480. *Some 6-Alkyl-5- and 7-Alkyl-8-aminoquinolines.*

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6- and 7-Alkylquinolines, as far as the butyl members, have been prepared from *p*- and *m*-alkylanilines by the Skraup reaction. Nitration converted the 6-alkylquinolines into 6-alkyl-5-nitroquinolines, but from the 7-alkyl compounds, besides 7-alkyl-8-nitroquinolines, minor products, probably 5-nitro-isomers, were isolated. A catalytic method of general usefulness was employed to reduce these products to 6-alkyl-5- and 7-alkyl-8-amino-quinolines. The picrates of the latter were noteworthy for their ability to retain up to three molecules of acetone in their crystals.

FOR work to be published later we required a number of compounds of the types named in the title. Recently (*J.*, 1953, 2066) we described the preparation of some *m*- and *p*-alkylanilines, and have now submitted these to the Skraup reaction. The resulting alkylquinolines were then nitrated and the products were reduced. In the Skraup reaction a *p*-alkylaniline can form only the 6-alkylquinoline, and the work of Bradford, Elliot, and Rowe (*J.*, 1947, 437) made it probable that the 7-alkylquinoline would be formed chiefly or exclusively from a *m*-alkylaniline. 6- and 7-Methylquinoline are well known, and Manske, Marion, and Leger (*Canad. J. Res.*, 1942, **20**, *B*, 133) reported the preparation of 7-ethylquinoline from *m*-ethylaniline but did not record its properties or establish its orientation. No other 6- or 7-alkylquinolines have been described previously.

Noelting and Trautmann (*Ber.*, 1890, **23**, 3654) prepared 6-methyl-8-nitroquinoline from 4-amino-3-nitrotoluene, and 8-hydroxy-7-methylquinoline from 3-amino-*o*-cresol (Me = 1). We found these reactions to be uncontrollably violent. Bradford *et al.* (*loc. cit.*) showed Skraup reactions to proceed satisfactorily when moderately dilute sulphuric acid was used, sodium *m*-nitrobenzenesulphonate being the oxidant. These conditions worked well in the two cases just mentioned, and were subsequently used in preparing 6-ethyl-, 6-butyl-, 7-butyl-, and 6-dodecyl-quinoline. Repetition of the Skraup reaction with *m*-ethylaniline, using the method described by Manske *et al.* (*loc. cit.*), showed it to work satisfactorily, although the yield of pure product was not so high as claimed by them. Their conditions have also been applied to the preparation of other compounds which we required, and the results allow some comparisons to be made between the two methods. The conditions described by the Canadian workers were unsuitable for the preparation of 6-dodecylquinoline, as charring occurred.

Noelting and Trautmann (*loc. cit.*) and Bogert and Fisher (*J. Amer. Chem. Soc.*, 1912, **34**, 1569), by nitrating 6-methylquinoline in sulphuric acid, obtained only 6-methyl-5-nitroquinoline. The products now similarly obtained from 6-ethyl-, -propyl-, -butyl-, and

-dodecyl-quinoline are regarded from analogy as the 5-nitro-compounds, and work to be described later justifies this assumption. The method used in working up the nitration solutions from the 6-alkylquinolines made unlikely the detection of minor products.

Tomisek, Graham, Griffith, Rose, and Christensen (*J. Amer. Chem. Soc.*, 1946, **68**, 1587) nitrated 7-methylquinoline in sulphuric acid, and proved the principal product to be 7-methyl-8-nitroquinoline. The same method has now been applied to 7-ethyl-, -propyl-, and -butyl-quinoline. The major product from 7-ethylquinoline has been proved (Ockenden and Schofield, unpublished work) to be 7-ethyl-8-nitroquinoline (thus proving the structure of 7-ethylquinoline also), and the same orientation is assumed in the other cases. Minor nitration products were also isolated from the ethyl and the butyl compound. Despite the suggestion implicit in the work of Capps (*J. Amer. Chem. Soc.*, 1947, **69**, 179), that 7-methylquinoline is to a small degree nitrated in the pyridine nucleus, a suggestion contrary to all known analogies (Schofield, *Quart. Reviews*, 1950, **4**, 393), we regard these minor isomers as 7-alkyl-5-nitroquinolines.

