50. *Some Bromine-substituted Derivatives of 8-Hydroxyquinoline.*

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3-Bromo-8-hydroxyquinoline can be prepared from 8-amino-3-bromoquinoline by vigorous hydrolysis, but not by the Bucherer reaction or through its diazonium salt. It gave 3-bromo-8-methoxyquinoline on methylation and 3 : 5 : 7-tribromo-8-hydroxyquinoline with phosphorus oxybromide.

A mixture of 4-bromo-8-methoxy- and 4-bromo-8-hydroxy-quinaldinic acid resulted from the action of phosphorus oxybromide on 8-methoxy-4-hydroxyquinaldinic acid (improved synthesis). From the former were prepared 4-bromo-8-methoxy-, 4-bromo-8-hydroxy-, and 4 : 5 : 7-tribromo-8-hydroxy-quinoline. 4-Bromo-8-hydroxyquinaldinic acid was also prepared by the action of phosphorus oxybromide on 4 : 8-dihydroxyquinaldinic acid.

A Skraup reaction on 4-bromo-2-methoxyaniline (improved synthesis) gave 6-bromo-8-methoxyquinoline from which 6-bromo- and 5 : 6 : 7-tribromo-8-hydroxyquinoline were prepared.

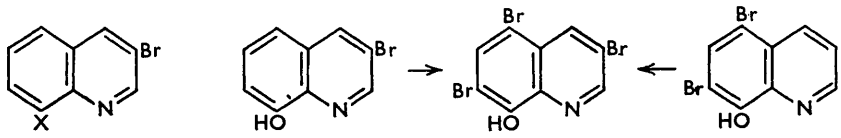
Substitution products of 8-hydroxyquinoline ("Oxine") have frequently been investigated as analytical reagents for metals, and useful differences in behaviour from the parent substance have been noted for 5 : 7-dihalogen substituted oxines in precipitation reactions,[1,2] in absorptiometry,[2,3] and in solvent extraction.[2,4,5] The new bromine-substituted oxines described below were synthesised as reference compounds in connection with another problem [6] and as part of a general study of oxine and its derivatives. They all resemble oxine in giving insoluble complexes with a variety of metals, and a deep green colour with traces of ferric iron: their potentialities as analytical reagents will be reported elsewhere. Indirect methods of synthesis had to be employed in certain cases because the halogenation of 8-hydroxy(or methoxy)-quinoline invariably leads to substitution in the 5- or the 5 : 7-positions, and the diazonium reaction can only exceptionally be used to introduce an 8-hydroxy-group in the quinoline series.

3-Bromo-8-hydroxyquinoline.—Although 3-chloro-8-methoxy-2 : 5-dimethylquinoline can be obtained from 2-methoxy-5-methylaniline and α-chlorocrotonaldehyde,[7] the

[1] Berg and Kustenmacher, *Z. anorg. Chem.*, 1932, **204**, 215; cf. Hollingshead, "Oxine and its Derivatives," Butterworths Scientific Publ., London, 1956, Vol. III.
[2] Moeller and Cohen, *Analyt. Chim. Acta*, 1950, **4**, 316.
[3] Tutt, B.Sc. Thesis, Oxford, 1946; Drysdale, B.Sc. Thesis, Oxford, 1951.
[4] Dyrssen, Dyrssen, and Johansson, *Acta Chem. Scand.*, 1956, **10**, 341.
[5] Irving, *Quart. Rev.*, 1951, **5**, 200.
[6] Irving and Pinnington, *J.*, 1957, preceding paper.
[7] Dicky and Duennebier, U.S.P. 2,507,146/1950.

reaction between *o*-anisidine and α-bromoacraldehyde failed to give an analogous product, ring-closure and dehalogenation occurring simultaneously as noted previously by Baker *et al.*[8] with nitroanilines. An intractable tar was the only product of the interaction of *o*-anisidine with ααβ-tribromopropionaldehyde or with α-bromocrotonaldehyde, although the latter is said to condense with aniline to form 3-bromoquinaldine.[7]

