac) as stated by these authors.

Under Dewar's conditions of nitration, 2-acetamido-5-methoxytoluene gave a complex mixture. The main product was the 4-nitro-derivative, but all three possible dinitro-compounds were also isolated. Despite careful fractionation by crystallisation and chromatography, no trace of the 3-nitro-derivative (II; R = Ac) could be detected. The dinitro-compound, m. p. 249—251°, was shown to be the 3 : 4-dinitro-derivative by reduction and quinoxaline formation; the other two isomers which are formed in low yield were not oriented. Similar results were obtained when nitration was carried out at 20°; in this case the 3 : 4-dinitro-compound was the main product.

A surprising feature of the above results was the complete absence of the 3-nitro-isomer (II; R = Ac) although position 3 in (I) is activated by the *o*-acetamido-group. The weak but definite basic properties shown by (I) suggested that this might be due to salt formation in the acidic nitrating medium (cf. Dadswell and Kenner, *J.*, 1927, 1102). To reduce this possibility, nitration of (I) was conducted in chloroform solution. Then, at −5° to −10°, the 3-nitro-derivative (II; R = Ac), m. p. 173—174°, was obtained in 50% yield together with the 4-nitro-isomer (IV; R = Ac) (40%). The former was oriented by hydrolysis to the corresponding amine (II; R = H), m. p. 134°, which afforded a phenanthrazine after reduction. Separation of the two isomers (II and IV; R = Ac) by fractional crystallisation was difficult and was more conveniently effected by hydrolysis of the mixture to the corresponding amines which were readily separated by their widely differing solubility in mineral acid.

The 3- and the 4-nitro-amine (II and IV; R = H) differed in their ease of acetylation. With acetic anhydride in pyridine at room temperature, the 4-nitro-compound readily afforded (IV; R = Ac) while the 3-nitro-amine was unaffected. Acetylation of the latter was accomplished by acetic anhydride and acetic acid under reflux. Short heating gave

a mixture of (II; R = Ac) and the diacetyl compound (VIII), but the latter was the sole product on further heating. The constitution of (VIII) was established by hydrolysis to, and formation from, the monoacetyl compound (II; R = Ac). These observations are in accord with the behaviour of other *o*-nitro-amines towards acylating agents (Bell, *J.*, 1929, 2787).

Through the kindness of Professor M. J. S. Dewar, who is warmly thanked for placing his specimens at the author's disposal, it was possible to compare directly his amine and acetamide with their counterparts of established structure in the 3- and 4-nitro-series. His acetamido-compound was the 4-nitro-isomer (IV; R = Ac) whilst the 3-nitro-structure (II; R = H) of his nitro-amine was confirmed. This suggested that Dewar's crude product, m. p. 173—176°, was a mixture of the 3- and 4-nitro-isomers from which the latter was obtained pure only after repeated crystallisation.

Next, the 3- and 4-nitro-isomers (II and IV; R = Ac) were separately oxidised to the *N*-acetylanthranilic acids (III and V; R = Ac) respectively, and the latter compounds hydrolysed to the corresponding anthranilic acids (III and V; R = H). As might be expected, oxidation of (IV; R = Ac) took place more readily than that of (II; R = Ac). The 4-nitroanthranilic acid (V; R = H) was obtained in interconvertible very dark red and brick-red forms, both of which were unexpectedly deeper in colour than the 3-nitro-isomer (III; R = H). The structure (V; R = H) for the dimorphous anthranilic acid was, however, confirmed by deamination to 3-methoxy-4-nitrobenzoic acid.

The anthranilic acid and *N*-acetyl derivative, described by Dewar as the 3-nitro-compounds (III; R = H and Ac), were shown by direct comparison to be identical with the acids (V; R = H and Ac). Therefore the nitro-4-chloro-6-methoxyquinazoline and intermediate compounds prepared by Dewar (*loc. cit.*) are derived from 2-acetamido-5-methoxy-4-nitrotoluene (IV; R = Ac) and not from the 3-nitro-isomer (II; R = Ac).