Reduction of 6-methyl-5-nitroquinoline with iron filings and dilute acetic acid, as described by Noelting and Trautmann (*loc. cit.*), although laborious was satisfactorily applied to the large scale. Preparation of 8-amino-7-methylquinoline with the same reagents, as described by Elderfield *et al.* (*J. Amer. Chem. Soc.*, 1946, **68**, 1524), was unsatisfactory. With some modification the method yielded 47% of the amine.

Several workers have reduced nitroquinolines to the amines by catalytic procedures (Capps, *loc. cit.*; *J. Amer. Chem. Soc.*, 1950, **72**, 4069; Rudy, *Ber.*, 1938, **71**, 847; Haskelberg, *J. Org. Chem.*, 1947, **12**, 434). Fieser and Hershberg (*J. Amer. Chem. Soc.*, 1940, **62**, 1640) reduced 5- and 8-nitroquinoline using Adams' platinum oxide, and claimed that ethanol was an unsatisfactory solvent since sparingly soluble intermediate hydroxylamines were sensitive to hot alcohol. This statement is not wholly consistent with the experiments which they describe. Our attempts to repeat this work failed. Reduction to the hydroxylamine (which separated) occurred rapidly, but reduction then ceased. The same workers claimed the rapid reduction of 8-nitroquinoline in a mixture of ethyl acetate, ethanol, and ether, but we found this reaction to need several days. This was also the case with 7-methyl-8-nitroquinoline under these conditions, and here separation of the green hydroxylamine was also observed.

Finally we found that a modification of the method used by Langenbeck, Juttermann, and Hellrung (*Annalen*, 1932, **499**, 201) for reducing 5-nitroquinoline was generally applicable to nitroquinolines. In relatively dilute methanolic solution, with 5% palladium–charcoal, reduction was rapid, no intermediate compound separated, and the pure amine was easily isolated. By this method the 6-alkyl-5- and 7-alkyl-8-nitroquinolines described above were all successfully converted into the corresponding amines.

The 6- and 7-alkylquinolines were very pale yellow, highly refractive oils, the b. p.s of which increased as the series was ascended. The 6-alkylquinoline picrates showed a lower m. p. than the 7-isomers, m. p.s in both series decreasing as the series was ascended. 7-Alkyl-8-nitroquinolines melted at higher temperatures than the 6-isomers; in each series the m. p. fell with increasing size of the alkyl group. Only 6-butyl- and 6-dodecyl-5-nitroquinoline appeared to form stable hydrates. The aminoquinolines were prone to form hydrates, a property which rendered the criterion of constant m. p. of little value as a test for purity. Because of hydrate formation the m. p.s of the 6-alkyl-5-aminoquinolines showed no definite trend, but in the 7-alkyl series they decreased as the series was ascended, 8-amino-7-ethyl-, -7-propyl-, and -7-butyl-quinoline being liquids. The amino-alkylquinolines formed highly crystalline picrates. Those derived from 7-alkyl-8-aminoquinolines crystallised normally from methanol, but from acetone formed bright scarlet crystals which retained up to three molecules of the solvent. 6-Alkyl-5-aminoquinoline picrates did not possess this property.

EXPERIMENTAL

Extracts were dried with anhydrous sodium sulphate.

Skraup Reactions.—(*a*) The amine, glycerol, sodium *m*-nitrobenzenesulphonate, and sulphuric acid (75% w/w) were stirred under gentle reflux. After being set aside overnight the mixture was diluted, treated with excess of sodium nitrite, and then boiled. The mixture was rendered strongly alkaline and steam-distilled, except in the case of 6-butyl- and 6-dodecyl-quinoline, which were extracted with ether, and of 6-methyl-8-nitroquinoline which separated as a solid and was collected. The distillates were extracted with ether and the oils recovered from the extracts were distilled. In the case of 8-hydroxy-7-methylquinoline the Skraup reaction mixture was basified, acidified with acetic acid, and then treated with excess of ammonia. Steam-distillation and addition of aqueous ammonia to the distillate gave the pure product. Results are in Table 1.

(*b*) The amine, boric acid, ferrous sulphate, *o*-nitrophenol, glycerol, and concentrated sulphuric acid were refluxed together. After being kept overnight the mixture was processed as in (*a*). Results are in Table 2. The stated yield of 7-propylquinoline is of doubtful significance since the starting amine was impure.