Reduction of 3-bromo-8-nitroquinoline[9] (I; X = NO_2) provides a convenient source of 8-amino-3-bromoquinoline (I; X = NH_2) but we have failed to replace the amino-group by a hydroxy-group by the Bucherer reaction under a wide variety of conditions. Diazotisation of 8-amino-3-bromoquinoline gave a red granular solid which could not be



hydrolysed to 3-bromo-8-hydroxyquinoline by acid either under reflux at 100° or in a sealed tube at 225°. However, the diazonium solution readily gave 3 : 8-dibromoquinoline in a Sandmeyer reaction, as reported by Claus and Howitz.[10] Similar inertness to hydrolysis has been observed with diazonium solutions prepared from 8-amino-derivatives of 5- and 7-trifluoromethylquonoline,[11] of 6-chloro- and 6-methoxy-quinoline, and of quinoline itself.[12] Since 2-, 3-, and 4-aminoacridine give the normal reactions on diazotisation while 1-aminoacridine forms an inert product,[13] it appears that the anomalous behaviour is due to the formation of a stable triazen ring system bridging the 1- and the 8-position.[14]

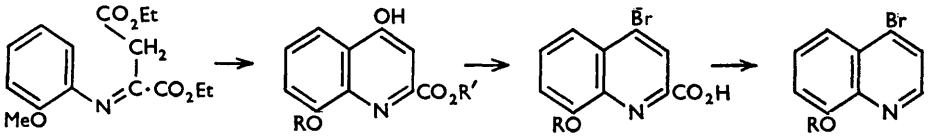
The direct hydrolysis of 8-amino- to 8-hydroxy-6-methoxyquinoline can be effected quantitatively[15] with 40% sulphuric acid at 225°. With aza-derivatives of 8-amino-quinoline somewhat different conditions are applicable: 8-amino-1 : 4 : 5- and -1 : 4 : 7-triazanaphthalene were best hydrolysed by 3 hours' heating at 140° with 5N-sodium hydroxide.[16] We obtained 3-bromo-8-hydroxyquinoline (II) in 60% yield by heating the amino-compound (I; X = NH_2) with 50% sulphuric acid for 4 hours at 225°. That the 3-bromine atom did not migrate under these conditions[6] was established by converting the product (II) quantitatively by potassium bromate–potassium bromide into 3 : 5 : 7-tribromo-8-hydroxyquinoline (III) identical with a specimen obtained by the action of phosphorus pentabromide upon 5 : 7-dibromo-8-hydroxyquinoline[17] (IV). Dimethyl sulphate and alkali convert the bromohydroxyquinoline (II) into 3-bromo-8-methoxyquinoline.

4-Bromo-8-hydroxyquinoline.—Xanthurenic acid (VI; R = R′ = H) has been synthesised from the anil of oxaloacetic ester and *o*-anisidine.[18,19] By cyclising the anil (V) in boiling diphenyl we obtained ethyl 4-hydroxy-8-methoxyquinoline-2-carboxylate (VI; R = Me, R′ = Et) purer than it was obtained by the previous authors who may not have recognised the ease with which the ester is hydrolysed. Indeed it is best to extract the crude cyclisation product with boiling 2N-hydrochloric acid whereby the ester is hydrolysed

[8] Baker, Tinsley, Butler, and Riegel, *J. Amer. Chem. Soc.*, 1950, **72**, 393.
[9] Hauser, Bloom, Breslow, Adams, Amore, and Weiss, *ibid.*, 1946, **68**, 1544.
[10] Claus and Howitz, *J. prakt. Chem.*, 1893, **48**, 151.
[11] Belcher, Stacey, Sykes, and Tatlow, *J.*, 1954, 3846.
[12] Berkenheim and Spasokukotskii, *J. Gen. Chem.* (*U.S.S.R.*), 1941, **11**, 541; Boehringer and Söhne, G.P. 576,119 (Friedlander, 1933, I, 716).
[13] Albert, "The Acridines," Edward Arnold and Co., London, 1951, p. 153.
[14] Cook, Heilbron, Hey, Lambert, and (in part) Spinks, *J.*, 1943, 404.
[15] Mietzsch and Klos, G.P. 485,315 (Friedlander, 1927, II, 2667).
[16] Albert and Hampton, *J.*, 1952, 4985.
[17] Claus and Howitz, *J. prakt. Chem.*, 1895, **52**, 545.
[18] Mebane and Oroshnik, *J. Amer. Chem. Soc.*, 1951, **73**, 3520.
[19] Furst and Olsen, *J. Org. Chem.*, 1951, **16**, 412.

