49. *The Bromination of 8-Methoxyquinaldine.*

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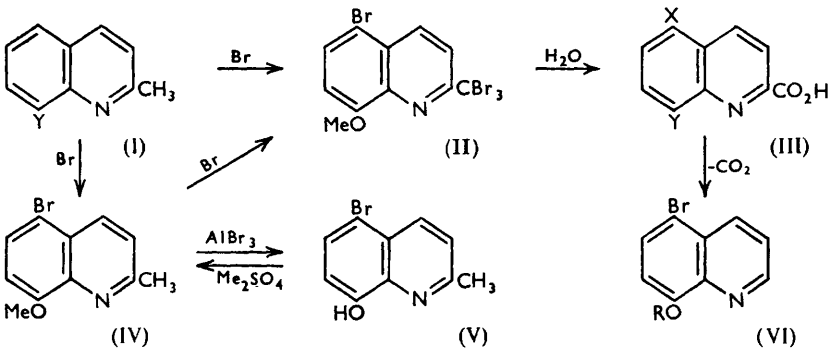
Bromination of 8-methoxyquinaldine gave in succession the 5-bromo- and the 5-bromo-2-tribromomethyl derivative. The latter was hydrolysed with difficulty to 5-bromo-8-methoxyquinaldinic acid which yielded 5-bromo-8-methoxyquinoline on decarboxylation. Demethylation with aluminium bromide gave 5-bromo-8-hydroxyquinoline, but refluxing with hydrobromic acid gave a mixture in which 5 : 7-dibromo-8-hydroxyquinoline predominated. The lability of the halogen in 5-bromo-8-methoxyquinoline towards cationoid, but not anionoid, reagents was confirmed. 5-Bromo-8-hydroxy(or methoxy)-quinoline and 5-bromo-8-hydroxy(or methoxy)quinaldine have been prepared by unambiguous syntheses.

The analytical reagent quinaldinic acid (III; X = Y = H) is conveniently prepared [1] by hydrolysis of 2-tribromomethylquinoline obtainable by ω-bromination of quinaldine (I; Y = H). The recent successful preparation of 5- and 7-chloroquinaldinic acid from the corresponding chloroquinaldines by this route [2] suggested that it might serve for the preparation of 8-methoxyquinaldinic acid (III; X = H, Y = OMe) which was required as an intermediate for the preparation of 8-hydroxyquinaldinic acid (III; X = H, Y = OH), a compound having potentialities as a chelating agent.[3]



This expectation was not realised, for the action of bromine at 80° on 8-methoxyquinaldine (I; Y = OMe) in glacial acetic acid containing anhydrous sodium acetate was to produce a tetrabromo-substitution product (A). The yield was greatest when 4 equivalents of bromine were employed, but the same product was obtained when the proportion of bromine was reduced. Although 2-tribromomethylquinoline is readily hydrolysed to quinaldinic acid by refluxing it with 10% sulphuric acid for 2 hr.,[1] the tetrabromo-compound (A) remains unchanged under these conditions and resembles rather 5- and

[1] Hammick, *J.*, 1926, 1302.
[2] Spivey and Curd, *J.*, 1949, 2656.
[3] Irving and Pinnington, *J.*, 1954, 3782.

7-chloro-2-tribromomethylquinoline which are only partially hydrolysed by 20 hours' boiling with 20% sulphuric acid.[2] However, when boiled under reflux for 30—35 hr. with 20% sulphuric acid the tetrabromo-compound (A) gave a monobromo-8-methoxyquinaldinic acid (B), which was subsequently obtained in much better yield by heating the compound (A) under reflux with silver nitrate in a mixture of acetone, ethanol, and water, or in aqueous dioxan. The three bromine atoms thus eliminated must therefore have been present in the side chain as a 2-tribromomethyl group.

Decarboxylation of the bromo-acid (B) in boiling diphenyl gave a monobromo-8-methoxyquinoline (C), m. p. 88°, which was clearly not identical with 7-bromo-8-methoxyquinoline,[4] m. p. 78°, and could not be positively identified with the only other known isomer, 5-bromo-8-methoxyquinoline, which Howitz and Witte describe[4] as forming a trihydrate of m. p. 82°. When heated under reflux with fuming hydrobromic acid the bromomethoxyquinoline (C) gave a mixture in which 5 : 7-dibromo-8-hydroxyquinoline predominated. Since this could only have been produced by the labilisation of a bromine atom under the influence of the hydrobromic acid, the production of a 5 : 7-isomer served only to indicate that the original halogen occupied the 5- or 7-position.