The properties of the *quinolines* prepared in (*a*) and (*b*), and of their picrates, are recorded in Table 3.

TABLE 1.

Quinoline	Starting amine (g.)	75% w/w H_2SO_4 (g.)	Sodium *m*-nitro-benzene-sulphonate (g.)	Glycerol (g.)	Temp.	Time (hr.)	Yield (%) (pure)
8-Hydroxy-7-methyl ...	5	40	10	18·8	120—125°	8	54
6-Methyl-8-nitro	105	500	200	125	140	9	73
6-Ethyl	30	165	75	42·5	130—140	,,	75
6-Butyl	52	250	100	72·5	,,	11·5	82
7-Butyl	18·4	90	35	22	140	12	70
6-Dodecyl	54·7	150	60	23	150—160	10	56

TABLE 2.

Quinoline	Starting amine (g.)	$FeSO_4$ (g.)	H_3BO_3 (g.)	*o*-Nitro-phenol (g.)	Glycerol (g.)	Conc. H_2SO_4 (c.c.)	Time (hr.)	Yield (pure) (%)
8-Hydroxy-7-methyl	5	1·8	3·3	4·2	18·8	9	6	32
6-Ethyl	24	7·2	13	16·4	75	36	7·5	82
7-Ethyl	36	10·5	19·5	24·9	82·5	54	,,	74
6-Propyl	31	,,	,,	,,	112·5	,,	8	68
7-Propyl	10	6	11	14	64	30	14	45
6-Butyl	39·5	8·7	16·3	20·8	93·7	45	10·5	82
7-Butyl	10	2·5	4·5	6	26	13	6	64·5

TABLE 3. 6- *and* 7-*Alkylquinolines obtained by Skraup reactions.*

No.	Quinoline	B. p. (°/mm.)	n[a]	Formula	Found (%): C	Found (%): H	Reqd. (%): C	Reqd. (%): H	Picrate: Form[b]	Picrate: M. p.	Picrate: Solvent
1	6-Ethyl	140—142/12	1·6012	$C_{11}H_{11}N$	83·2	7·0	84·0	7·05	Needles	200—201	Aq. $COMe_2$
2	7-Ethyl	128—129/6	1·6012	—	—	—	—	—	,,	231—233[c]	MeOH–$COMe_2$
3	6-Propyl	140/7	1·5878	$C_{12}H_{13}N$	84·4	8·1	84·2	7·7	,,	171—172	,,
4	7-Propyl	145—147/7	1·5900	,,	84·0	7·9	,,	,,	,,	191—193	,,
5	6-Butyl	161—164/12	1·5802	$C_{13}H_{15}N$	85·5	8·3	84·3	8·2	Prisms	162	MeOH
6	7-Butyl	152—154/6	1·5828	,,	83·7	8·1	,,	,,	Needles	180	$COMe_2$
7	6-Dodecyl	196—198/0·5	1·5345	$C_{21}H_{31}N$	84·9	10·3	84·75	10·5	Flakes	131	MeOH

Picrate 1. Found : C, 53·1; H, 3·7. $C_{11}H_{11}N,C_6H_3O_7N_3$ requires C, 52·9; H, 3·65%.
,, 3. ,, C, 54·0; H, 3·9. $C_{12}H_{13}N,C_6H_3O_7N_3$,, C, 54·0; H, 4·0%.
,, 4. ,, C, 53·7; H, 3·8. ,, ,, ,, ,, ,,
,, 5. ,, C, 55·1; H, 4·3. $C_{13}H_{15}N,C_6H_3O_7N_3$,, C, 55·05; H, 4·4%.
,, 6. ,, C, 55·3; H, 4·4. ,, ,, ,, ,, ,,
,, 7. ,, C, 61·2; H, 6·6. $C_{21}H_{31}N,C_6H_3O_7N_3$,, C, 61·6; H, 6·5%.

[a] Determined by daylight. The high viscosity of the liquids made it difficult to obtain closely reproducible values for this constant. [b] All yellow. [c] Manske *et al.* (*loc. cit.*) gave m. p. 229°.