to the acid (VI; R = Me, R′ = H) which can be readily demethylated to xanthurenic acid.[19]

Boiling phosphorus oxybromide converts 4-hydroxy-8-methoxyquinaldinic acid (VI; R = Me, R′ = H) into a mixture of 4-bromo-8-methoxy- (VII; R = Me) and 4-bromo-8-hydroxy-quinaldinic acid (VII; R = H), the latter identical with the product obtained



(V) (VI) (VII) (VIII)

similarly from 4 : 8-dihydroxyquinaldinic acid (VI; R = R′ = H). The partial demethylation recalls the formation of 4 : 7-dichloro-8-hydroxy- with 4 : 7-dichloro-8-methoxy-quinoline on reaction of phosphorus oxychloride with 7-chloro-4-hydroxy-8-methoxy-quinoline.[20]

Decarboxylation of 4-bromo-8-methoxyquinaldinic acid yielded 4-bromo-8-methoxy-quinoline (VIII; R = Me), and this gave 4-bromo-8-hydroxyquinoline (VIII; R = H) on demethylation.

6-Bromo-8-hydroxyquinoline.—*NN′*-Di-*o*-methoxyphenylurea, prepared[21] from urea and *o*-anisidine at 160°, was brominated in tetrachloroethane solution to give di-(4-bromo-2-methoxyphenyl)urea in good yield.[22] Hydrolysis to 4-bromo-2-methoxyaniline was achieved by heating small quantities in a sealed tube with aqueous ammonia to 160° for 8 hours[22] but a better procedure for larger quantities was to heat the urea under reflux with acetic anhydride and anhydrous sodium acetate. The *NN*-diacetyl-4-bromo-2-methoxyaniline which resulted was easily hydrolysed to 4-bromo-2-methoxyaniline. A Skraup reaction on this base, with arsenic pentoxide as oxidant, gave 6-bromo-8-methoxy-quinoline, an oil which readily formed a hydrate, m. p. 49—51°, containing 1½ mols. of water. Demethylation with aluminium tribromide gave 6-bromo-8-hydroxyquinoline, which with potassium bromide–bromate quantitatively formed 5 : 6 : 7-tribromo-8-hydroxyquinoline.

Experimental

Apparatus for Hydrolysis under Pressure.—Hydrolysis in acid or alkaline solutions at above the b. p. of water, carried out in a metal bomb may be complicated by attack on the container if the reaction mixture or products form stable complexes with metals. In the present work the reaction mixtures were sealed in Pyrex glass tubes enclosed in a high-grade steel pressure bottle, about 10 in. long, with a screw cap, and three-quarters filled with water. The pressure vessel was heated in an electric oven controlled within ±5° to about 300°.

Hydrolysis of 8-Amino-3-bromoquinoline (I; X = NH_2).—8-Amino-3-bromoquinoline (0·62 g.), prepared from 8-nitroquinoline by the method of Hauser *et al.*,[9] was heated as above with 98% sulphuric acid (1·6 ml.) and water (1·1 ml.) at 220° for 8 hr. When cold, the mixture was poured into water, just basified with dilute aqueous sodium hydroxide, and then made just acid with acetic acid. *3-Bromo-8-hydroxyquinoline* which separated as a white solid was purified from tarry by-products by steam-distillation followed by recrystallisation from aqueous alcohol and sublimation *in vacuo*. It formed colourless needles, m. p. 111° (62%), soluble in cold 2N-alkali and in ether and benzene (Found : C, 48·4; H, 2·8; Br, 35·5. C_9H_6ONBr requires C, 48·2; H, 2·7; Br, 35·7%).

Bromination of 3-Bromo-8-hydroxyquinoline (II).—3-Bromo-8-hydroxyquinoline (0·6 g.) in 50% hydrobromic acid (2·0 m.) and water (10 ml.) was treated with a small excess of

[20] Lauer, Arnold, Tiffany, and Tinker, *J. Amer. Chem. Soc.*, 1946, **68**, 1268.
[21] Jadhar, *J. Indian Chem. Soc.*, 1931, **7**, 681.
[22] Fitzky, G.P. 523,437 (Friedlander, 1930, I, 460).