The orientation of the fourth bromine atom in the tetrabromo-compound (A) was finally established when, with an excess or with one equivalent of bromine at 15—20°, 8-methoxyquinaldine yielded a monobromo-product (D). Demethylation by aluminium bromide[5] gave the corresponding monobromo-8-hydroxyquinaldine, which, when treated in acid solution with a bromate–bromide mixture, was quantitatively monobrominated to 5 : 7-dibromo-8-hydroxyquinaldine, identical with an authentic specimen obtained by dibromination of 8-hydroxyquinaldine. That the first bromine atom had entered 8-methoxyquinaldine in the 5- rather than in the 7-position was proved by the identity of the monobromo-derivative (D) with 5-bromo-8-methoxyquinaldine (IV) obtained by the action of dimethyl sulphate and alkali on 5-bromo-8-hydroxyquinaldine (V), itself synthesised from 2-amino-4-bromophenol and crotonaldehyde by the Doebner–Miller method. Since the tetrabromo-compound (A) could be obtained in quantitative yield by the action of three equivalents of bromine at 80° on 5-bromo-8-methoxyquinaldine (IV; compound D), it must be formulated as 5-bromo-2-tribromomethyl-8-hydroxyquinoline (II).

The monobromo-8-methoxyquinoline (C) was independently identified as 5-bromo-8-methoxyquinoline (VI; R = Me) by comparison with an authentic specimen prepared by the methylation of 5-bromo-8-hydroxyquinoline (VI; R = H), itself prepared both from 2-amino-4-bromophenol by the Skraup reaction, and more conveniently from 5-amino-8-hydroxyquinoline by a Sandmeyer reaction.

A careful re-investigation of the demethylation of 5-bromo-8-methoxyquinoline by boiling hydrobromic acid showed that the least soluble product, 5 : 7-dibromo-8-hydroxyquinoline, was accompanied by smaller amounts of 5-bromo-8-hydroxyquinoline and 8-hydroxyquinoline itself. The lability of a 5-bromine atom under such conditions has recently been noted by Lauer, Korff, Klaus, and Sundett[6] who found that when 8-amino-5-bromo-6-methoxyquinoline was treated with 10% hydrobromic acid the bromine atom migrated to the 7-position, yielding 8-amino-7-bromo-5-methoxyquinoline in good yield. The exchange of halogen atoms when 5-bromo-8-methoxyquinoline and analogous compounds are boiled with concentrated hydrochloric acid has long been known,[7] and Norgradi[8] isolated both 5 : 7-dichloro-8-hydroxyquinoline and 8-hydroxy-5 : 7-di-iodoquinoline when 5-chloro-8-hydroxy-7-iodoquinoline was heated under reflux with water–dioxan. Lauer *et al.*[6] noted that the bromine atom in 8-amino-5-bromo-6-methoxyquinoline was not attacked by anionoid reagents such as methanolic ammonia or sodium

[4] Howitz and Witte, *Ber.*, 1905, **38**, 1260.
[5] Albert and Hampton, *J.*, 1952, 4985.
[6] Lauer, Klaus, Korff, and Sundett, *J. Amer. Chem. Soc.*, 1948, **71**, 3986
[7] Claus and Howitz, *J. prakt. Chem.*, 1891, **44**, 444.
[8] Norgradi, *Chem. Ber.*, 1952, **85**, 104.

methoxide. We find that 5-bromo-8-methoxyquinoline is also unaffected by sodium methoxide in methanol during several hours at 120°.

We have never been able to obtain our 5-bromo-8-methoxyquinoline in the form of a trihydrate as reported by Howitz and Witte [4] for the compound they obtained by the action of methyl iodide and alkali upon the 5-bromo-8-hydroxyquinoline which they separated from the mixed bromination products of 8-hydroxyquinoline.[7] The methiodide [m. p. 188° (decomp.)] of our material melts at an appreciably higher temperature than that recorded for the methiodide (m. p. 161°) of Howitz and Witte's compound. We have not resolved these discrepancies.