Nitrations.—(a) 6-*Alkylquinolines.* The quinoline in concentrated sulphuric acid was treated, whilst being stirred, with a solution of nitric acid (*d* 1·42) in concentrated sulphuric acid, the temperature being kept below 5° (below 0° for 6-dodecylquinoline to prevent oxidation). The nitration solution was poured on ice (with 6-dodecylquinoline this precipitated the hydrated nitro-compound); the product precipitated by neutralisation with sodium carbonate was collected and recrystallised. When the nitration solution from 6-butylquinoline was poured on ice and water (1·5 l.) a yellow precipitate was obtained, only partly soluble in organic solvents. This mixture of the nitro-compound and its nitrate was triturated with ammonia, and the resulting solid was combined with that obtained by basifying the mother-liquor. The total product was dried *in vacuo*, a dark brown oil resulting. The yield of this material is recorded below. When exposed to the atmosphere this oil was transformed into clusters of stout, pale yellow needles of *6-butyl-5-nitroquinoline hemihydrate*, m. p. 35—37° (Found: C, 64·9; H, 5·9. $C_{13}H_{14}O_2N_2,\frac{1}{2}H_2O$ requires C, 65·2; H, 6·3%).

(b) *7-Alkylquinolines.* The method was similar to that described in (*a*) except that fuming nitric acid was the nitrating agent. In all cases dilution of the nitration solution precipitated the main bulk of the product, which was collected and recrystallised. The acid mother-liquors from 7-ethyl- and -butyl-quinoline were neutralised with aqueous ammonia, and the product was either collected (ethyl) or extracted with chloroform (butyl). Both compounds were crystallised from aqueous methanol. *7-Ethyl-5(?)-nitroquinoline* gave soft pale yellow plates, m. p. 47—49° (Found: C, 65·4; H, 5·4. $C_{11}H_{10}O_2N_2$ requires C, 65·3; H, 5·0%), and *7-butyl-5(?)-nitroquinoline* crisp yellowish-brown plates, m. p. 73—74° (Found: C, 66·5; H, 6·0. $C_{13}H_{14}O_2N_2,\frac{1}{4}H_2O$ requires C, 66·5; H, 6·2%). The *picrate* from the former compound formed soft yellow plates, m. p. 126—127° (Found: C, 46·4; H, 3·4. $C_{11}H_{10}O_2N_2,C_6H_3O_7N_3$ requires C, 47·3; H, 3·0%), and from the latter, clusters of bright yellow needles, m. p. 129° (Found: C, 49·7; H, 3·7. $C_{13}H_{14}O_2N_2,C_6H_3O_7N_3$ requires C, 49·7; H, 3·7%), from methanol–ether.

The results and *products* of these nitrations are in Table 4.

TABLE 4.

Quinoline in concn. H_2SO_4	(g.)	(c.c.)	H_2SO_4 (c.c.)	HNO_3 (c.c.)	Fuming nitric acid (c.c.)	Recrystd. from *	Pure product (g.)	Pure product (%)
6-Methyl ...	220	550	200	125	—	$COMe_2$	217	75
7-Methyl ...	80	200	—	—	32	,,	76	72
6-Ethyl ...	40	105	25	20	—	Et_2O–Pet	45	85
7-Ethyl ...	16	45	—	—	7·5	Aq. $COMe_2$	13	63
6-Propyl ...	26·7	67	17	13·5	—	Pet	31	92
7-Propyl ...	3·7	10	—	—	1·5	,,	3·1	65
6-Butyl ...	42	100	70	22	—	—	44	84
7-Butyl ...	15·5	40	—	—	6·0	Et_2O–Pet	13·7	71
6-Dodecyl	35	175	54	12	—	Aq. MeOH	30·6	74

* Pet = light petroleum.

Quinoline Alkyl	NO₂	M. p	Form	Found (%): C	Found (%): H	Formula	Reqd. (%): C	Reqd. (%): H
6-Me	5	116—117°	—	—	—	—	—	—
7-Me	8	183—184	—	—	—	—	—	—
6-Et	5	52—53	Prisms	65·7	4·9	$C_{11}H_{10}O_2N_2$	65·3	5·0
7-Et	8	136	Needles	65·2	4·85	,,	,,	,,
6-Pr	5	23—25	Plates	66·75	5·4	$C_{12}H_{12}O_2N_2$	66·65	5·6
7-Pr	8	58—59	Needles	66·5	5·7	,,	,,	,,
6-Bu	5	†	—	—	—	—	—	—
7-Bu	8	71	,,	67·6	6·1	$C_{13}H_{14}O_2N_2$	67·8	6·1
6-$C_{12}H_{25}$	5	53—55	,,	70·1	8·9	$C_{21}H_{30}O_2N_2,H_2O$	70·0	8·95

† The anhydrous product is an oil, b. p. 128°/0·2 mm. For the hydrate see text.