M/60-potassium bromide–bromate, and the excess back-titrated with potassium iodide and 0·1N-sodium thiosulphate under conditions used for the volumetric determination of oxine.[23] Exactly two equivalents of bromine were used. The solution was then neutralised, 3 : 5 : 7-tribromo-8-hydroxyquinoline (III) separating as a greyish-white precipitate which was purified by recrystallisation from aqueous alcohol and sublimation *in vacuo*. It then formed long white needles, m. p. 170°, which did not depress the m. p. of a specimen prepared by the action of phosphorus pentabromide on 5 : 7-dibromo-8-hydroxyquinoline [17] (Found : Br, 62·5. Calc. for $C_9H_4ONBr_3$: Br, 62·8%).

3-Bromo-8-methoxyquinoline (I; X = OMe).—A solution of 3-bromo-8-hydroxyquinoline (0·34 g.) in water (20 ml.) and sodium hydroxide (0·3 g.) was treated with dimethyl sulphate (0·46 g.). After being shaken for 10 min. the red alkaline solution was extracted with ether and the solvent allowed to evaporate. After recrystallisation from aqueous alcohol and sublimation *in vacuo*, *3-bromo-8-methoxyquinoline* formed tan-coloured needles, m. p. 83—84° (Found : C, 49·8; H, 2·8; N, 5·75; Br, 34·4. $C_{10}H_8ONBr$ requires C, 50·4; H, 3·4; N, 5·9; Br, 33·6%). The *picrate* formed pale yellow needles (from 95% alcohol), m. p. 173—174° (Found : C, 40·8; H, 2·6. $C_{10}H_8ONBr,C_6H_3O_7N_3$ requires C, 41·1; H, 2·4%).

Preparation of 4-Hydroxy-8-methoxyquinaldinic Acid.—Diethyl α-*o*-methoxyanilosuccinate [19] (V) (9 g.) was added rapidly to boiling diphenyl (30 g.) and heated under reflux for 10 min. After being cooled to about 100° the mixture was extracted several times with boiling 2N-hydrochloric acid. After the diphenyl had solidified it was separated by decantation followed by filtration. On being neutralised the acid extracts deposited yellow *4-hydroxy-8-methoxyquinaldinic acid* (VI; R = Me, R′ = H), which recrystallised from water as almost colourless needles (3·1 g.), m. p. 259° (Found : C, 60·1; H, 4·35; N, 6·3. $C_{11}H_9O_4N$ requires C, 60·3; H, 4·1; N, 6·4%). This acid is very sparingly soluble in alcohol, light petroleum, chloroform, benzene, and cold water, dissolves in 2N-acid and -alkali and is very soluble in hot and cold pyridine. A mixture of pyridine and light petroleum can be used as a solvent in place of boiling water for recrystallisation.

Esterification of the acid (1·7 g.) by the Fischer–Speier method gave colourless ethyl 4-hydroxy-8-methoxyquinoline-2-carboxylate (1·3 g.), m. p. 107—108° (from light petroleum), which did not depress the melting point of an authentic specimen.[19]

4-Bromo-8-methoxy- and 4-Bromo-8-hydroxy-quinaldinic Acid.—Phosphorus oxybromide (15 ml.) and 4-hydroxy-8-methoxyquinaldinic acid (2·0 g.) were heated at 100°. Hydrogen bromide was evolved and the solid dissolved slowly to a deep red solution. After being heated for 1 hr. more the mixture was cooled and poured on crushed ice (100 g.) and water (100 ml.), neutralised, and set aside for 12 hr. The yellow solid which separated was filtered off from the mother-liquors (A). After extraction with 250 ml. of boiling water (B) the yellow insoluble portion (1·2 g.) melted at 132—134°. Recrystallisation from aqueous dioxan and dioxan–light petroleum gave *4-bromo-8-methoxyquinaldinic acid* as very pale yellow crystals, m. p. 134—135° (Found : Br, 28·5. $C_{11}H_8O_3NBr$ requires Br, 28·3%), almost insoluble in cold water and light petroleum, only sparingly soluble in alkali and in acid, but soluble in hot benzene, dioxan, and alcohol.