Experimental

Bromination of 8-Methoxyquinaldine at 80°.—Bromine (64·0 g., 0·4 mole) in glacial acetic acid (150 ml.) was added during ½ hr. to a stirred solution of 8-methoxyquinaldine [3] (17·3 g., 0·1 mole) and anhydrous sodium acetate (50 g.) in glacial acetic acid (150 ml.) at 80°. The colour of free bromine suddenly faded to a pale brownish-yellow. Heating was then continued for 10 min. during which a solid began to separate. After being allowed to cool, the grey solid was collected, and washed with small portions of glacial acetic acid, and finally with much cold water. After being dried in a steam-bath it was extracted with hot benzene. The filtered extract on cooling deposited pale yellow crystals of *5-bromo-8-methoxy-2-tribromomethylquinoline* (II; compound A). The yield (22·0 g., 45%) could be augmented by concentrating the mother-liquors. After recrystallisation from hot benzene the almost white crystals had m. p. 202° (decomp.) (Found: C, 27·2; H, 1·7; N, 3·0; Br, 64·9. $C_{11}H_7ONBr_4$ requires C, 27·0; H, 1·4; N, 2·9; Br, 65·4%). The same product was obtained in progressively smaller yield when the bromination of 8-methoxyquinaldine was conducted at 80° with 3, 2, and 1 equivs. of bromine. The tetrabromo-compound (A) was also obtained in 19% yield, and accompanied by much tar, when the reaction mixture was heated under reflux.

Hydrolysis of 5-Bromo-8-methoxy-2-tribromomethylquinoline (II).—(a) *By sulphuric acid.* The tetrabromo-compound (2 g.) was heated under reflux for 20—30 hr. with 20% sulphuric acid (320 ml.). The solid residue was then separated and heated under reflux with a fresh portion of 20% sulphuric acid (60 ml.) for 6 hr. The combined hydrolysates were then made almost neutral by the addition of concentrated sodium hydroxide solution. The solid which separated was collected and crystallised a number of times from benzene, *5-bromo-8-methoxyquinoline-2-carboxylic acid* (III; X = Br, Y = OMe) separating as yellow crystals, m. p. 170—171°. This acid is very sparingly soluble in cold dioxan, ethanol, and water. Its solution in aqueous acetic acid did not give a precipitate with an aqueous solution of copper sulphate. The solution of the crude acid in hot benzene was strongly fluorescent (Found: C, 46·5; H, 2·9; N, 5·1; Br, 28·0. $C_{11}H_8O_3NBr$ requires C, 46·8; H, 2·9; N, 5·0; Br, 28·3%).

(b) *By silver nitrate.* A solution of the tetrabromo-compound (II; 8·4 g.) in dioxan (70 ml.) was heated under reflux and a solution of silver nitrate (8·4 g.) in water (2·5 ml.) was added in one portion. Silver bromide separated immediately. After being heated under reflux for 2 hr. the mixture was filtered hot and the silver bromide (9·3 g., 100%) was collected and washed in portions with hot dioxan (30 ml.). The filtrate and washings were concentrated on a water-bath to about 30 ml. After cooling, 5-bromo-8-methoxyquinoline-2-carboxylic acid (m. p. 166°) was collected, washed with a little cold dioxan, and recrystallised twice from hot benzene from which it separated as golden needles, m. p. 170—171° (3·1 g., 85%).

Decarboxylation of 5-Bromo-8-methoxyquinaldinic Acid (*Compound B*).—The bromo-acid (1·6 g.) was heated under reflux with boiling diphenyl (30 g.) for 5 min. The reaction mixture was allowed to cool and then extracted with boiling 2N-hydrochloric acid (2 × 50 ml.). When cold the acid extract was neutralised with 2N-sodium hydroxide, a dark oil separating which solidified (m. p. 75—77°). Recrystallisation from aqueous alcohol and then light petroleum (b. p. 60—80°), and sublimation *in vacuo*, gave colourless *5-bromo-8-methoxyquinoline* (1·08 g., 80%), m. p. 88°, which became greenish-yellow when kept [Found: C, 51·0; H, 3·6; N, 6·0; Br, 33·4%; *M* (Rast), 235, 225. $C_{10}H_8ONBr$ requires C, 50·4; H, 3·4; N, 5·9; Br, 33·6%; *M*, 238].