The same considerations almost certainly apply to an identical series of compounds independently described by Elderfield *et al.* (*loc. cit.*). There seems little doubt that the amino-6-methoxyquinazoline and derivatives described by these authors possess the 7-amino-structure and therefore are not quinazoline analogues of plasmoquine.

Experimental

M. p.s are uncorrected. Microanalyses were carried out by Drs. Weiler and Strauss, Oxford, and by Mr. W. Brown.

2-Acetamido-5-methoxytoluene, m. p. 134°, prepared from 3-methoxy-6-nitrotoluene (Cook, Dickson, Ellis and Loudon, *J.*, 1949, 1074) by reduction and acetylation, readily dissolved in 4N-hydrochloric acid. From this solution it was precipitated by addition of water, redissolving on addition of concentrated hydrochloric acid. Treatment of its benzene solution with hydrogen chloride gave an air-sensitive hydrochloride.

Nitration of 2-Acetamido-5-methoxytoluene (I).—(*a*) The procedure of Elderfield *et al.* (*loc. cit.*) gave *2-acetamido-5-methoxy-4-nitrotoluene* (IV; R = Ac), long pale yellow needles (65—70%), m. p. 187°, from ethyl acetate (Found: C, 53·6; H, 5·5; N, 12·5. $C_{10}H_{12}O_4N_2$ requires C, 53·6; H, 5·4; N, 12·5%). It was identical (mixed m. p., infra-red spectrum, and dielectric constant) with the nitro-2-acetamido-5-methoxytoluene described by Dewar (*loc. cit.*).

(*b*) The crude dried product (8 g.), m. p. 125—190°, obtained by nitration of 2-acetamido-5-methoxytoluene (6·7 g.) under Dewar's conditions (*loc. cit.*), was finely powdered and extracted with cold chloroform (150 ml.). The chloroform-insoluble fraction crystallised from acetic acid in small yellow needles (1·1 g.), m. p. 249—251° (decomp.), of *2-acetamido-5-methoxy-3 : 4-dinitrotoluene* (Found: C, 44·8; H, 4·2; N, 16·0. $C_{10}H_{11}O_6N_3$ requires C, 44·6; H, 4·1; N, 15·6%). The *quinoxaline*, prepared by reaction of the crude, Raney nickel reduction product of the 3 : 4-dinitro-compound with benzil, crystallised in yellow needles, m. p. 229—230°, from methanol (Found: C, 75·1; H, 5·8; N, 11·1. $C_{24}H_{21}O_2N_3$ requires C, 75·2; H, 5·5; N, 11·0%).

Hydrolysis of the 3 : 4-dinitro-compound (1·0 g.) with concentrated hydrochloric acid (3 ml.) in methanol (12 ml.) by boiling under reflux (12 hours) gave *2-amino-5-methoxy-3 : 4-dinitrotoluene*, long red needles, m. p. 174—175°, from benzene (Found: C, 42·1; H, 4·1; N, 18·2. $C_8H_9O_5N_3$ requires C, 42·3; H, 4·0; N, 18·5%).

The chloroform-soluble fraction of the crude nitration product partly crystallised from ethyl acetate in long pale yellow needles (2·3 g.), m. p. and mixed m. p. with 2-acetamido-5-methoxy-

4-nitrotoluene, obtained as in (*a*), 187°. Concentration of the ethyl acetate mother-liquors gave 1·2 g. of material, m. p. 140—160°, which was separated into a benzene-insoluble and a benzene-soluble fraction. Chromatography of the latter in benzene (100 ml.) on alumina (pH 4; 1·0 × 12·5 cm.), activated at 250°/15 mm. for 3 hours, and elution with benzene gave (i) the 3 : 4-dinitro-compound (5 mg.), m. p. 249—251° (decomp.), (ii) 2-*acetamido-5-methoxy*-4(*or* 3) : 6-*dinitrotoluene*, pale yellow needles (65 mg.), m. p. 166—168°, from methanol (Found: C, 45·0; H, 4·2; N, 15·6. $C_{10}H_{11}O_6N_3$ requires C, 44·7; H, 4·1; N, 15·6%), and (iii) 2-*acetamido-5-methoxy*-3(*or* 4) : 6-*dinitrotoluene*, yellow needles (50 mg.), m. p. 232—234°, from acetic acid, depressed below 218° on admixture with fraction (i) (Found: C, 44·6; H, 4·1; N, 16·3%). From the benzene-insoluble fraction there were isolated, by successive crystallisation from acetic acid, ethyl acetate, and methanol, the 3 : 4-dinitro- (1 mg.), m. p. 249—251° (decomp.), the 4(or 3) : 6-dinitro- (15 mg.), m. p. 166—168°, and the 4-nitro-derivative (2 mg.), m. p. 187°.