The aqueous extract (B) and the mother-liquors (A) were combined and concentrated to 50 ml. on a water-bath. On being cooled, *4-bromo-8-hydroxyquinaldinic acid* (VII; R = Me) separated as a cream-coloured solid (0·25 g.; m. p. 190—195°). It was taken up in 2N-sodium hydroxide, filtered, and reprecipitated by neutralisation. It recrystallised from water or aqueous dioxan as a yellow powder, m. p. 199—200° (decomp.) (Found : C, 44·8; H, 2·3; N, 5·1; Br, 29·4. $C_{10}H_6O_3NBr$ requires C, 44·8; H, 2·3; N, 5·2; Br, 29·8%), insoluble in benzene and light petroleum, but soluble in hot water, dioxan, and alcohol.

Both the hydroxy- and the methoxy-acid shared with 8-hydroxyquinaldinic acid [24] the property of having their m. p.s depressed by 5° to 15° on recrystallisation from aqueous alcohol.

Preparation of 4-Bromo-8-hydroxyquinaldinic Acid from Xanthurenic acid (VI; R = R′ = H),—Xanthurenic acid (0·5 g.), prepared by the demethylation of 4-hydroxy-8-methoxyquinaldinic acid or its ethyl ester by Fursten and Olsen's method [19] and recrystallised to m. p. 297° as described by Mebane and Oroshnik,[18] was heated on a water-bath with phosphorus oxybromide (10 g.). After 2 hr. the solid had dissolved to a red solution and no more hydrogen bromide was being evolved. The mixture was cooled, poured on crushed ice (150 g.),

[23] Kolthoff and Sandell, " Quantitative Inorganic Analysis," The Macmillan Company, New York, 1952, p. 86. [24] Irving and Pinnington, *J.*, 1954, 3782.

and neutralised. A solid separated (0·4 g.; m. p. 188—192°) which was collected and washed with a little cold water. 4-Bromo-8-hydroxyquinaldinic acid, m. p. 198—200°, was obtained as yellow crystals (from water) and did not depress the m. p. of the sample obtained by the partial demethylation of 4-bromo-8-methoxyquinaldinic acid.

4-Bromo-8-methoxyquinoline (VIII; R = Me).—4-Bromo-8-methoxyquinaldinic acid (0·45 g.) was heated for 10 min. at 230° by adding it to boiling diphenyl (10 g.). The cooled mixture was extracted with hot 2N-hydrochloric acid (2 × 50 ml.). The acid extract was neutralised with aqueous ammonia, an oil which separated slowly solidifying to form white needles. These were collected, washed with cold water, taken up in cold 2N-sulphuric acid, and filtered, and the filtrate was neutralised with N-sodium carbonate. The greenish crystals which separated (m. p. 68—72°) were collected, dried, recrystallised from aqueous alcohol, and sublimed *in vacuo*. *4-Bromo-8-methoxyquinoline* then formed white crystals (0·23 g.), m. p. 86—87° (Found: C, 50·1; H, 4·0; Br, 33·9. $C_{10}H_8ONBr$ requires C, 50·4; H, 3·4; Br, 33·6%). The *picrate* formed pale yellow needles, m. p. 248°, from 95% ethanol (Found: C, 41·1; H, 2·5; N, 12·15. $C_{10}H_8ONBr,C_6H_3O_7N_3$ requires C, 41·1; H, 2·4; N, 12·0%).

4-Bromo-8-hydroxyquinoline (VIII; R = H).—4-Bromo-8-methoxyquinoline (0·12 g.) was heated under reflux for 6 hr. with freshly distilled constant-boiling hydrobromic acid (10 ml.), then poured into water (50 ml.) and left overnight. On being neutralised the mixture deposited a white solid which was purified by steam-distillation. The volatile *4-bromo-8-hydroxyquinoline* were recrystallised from aqueous alcohol and sublimed *in vacuo*, forming white needles (0·06 g.), m. p. 134—135° (Found: C, 49·0; H, 3·1; Br, 34·9%).

Preparation of Di-(4-bromo-2-methoxyphenyl)urea.—A solution of *NN'*-di-*o*-methoxyphenylurea [21] in tetrachloroethane was brominated as described by Fitzky [22] who obtained crude di-(4-bromo-2-methoxyphenyl)urea, m. p. 235—240°, but did not analyse it. The product was taken up in refluxing acetone in which, though very soluble, it dissolved extremely slowly. Cautious addition of warm water precipitated the *urea* and after three such recrystallisations it formed white platelets, m. p. 260—261° (Found: Br, 37·1. $C_{15}H_{14}O_3N_2Br_2$ requires Br, 37·2%).