The *picrate*, prepared in and recrystallised from alcohol, formed golden-yellow needles,

m. p. 197—198° (Found: C, 41·6; H, 2·2; N, 11·9. $C_{10}H_8ONBr$ requires C, 41·1; H, 2·4; N, 12·0%).

Demethylation of 5-Bromo-8-methoxyquinoline with Hydrobromic Acid.—5-Bromo-8-methoxyquinoline (1·81 g.) was heated under reflux with 50% hydrobromic acid (20 ml.) for 6 hr. When cold the mixture was poured into water (60 ml.) and slowly neutralised with aqueous sodium hydroxide; a greyish solid (1·7 g.; m. p. 120—130°) separated. This was dissolved in hot ethanol (65 ml.), and sufficient hot water (130 ml.) added to precipitate a white solid. (The mother-liquors were worked up as described below.) The solid was collected and dried (1·09 g.; m. p. 150—160°), dissolved in 10N-hydrochloric acid, reprecipitated by the cautious addition of water, and recrystallised repeatedly from aqueous alcohol from which it separated as colourless needles, m. p. 198°, which did not depress the m. p. of authentic 5 : 7-dibromo-8-hydroxyquinoline (Found: Br, 52·65. Calc. for $C_9H_5ONBr_2$: Br, 52·8%).

The mother-liquors (see above) were concentrated to 25 ml. On addition of water (50 ml.) a white solid separated (0·52 g.; m. p. 110—120°) which was first purified by steam-distillation and then recrystallised repeatedly from hot water and from aqueous alcohol. It formed creamy white crystals, m. p. 123—124°, which did not depress the m. p. of authentic 5-bromo-8-hydroxyquinoline (see below) (Found: Br, 35·2. Calc. for C_9H_6ONBr: Br, 35·7%). On working up of the mother-liquors a small amount of a bromine-free material, m. p. 72—75°, was obtained which showed all the reactions of 8-hydroxyquinoline.

Bromination of 8-Methoxyquinaldine at Room Temperature. Preparation of 5-Bromo-8-methoxyquinaldine.—8-Methoxyquinaldine (8·65 g., 0·05 mole) and freshly prepared anhydrous sodium acetate (25 g.) were dissolved in hot glacial acetic acid (50 ml.), and the solution cooled, with continuous stirring, to 15—20°. Bromine (8·0 g., 0·05 mole) in cold glacial acetic acid (25 ml.) was added during ½ hr. After being stirred for a further 2 hr. the mixture was set aside overnight, then poured into water (1 l.). On neutralisation, a slightly tarry material separated which was distilled in steam (14 hr.), and the white product which came over was collected, dried, and distilled *in vacuo*. *5-Bromo-8-methoxyquinaldine* (7·7 g., 44%) formed long pale fawn needles, m. p. 114°, from light petroleum (b. p. 60—80°) (Found: C, 52·1; H, 4·0; N, 5·5; Br, 31·6. $C_{11}H_{10}ONBr$ requires C, 52·4; H, 4·0; N, 5·6; Br, 31·7%).

Bromination of 5-Bromo-8-methoxyquinaldine. Preparation of 5-Bromo-8-methoxy-2-tribromomethylquinoline (II).—5-Bromo-8-methoxyquinaldine (1·26 g., 0·005 mole) and freshly prepared anhydrous sodium acetate (4·0 g.) were dissolved in glacial acetic acid (30 ml.) and heated to 100° on a water-bath. A solution of bromine (2·4 g., 0·015 mole) in glacial acetic acid (10 ml.) was added slowly in 1 ml. portions with shaking. When the mixture had cooled to room temperature 5-bromo-8-methoxy-2-tribromomethylquinoline (II) was collected and washed with a little cold acetic acid, then with hot water (2·3 g., 94%; m. p. 190—195°). After recrystallisation from benzene the pale yellow needles, m. p. 201—202°, did not depress the m. p. of the sample prepared by bromination of 8-methoxyquinaldine at 80°.