Alkylaminoquinolines.—(a) *5-Amino-6-methylquinoline.* The nitro-compound (152 g.) in acetic acid (200 c.c.) and water (3·5 l.) was stirred with iron pin dust (100 g.) at 95° for 9—10 hr. The mixture was filtered, the filtrate was basified with ammonia, and the dark green product was crystallised from boiling water. The iron residues were extracted with boiling water to afford a further quantity of material. 5-Amino-6-methylquinoline (103 g., 80%) separated from water as green needles, m. p. 135° (Bogert and Fisher, *loc. cit.*, gave m. p. 135°. Noelting and Trautmann, *loc. cit.*, gave m. p. 145°). Recrystallisation from ethanol changed the m. p. to 75—85°. The product produced by catalytic reduction in methanol (see below) had an indefinite m. p., softening at 70°, and finally melting at 90—93°.

(b) *8-Amino-7-methylquinoline.* 7-Methyl-8-nitroquinoline (20 g.), etched pin dust (20 g.), acetic acid (40 c.c.), and water (200 c.c.) were stirred at 95° for 24 hr. By basification of the filtrate from this mixture a wet sludge was obtained which was extracted several times with boiling acetone. The iron residues were similarly treated, and the combined extracts were diluted with ether, separated from an aqueous layer, and dried. The product isolated by removal of the solvent was distilled, giving a fraction, b. p. 154—156°/6—8 mm., m. p. 40—45°. Crystallisation from aqueous alcohol gave yellow needles, m. p. 41—44°. On exposure of this solid to the atmosphere the m. p. changed to 58—59° (cf. Elderfield *et al.*, and Capps, *locc. cit.*).

(c) *Catalytic reductions.* The nitroquinoline, 5% palladium–charcoal, and methanol were shaken with hydrogen at atmospheric pressure. When reduction was complete the catalyst was removed and the solution was concentrated. Solid amines were precipitated by water, but oils were distilled. The details are in Table 5. The following data refer to the products.

(1) 5-*Amino*-6-*methylquinoline picrate*, orange-red needles, m. p. 225—227° (decomp.) (Found: C, 49·7; H, 3·6. $C_{10}H_{10}N_2,C_6H_3O_7N_3$ requires C, 49·6; H, 3·4%).

(2) 8-*Amino*-7-*methylquinoline hemihydrate* (Found: C, 72·2; H, 6·4. $C_{10}H_{10}N_2,\frac{1}{2}H_2O$ requires C, 71·8; H, 6·6%), greenish-yellow needles from aqueous methanol. *Picrate*, orange-yellow needles, m. p. 224—226° (Found: C, 49·7; H, 3·4%), from methanol, or scarlet needles, m. p. 200—220° (decomp.) (Found: C, 53·1; H, 3·8. $C_{10}H_{10}N_2,C_6H_3O_7N_3,2C_3H_6O$ requires C, 52·5; H, 5·0. $C_{10}H_{10}N_2,C_6H_3O_7N_3,3C_3H_6O$ requires C, 53·5; H, 5·6%), from acetone.

(3) 5-*Amino*-6-*ethylquinoline hydrate* (Found: C, 69·75; H, 7·5. $C_{11}H_{12}N_2,H_2O$ requires C, 69·4; H, 7·4%), greenish-yellow blades from aqueous methanol. *Picrate*, reddish-orange needles, m. p. 220—222° (Found: C, 49·7; H, 3·6. $C_{11}H_{12}N_2,C_6H_3O_7N_3$ requires C, 50·8; H, 3·8%), from methanol.