(*c*) Nitration was effected as in (*a*), but with the temperature kept at 20° during the addition of 2-acetamido-5-methoxytoluene (6·7 g.) and for a further ½ hour. The crystalline material which separated at room temperature overnight was collected and recrystallised from acetic acid in small yellow needles (2·4 g.) of the 3 : 4-dinitro-compound, m. p. 249—251° (decomp.). Dilution of the reaction mother-liquors and fractional crystallisation of the resultant precipitate from methanol yielded (i) the 3 : 4-dinitro- (500 mg.), m. p. 249—251° (decomp.), (ii) the 4-nitro- (1·3 g.), m. p. 187°, (iii) the 4(or 3) : 6-dinitro- (500 mg.), m. p. 166—168°, and (iv) the 3(or 4) : 6-dinitro-compound (10 mg.), m. p. 232—234°.

(*d*) A solution of 2-acetamido-5-methoxytoluene (5 g.) in chloroform (30 ml.) was kept between −5° and −10° while nitric acid (8·5 ml.; *d* 1·42) was added during 1½ hours. After a further 1½ hours' stirring at −5° to −10°, water (50 ml.) was added and the solid (A) which separated on stirring was collected. The chloroform layer, after separation from the aqueous layer, was again washed with water (50 ml.). Overnight, more solid (B) separated. Finally, concentration of the chloroform layer after further washing yielded a third fraction (C).

Fraction (A) consisted of the 4-nitro-compound (IV; R = Ac)(1·1 g.), m. p. 187°. Crystallisation of fraction (B) from ethyl acetate afforded 2-*acetamido-5-methoxy-3-nitrotoluene* (II; R = Ac), in long pale yellow needles (1·35 g.), m. p. 173—174° (Found: C, 53·75; H, 5·3; N, 12·4%).

The materials recovered from the mother-liquors of fractions (A) and (B) were combined with fraction (C) and hydrolysed by concentrated hydrochloric acid (6 ml.) and methanol (25 ml.) under reflux for 8 hours. On cooling, ruby-red prisms (1·4 g.), m. p. 134°, were obtained of 2-amino-5-methoxy-3-nitrotoluene (see below). Basification of the mother-liquors with sodium carbonate, after removal of the methanol, gave 2-amino-5-methoxy-4-nitrotoluene (0·6 g.), m. p. 77—78°, described below.

2-*Amino-5-methoxy-4-nitrotoluene* (IV; R = H).—2-Acetamido-5-methoxy-4-nitrotoluene (2·25 g.), in methanol (22·5 ml.), was heated under reflux for 6 hours with 2N-hydrochloric acid (22·5 ml.). The *hydrochloride* which separated on cooling crystallised from 2N-hydrochloric acid in straw-coloured needles (2·0 g.), decomp. >200° (Found: C, 43·85; H, 4·9; N, 13·0; Cl, 16·35. $C_8H_{11}O_3N_2Cl$ requires C, 43·9; H, 5·0; N, 12·8; Cl, 16·3%). The free *amine*, obtained by decomposition of the hydrochloride with aqueous sodium carbonate, was combined with a small quantity recovered from the basified reaction mother-liquors and crystallised from benzene in deep red prisms (1·8 g.), m. p. 77—78° (Found: C, 52·5; H, 5·6; N, 15·1. $C_8H_{10}O_3N_2$ requires C, 52·7; H, 5·5; N, 15·4%). Treatment of the amine in pyridine with acetic anhydride at room temperature overnight gave 2-acetamido-5-methoxy-4-nitrotoluene, m. p. 187°, identified by mixed m. p. and infra-red spectrum.