Demethylation of 5-Bromo-8-methoxyquinaldine.—5-Bromo-8-methoxyquinaldine (2·8 g.) and aluminium bromide (9·2 g.) were gradually heated to 160° and after the initial violent reaction had subsided the mixture was kept at 160° for a further 4½ hr. When cold, the resulting black mass was boiled for 1 hr. with dilute hydrobromic acid (50% hydrobromic acid, 5 ml.; water 50 ml.), and the red solution allowed to cool before being filtered. The filtrate was neutralised and steam-distilled, *5-bromo-8-hydroxyquinaldine* being obtained as a low-melting solid (0·88 g.) which was taken up in cold 2N-sodium hydroxide and, after filtration, reprecipitated by careful neutralisation. After recrystallisation from aqueous alcohol and sublimation *in vacuo* it formed white needles, m. p. 67° (Found: C, 50·0; H, 3·5; Br, 34·0. $C_{10}H_8NOBr$: Br, requires C, 50·4; H, 3·4; Br, 33·6%).

Bromination of 5-Bromo-8-hydroxyquinaldine. Preparation of 5 : 7-Dibromo-8-hydroxyquinaldine.—5-Bromo-8-hydroxyquinaldine (0·80 g.), dissolved in 6N-hydrobromic acid (10 ml.), was titrated quantitatively with a standard bromide–bromate solution as in the volumetric determination of 8-hydroxyquinoline.[9] Exactly one equivalent of bromine was required. The crude reaction product (m. p. 115°) was isolated by making the solution neutral and steam-distilling it. After recrystallisation from aqueous alcohol and sublimation *in vacuo* 5 : 7-dibromo-8-hydroxyquinaldine (0·88 g., 81%) was obtained as white crystals, m. p. 125°, which did not depress the m. p. of a specimen prepared by quantitative dibromination of 8-hydroxy-

[9] Kolthoff and Sandell, "Quantitative Inorganic Analysis," Macmillan Co., New York, 1952, p. 608.

quinaldine with potassium bromide–bromate solution [10] (Found: Br, 50·6. Calc. for $C_{10}H_7ONBr_2$: Br, 50·4%).

Synthesis of 5-Bromo-8-hydroxyquinaldine (VI; R = H).—4-Bromo-2-nitrophenol [11] was hydrogenated (20 g.) in ethanol (100 ml.) at room temperature and atmospheric pressure in the presence of Raney nickel. The theoretical amount of hydrogen was absorbed very rapidly. After removal of the catalyst the filtered solution was concentrated on a water-bath, 2-amino-4-bromophenol separating as orange needles which, after recrystallisation from hot water (charcoal), had m. p. 134—135° (17·4 g., 78%). On standing the crystals darkened. Schutt [12] gives m. p. 128°.

2-Amino-4-bromophenol (28·5 g., 0·15 mole), arsenic pentoxide (3 g.), and concentrated hydrochloric acid (100 ml.) were heated to 120° (oil-bath) under reflux with vigorous stirring. Crotonaldehyde (13 g., 0·18 mole) was added dropwise during 5 min. and heating was continued for a further 15 min. Steam was blown through the acid mixture to remove volatile impurities, the residue made just neutral with concentrated sodium hydroxide, and 5-bromo-8-hydroxyquinaldine distilled off in steam. A second distillation in steam, followed by recrystallisation from aqueous alcohol, gave almost colourless needles (13·7 g., 37%) of m. p. 68°, unchanged on admixture with the substance produced by the demethylation of compound (D) with aluminium bromide (see above).

5-Bromo-8-methoxyquinaldine.—5-Bromo-8-hydroxyquinaldine (1·2 g.), in a Schotten–Baumann reaction, gave 5-bromo-8-methoxyquinaldine (0·8 g., 70%), hair-like needles, m. p. 114° [from light petroleum (b. p. 60—80°)], which did not depress the m. p. of the specimen obtained by the monobromination of 8-methoxyquinaldine (Found: N, 5·65; Br, 31·8%). The *picrate*, prepared in and recrystallised from, ethanol in which it is very sparingly soluble, formed yellow needles, m. p. 238° (Found: N, 11·4. $C_{11}H_{10}ONBr,C_6H_3O_7N_3$ requires N, 11·65%).