Hydrolysis of Di-(4-bromo-2-methoxyphenyl)urea.—The bromoethoxycarbanilide (10·3 g.) was heated under reflux for 4 hr. at 145° with acetic anhydride (75 ml.) and freshly dehydrated sodium acetate (20 g.). The cooled mixture was poured, with stirring, into water (750 ml.), and the dirty grey solid (11·7 g.; m. p. 80—82°) which slowly separated was collected. NN-*Diacetyl-4-bromo-2-methoxyaniline* formed white cubes, m. p. 96°, from aqueous alcohol or light petroleum (b. p. 60—80°) (Found: C, 46·2; H, 4·4; N, 5·2; Br, 28·1. $C_{11}H_{12}O_3NBr$ requires C, 46·2; H, 4·2; N, 4·9; Br, 27·9%).

This derivative (6·7 g.) was heated under reflux for 1 hr. with alcoholic hydrochloric acid, then neutralised, and 4-bromo-2-methoxyaniline was then distilled in steam, recrystallised from aqueous alcohol and redistilled in steam (3·7 g.; m. p. 60—61°).

6-Bromo-8-methoxyquinoline.—4-Bromo-2-methoxyaniline (6·7 g.), arsenic pentoxide (4·6 g.), glycerol (9·5 g.), and 98% sulphuric acid (13·2 g.) were heated for a short while at 160—170° until a vigorous reaction set in. When this had subsided the mixture was kept at 140—150° for 5 hr. When cooled, the black mixture was poured into water, neutralised, and distilled in steam. The involatile residue was collected, dried in air, and distilled *in vacuo*, 6-bromo-8-methoxyquinoline (b. p. 70—80°/24—28 mm.) gradually forming grey-white needles in moist air. Recrystallisation from aqueous alcohol gave white needles of a hydrate, m. p. 49—51° (Found: C, 44·9; H, 4·2; N, 5·35; loss of wt. over $CaCl_2$ *in vacuo*, 10·3. $C_{10}H_8ONBr,1\frac{1}{2}H_2O$ requires C, 45·3; H, 4·2; N, 5·3; H_2O, 10·2%). The base was further characterised as its *picrate*, m. p. 210° (from benzene–alcohol) (Found: N, 11·6; Br, 16·9. $C_{10}H_8ONBr,C_6H_3O_7N_3$ requires N, 12·0; Br. 17·1%).

6-Bromo-8-hydroxyquinoline.—An intimate mixture of 6-bromo-8-methoxyquinoline (0·6 g.) and aluminium trichloride (1·5 g.) was carefully warmed to 120°; a vigorous reaction commenced which was completed by further heating at 140° for 4 hr. The tarry product was extracted with boiling 2N-hydrochloric acid (2 × 50 ml.), and the acid filtrate treated first with sodium hydroxide and then potassium hydrogen carbonate until a precipitate just persisted. Sufficient 2N-hydrochloric acid was then added to give a clear solution whereafter the addition of a solution of copper sulphate caused the precipitation of the copper complex of 6-bromo-8-hydroxyquinoline. The *6-bromo-oxine* itself was isolated (0·15 g.; m. p. 123—126°) by treating this with hydrogen sulphide in the usual way (cf. ref. 6). A further amount (0·11 g.), adsorbed on the copper sulphide, was recovered by vacuum-sublimation. After distillation

in steam, recrystallisation from aqueous alcohol, and sublimation *in vacuo* it formed pale cream-coloured needles, m. p. 138—139° (Found: C, 47·9; H, 2·6; N, 6·4; Br, 36·4%).

5 : 6 : 7-*Tribromo*-8-*hydroxyquinoline*.—A solution of 6-bromo-8-hydroxyquinoline in 2N-hydrochloric acid was treated with standard bromate–bromide mixture.[23] Exactly two equivs. of bromine were absorbed. The white *tribromo-compound* which was precipitated on dilution gave slightly grey needles, m. p. 192° (0·8 g.), from aqueous alcohol. It was soluble only with difficulty in 10N-hydrochloric acid (Found: Br, 62·4. $C_9H_4ONBr_3$ requires Br, 62·8%).

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