Deamination was effected by addition of cold hypophosphorous acid (10 ml.) to a filtered and ice-cold diazo-solution of the amine (400 mg.). After 2 days at 0°, the precipitate was collected and crystallised from light petroleum (b. p. 40—60°) in fawn-coloured needles, m. p. 58—59°, undepressed on admixture with 3-methoxy-4-nitrotoluene, obtained by methylation of 3-hydroxy-4-nitrotoluene in methanol with diazomethane.

2-*Amino-5-hydroxy-4-nitrotoluene* (VII).—2-Acetamido-5-methoxy-4-nitrotoluene (500 mg.) was heated under reflux for 1 minute with 70% sulphuric acid (2 ml.). The diluted red-brown solution was adjusted to pH 7·5 and the resultant *aminophenol* crystallised from benzene in dark red prisms, m. p. 126—127° (Found: C, 50·1; H, 4·75; N, 16·4. $C_7H_8O_3N_2$ requires C, 50·0; H, 4·7; N, 16·7%); the *diacetyl* derivative formed yellow needles (from ethyl acetate), m. p. 187°, depressed below 160° on admixture with 2-acetamido-5-methoxy-4-nitrotoluene (Found: C, 52·4; H, 4·8; N, 11·1. $C_{11}H_{12}O_5N_2$ requires C, 52·4; H, 4·8; N, 11·1%).

2 : 4-*Diamino-5-methoxytoluene* (VI).—2-Amino-5-methoxy-4-nitrotoluene (600 mg.) in

methanol (50 ml.) was hydrogenated with Raney nickel (1·0 g.) at room temperature and pressure. Removal of the catalyst and concentration gave a violet-tinged gum from which the *diamine* was obtained as colourless needles, m. p. 100°, from benzene (charcoal) (Found: C, 63·1; H, 8·1; N, 18·5. $C_8H_{12}ON_2$ requires C, 63·1; H, 7·9; N, 18·4%); the *diacetyl* derivative crystallised in colourless needles, m. p. 215—217°, from aqueous methanol (Found: C, 56·3, 56·8; H, 6·9, 6·9; N, 11·4, 11·0. $C_{12}H_{16}O_3N_2,H_2O$ requires C, 56·7; H, 7·1; N, 11·0%). The diacetyl compound, m. p. 215—217°, was also prepared by acetylation of 2-*acetamido*-4-*amino*-5-*methoxytoluene*, colourless needles, m. p. 177—178°, from ethanol (Found: C, 62·0; H, 7·2; N, 14·6. $C_{10}H_{14}O_2N_2$ requires C, 61·85; H, 7·2; N, 14·4%), which in turn was prepared by reduction of 2-acetamido-5-methoxy-4-nitrotoluene in ethanol with Raney nickel.

2-*Amino*-5-*methoxy*-3-*nitrotoluene* (II; R = H).—2-Acetamido-5-methoxy-3-nitrotoluene (500 mg.) in methanol (6 ml.) was heated under reflux for 8 hours with concentrated hydrochloric acid (2 ml.). The 3-*nitro-amine*, which separated on cooling, crystallised from ethyl acetate in ruby-red prisms (370 mg.), m. p. 134°, undepressed on admixture with a sample of the amine, m. p. 134°, described by Dewar (*loc. cit.*) (Found: C, 52·9; H, 5·4; N, 15·2. Calc. for $C_8H_{10}O_3N_2$: C, 52·7; H, 5·5; N, 15·4%). The *phenanthrazine*, obtained by reduction of the nitro-amine with Raney nickel followed by reaction with phenanthraquinone, crystallised from 2-methoxyethanol in fawn-coloured needles, m. p. and mixed m. p. with a sample of Dewar's phenanthrazine, 218—219° (Found: C, 81·8; H, 5·3; N, 8·7. Calc. for $C_{22}H_{16}ON_2$: C, 81·5; H, 5·0; N, 8·6%).