Synthesis of 5-Bromo-8-hydroxyquinoline.—(*a*) 4-Bromo-2-nitrophenol, prepared by the decomposition of *p*-bromobenzenediazonium sulphate in 10% nitric acid, was obtained as deep yellow crystals, m. p. 88°, from ethanol.[11] 4-Bromo-2-nitrophenol (10 g.), glacial acetic acid (20 ml.), glycerol (20 ml.), and concentrated sulphuric acid (20 ml.) were heated under reflux for 6 hr. The tarry product was neutralised and distilled in steam. The pale yellow volatile solid was further purified by steam-distillation and then recrystallised from hot water and then from aqueous acetone. 5-Bromo-8-hydroxyquinoline (0·8 g.) then formed white needles, m. p. 124—125°. The poor yield contrasts with that obtained by Bose [13] who claimed to have prepared 5-chloro-8-hydroxyquinoline from 4-chloro-2-nitrophenol in 60% yield by this procedure.

(*b*) (With Miss Massey-Beresford.) 8-Hydroxy-5-nitrosoquinoline [14] was reduced catalytically (Raney nickel) as described by Albert and Magrath.[15] The hydrochloride of 5-amino-8-hydroxyquinoline (9·8 g., 0·05 mole) was dissolved in concentrated hydrobromic acid (20 ml.) and water (50 ml.) and diazotised slowly at −5° with sodium nitrite (3·5 g. in 7·5 ml. of water). At the same time a mixture of sodium bromide dihydrate (8·4 g., 0·06 mole), copper sulphate pentahydrate (3·15 g., 0·0125 mole), copper turnings (1 g.), and concentrated sulphuric acid (8·2 ml., 0·14 mole) and water (50 ml.) was heated under reflux for 3½ hr. Any colour then remaining was discharged by the addition of a solution of sodium hydrogen sulphite, and the diazonium solution prepared from 5-amino-8-hydroxyquinoline was added dropwise to the boiling solution of cuprous bromide. After ½ hr., the boiling solution was saturated with hydrogen sulphide and then filtered. The precipitate of copper sulphide was boiled with several portions of 2N-sulphuric acid. These washings were added to the main filtrate which, after dilution, was again treated with hydrogen sulphide. After removal of precipitated copper sulphide the filtrate was made neutral and distilled in steam. The crude product (4 g., 36%) melted at 122—124°. After a second steam-distillation followed by recrystallisation from aqueous alcohol, 5-bromo-8-hydroxyquinoline was obtained as colourless needles, m. p. 124·5—125·5°. Sublimation at 80° *in vacuo* raised the m. p. to 126—126·5° (Found: C, 48·4; H, 2·65;

[10] (*a*) Irving, Butler, and Ring, *J.*, 1949, 1489; (*b*) Philips, Emery, and Price, *Analyt. Chem.*, 1952, **24**, 1033.
[11] Varma and Krishnamurthy, *J. Indian Chem. Soc.*, 1925, **3**, 322.
[12] Schutt, *J. prakt. Chem.*, 1885, **32**, 61.
[13] Bose, *J. Indian Chem. Soc.*, 1945, **22**, 169.
[14] Irving, Hollingshead, and Harris, *Analyst*, 1955, **80**, 260.
[15] Albert and Magrath, *Biochem. J.*, 1947, **41**, 531.

N, 6·4; Br, 35·55. Calc. for C_9H_6ONBr: C, 48·2; H, 2·7; N, 6·25; Br, 35·7%). This compound has apparently been synthesised by Claus and Howitz [7] by the same route. They gave no details and reported m. p. 124°.

5-Bromo-8-methoxyquinoline.—5-Bromo-8-hydroxyquinoline (1·0 g.) in 1% sodium hydroxide solution (15 ml.) was methylated with dimethyl sulphate (0·8 g.). After recrystallisation from light petroleum (b. p. 60—80°) and sublimation *in vacuo* (0·7 g., 65%), the bromoquinoline formed colourless needles, m. p. 88° (Found: Br, 33·7. Calc. for $C_{10}H_8ONBr$: Br, 33·6%). The picrate, after recrystallisation from boiling ethanol, melted at 197°. The identity of 5-bromo-8-methoxyquinoline with the compound (C) was established by mixed m. p. Their respective picrates were also identical.

The *methiodide* of 5-bromo-8-methoxyquinoline was readily formed in methanol at 80° (1 hr.). It crystallised from boiling water, in which it was moderately soluble, in orange plates, m. p. 187—188° (decomp.) (Found: N, 3·85. $C_{11}H_{11}ONBrI$ requires, N, 3·7%).

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