(4) 8-*Amino*-7-*ethylquinoline* (Found: C, 75·8; H, 7·0. $C_{11}H_{12}N_2$ requires C, 76·7; H, 7·0%), yellow oil. The *hydrated* amine (Found: C, 74·2; H, 6·5. $C_{11}H_{12}N_2,\frac{1}{4}H_2O$ requires C, 74·7; H, 7·1%) gave prisms from light petroleum (b. p. 40—60°). *Picrate*, orange needles, m. p. 203—204° (Found: C, 51·7; H, 3·8%) from methanol, or scarlet prisms, m. p. 180° (Found: C, 52·6; H, 4·1. $C_{11}H_{12}N_2,C_6H_3O_7N_3,C_3H_6O$ requires C, 52·3; H, 4·2%), from acetone.

(5) 5-*Amino*-6-*propylquinoline hydrate* (Found: C, 69·9; H, 7·9. $C_{12}H_{14}N_2,H_2O$ requires C, 70·55; H, 7·9%), felted needles from aqueous methanol. *Picrate*, crimson prisms, m. p. 227° (decomp.) (Found: C, 52·4; H, 4·2. $C_{12}H_{14}N_2,C_6H_3O_7N_3$ requires C, 52·1; H, 4·1%), from methanol.

TABLE 5.

					Pure product			
No.	Quinoline	(g.)	MeOH (c.c.)	Pd–C (g.)	g.	%	B. p. (°/mm)	M. p.[a]
1	6-Methyl-5-nitro	4	100	1	3·3	98	—	(90—93°) 135°
2	7-Methyl-8-nitro	20	550	2	16·3	97	156/6	(41—44) 58—59
3	6-Ethyl-5-nitro	,,	400	,,	15·5	91	—	(88) 104
4	7-Ethyl-8-nitro	12·9	420	1·5	10·7	98·5	167—168/8	32—35
5	5-Nitro-6-propyl	18	450	2	15·2	98	—	(69—73) 87—90
6	8-Nitro-7-propyl	2·3	50	0·2	2	100	180—182/10	5—10
7	6-Butyl-5-nitro	27·5	450	1·3	24·5	100	—	(55—60) 85—86
8	7-Butyl-8-nitro	10	250	1	8·55	98·2	177—178/6	14—15
9	6-Dodecyl-5-nitro	7	360	,,	6·1	95·5	—	67—69

[a] M. p.s in parentheses refer to unhydrated or lower hydrated forms.

(6) 8-*Amino*-7-*propylquinoline* (Found: C, 77·3; H, 7·6. $C_{12}H_{14}N_2$ requires C, 77·4; H, 7·6%), yellow oil at room temperature. The m. p. is approximate. *Picrate*, scarlet prisms, m. p. 197—199° (decomp.) (Found: C, 52·1; H, 3·9%), from methanol, or bright scarlet prisms, m. p. 163° (Found: C, 54·8; H, 4·7. $C_{12}H_{14}N_2,C_6H_3O_7N_3,3C_3H_6O$ requires C, 55·0; H, 5·9%), from acetone.

(7) 5-*Amino*-6-*butylquinoline hydrate* (Found: C, 70·9; H, 8·0. $C_{13}H_{16}N_2,H_2O$ requires C, 71·5; H, 8·3%), soft pale green prisms from aqueous methanol. *Picrate*, orange needles, m. p. 218—220° (decomp.) (Found: C, 53·6; H, 4·6. $C_{13}H_{16}N_2,C_6H_3O_7N_3$ requires C, 53·2; H, 4·5%), from methanol.

(8) 8-*Amino*-7-*butylquinoline* (Found: C, 78·5; H, 8·15. $C_{13}H_{16}N_2$ requires C, 77·9; H, 8·05%). *Picrate*, orange needles, m. p. 172—173° (Found: C, 53·65; H, 4·0%), from methanol, or orange crystals, m. p. 127—128° (Found: C, 55·1; H, 4·65. $C_{13}H_{16}N_2,C_6H_3O_7N_3,2C_3H_6O$ requires C, 55·0; H, 4·7%), from acetone.

(9) 5-*Amino*-6-*dodecylquinoline hemihydrate* (Found: C, 77·8; H, 9·8. $C_{21}H_{32}N_2,\frac{1}{2}H_2O$ requires C, 78·4; H, 10·3%), light brown prisms from aqueous methanol. *Picrate*, red-orange needles, m. p. 130° (Found: C, 60·0; H, 6·5. $C_{21}H_{32}N_2,C_6H_3O_7N_3$ requires C, 59·8; H, 6·5%), from methanol.

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