Acetylation of 2-*Amino*-5-*methoxy*-3-*nitrotoluene*.—(*a*) The amine (100 mg.) in acetic acid (0·3 ml.) was heated under reflux for ½ hour with acetic anhydride (0·2 ml.). Dilution of the mixture and crystallisation of the product from ethyl acetate afforded 2-acetamido-5-methoxy-3-nitrotoluene, m. p. 173—174°. The solid recovered from the ethyl acetate mother-liquors crystallised from benzene–light petroleum (1 : 1) in pale yellow needles of 2-N*N*-*diacetylamino*-5-*methoxy*-3-*nitrotoluene*, m. p. 88—89° (Found: C, 54·1; H, 5·4; N, 10·5. $C_{12}H_{14}O_5N_2$ requires C, 54·1; H, 5·3; N, 10·5%). Chromatography of the diacetyl derivative in benzene on alumina (pH 4) and elution of the yellow band of general absorption with benzene gave 2-acetamido-5-methoxy-3-nitrotoluene, m. p. and mixed m. p. 173—174°.

(*b*) When heating was continued for 4 hours, the diacetyl compound, m. p. 88—89°, was the sole product. It was also obtained from 2-acetamido-5-methoxy-3-nitrotoluene under these conditions.

N-*Acetyl*-5-*methoxy*-4-*nitroanthranilic Acid* (V; R = Ac).—Finely powdered 2-acetamido-5-methoxy-4-nitrotoluene (400 mg.), suspended in water (30 ml.) containing magnesium sulphate (600 mg. of heptahydrate), was oxidised with potassium permanganate (850 mg.) at 70—80° as described by Dewar (*loc. cit.*). The N-*acetyl-acid* crystallised from acetic acid in small chrome-yellow needles (330 mg.), m. p. 248—250° (decomp.) (Found: C, 47·2; H, 4·1; N, 11·0%; equiv., 266. $C_9H_9O_4N_2{\cdot}CO_2H$ requires C, 47·2; H, 4·0; N, 11·0%; equiv., 254).

N-*Acetyl*-5-*methoxy*-3-*nitroanthranilic Acid* (III; R = Ac).—2-Acetamido-5-methoxy-3-nitrotoluene (360 mg.) was oxidised as above except that the suspension was heated under reflux for 5 hours. The N-*acetyl-acid*, recovered from a sodium hydrogen carbonate extract of the crude product, crystallised from water containing acetic acid in orange needles (50 mg.), m. p. 206—208° (decomp.) (Found: C, 47·8; H, 4·0; N, 11·3%). Starting material (200 mg.) was recovered unchanged.

5-*Methoxy*-4-*nitroanthranilic Acid* (V; R = H).—*N*-Acetyl-4-nitroanthranilic acid (80 mg.) was hydrolysed as described by Dewar (*loc. cit.*). The *anthranilic acid* crystallised from methanol containing a little water in long, dark red needles and from water containing a little methanol in brick-red needles. Each form was readily converted into the other by crystallisation from the appropriate solvent with seeding. The darker form was converted into the lighter at 170—180°; both melted at 220—222° (decomp.) (Found: C, 45·7; H, 3·8; N, 13·5. $C_8H_8O_5N_2$ requires C, 45·3; H, 3·8; N, 13·2%). The red-black modification was identical (mixed m. p. and infra-red spectrum) with the anthranilic acid described by Dewar.

Deamination by treatment of a diazo-solution of the anthranilic acid with hypophosphorous acid afforded 3-methoxy-4-nitrobenzoic acid, m. p. 227—229°, identical (mixed m. p. and infra-red spectrum) with an authentic specimen prepared by oxidation of 3-methoxy-4-nitrotoluene.

5-*Methoxy*-3-*nitroanthranilic Acid* (III; R = H).—*N*-Acetyl-3-nitroanthranilic acid (70 mg.), in methanol (2 ml.), was heated under reflux for ¼ hour with concentrated hydrochloric acid (2 ml.). The *amino-acid*, recovered from a bicarbonate extract of the resultant solid, crystallised from methanol in scarlet needles, m. p. 240—242° (Found: C, 45·5; H, 3·6; N, 13·25%). The neutral material crystallised from methanol in fine red needles, m. p. 141—

142°. It contained nitrogen and a carbonyl group (infra-red) but there was insufficient for characterisation.

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