Reactions of 2,2-Dialkyl-1,2-dihydroquinolines. Part III.[1] Reactions of 4-Bromomethyl-1,2-dihydro-2,2-dimethylquinolines with Nucleophiles

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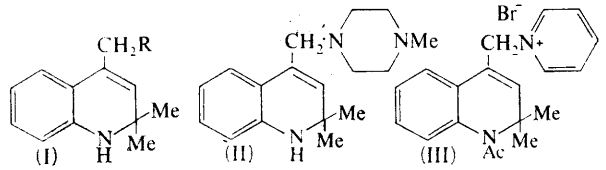
Four successive bromination products [1] of 1,2-dihydro-2,2,4-trimethylquinoline, all containing a 4-bromomethyl group, react with monofunctional nucleophiles, in the presence of acid acceptors, to give the expected products. Selective alkylation of certain bifunctional nucleophiles was possible. In the reaction with 2-dimethylaminoethanol, the 3-bromo-substituent of the tetrabromination product was also involved.

THE finding,[1] that bromination of the hydrobromide or of the 1-acetyl derivative of 1,2-dihydro-2,2,4-trimethylquinoline (I; R = H) gave products containing a 4-bromomethyl group in the first four stages, has enabled the search [2] for biologically active derivatives of this readily available heterocyclic base to be continued by introducing additional amino-groups and other groups of biological interest into the molecule. The free base (I; R = Br) from the monobromination product polymerises rapidly in alcoholic solvents and, apart from the small yield of a quaternary salt mentioned earlier,[1] products from the condensation of the monomeric base with nucleophiles were not isolated under these conditions.

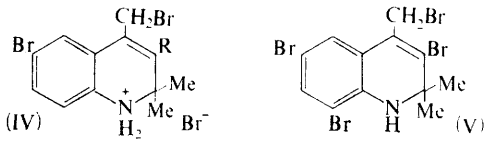


The *N*-acetyl derivative of the bromo-compound (I; R = Br) in benzene or in acetone reacted smoothly with the following nucleophiles: diethylamine, morpholine, 1-methylpiperazine (in excess), pyridine, potassium thiocyanate, and sodium benzothiazole-2-thiolate. The first three products were deacetylated with hydrochloric acid (alkaline deacetylation was slow) to give the diamines (I; R = $\cdot NEt_2$ or morpholino) and the triamine (II). The product (III) from pyridine was also obtained by monobromination of the 1-acetyl derivative of the base (I; R = H) in pyridine solution.

In the reactions with amines, a simpler way to avoid polymerisation of the free base (I; R = Br) is the addition of its powdered hydrobromide either to a solution of the amine in a hydrocarbon solvent or to a large excess of the liquid amine. The triamine (II) was made by this route also, as was another triamine (I; R = $\cdot NH\cdot[CH_2]_2\cdot NEt_2$) with a side-chain encountered in biologically active compounds. (If a substantial excess of the starting diamines is not used, ill-defined products containing quaternary nitrogen are obtained.)

The dibromination (IV; R = H) and tribromination (IV; R = Br) products also reacted with an excess of 2-diethylaminoethylamine in benzene solution to give crystalline triamines.

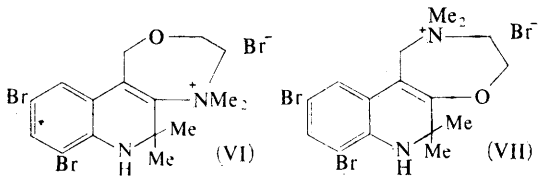
The tetrabromination product (V), a stable free-base, presented no difficulty and, in acetone or ethanolic solution, reacted with equimolar proportions of a variety of amines and other nucleophiles (see Table).



A two molecular proportion of the tetrabromo-compound (V) reacted with methylamine to give a tertiary amine and, in one run with 2-diethylaminoethylamine, an analogous by-product was isolated. With piperazine, both amino-groups were alkylated.

With ethanolamine, compound (V) yielded 3,6,8-tribromo-1,2-dihydro-4-(2-hydroxyethylaminomethyl)-2,2-dimethylquinoline, which gave a diacetyl derivative with acetic anhydride; the presence of ester and amide carbonyl groups and of secondary amino-groups was confirmed from the i.r. spectrum. The free amino-group was expected since product (V) itself (which does not even form a hydrobromide [1]) is recovered unchanged from boiling acetic anhydride. In one run an isomeric by-product was also isolated. This was at first thought to be the product of *O*-alkylation of the ethanolamine. With acetic anhydride it gave a compound the carbon and hydrogen contents of which were consistent with the expected monoacetyl derivative; the nitrogen content was, however, significantly low. The i.r. spectrum indicated monoacetylation at a hydroxy group and not at a primary amino-group. In two further experiments, this by-product was not isolated and it is thought probable that it arose from an impurity in the product (V) used for the first run, although the absence of an amino-group capable of acetylation is in any case hard to explain. Experiments with four possible impurities yielded negative results.

Participation of more than one bromine atom of the tetrabromo-compound (V) in the reaction was detected in only one case, namely, with 2-dimethylaminoethanol



(excess) at 95°. Analysis of the product showed that the expected condensation with loss of the elements of hydrogen bromide had occurred but the product contained ionic bromine. Structures (VI) and (VII)

[1] Part II, J. P. Brown and L. M. Jackman, *J. Chem. Soc.*, 1964, 3132.
[2] J. P. Brown, *J. Chem. Soc.*, 1964, 3012.

which contain a seven-membered ring, seem to be possibilities.

EXPERIMENTAL

4-Diethylaminomethyl-1,2-dihydro-2,2-dimethylquinoline.—A solution of 1-acetyl-4-bromomethyl-1,2-dihydro-2,2-dimethylquinoline (11·7 g.) in benzene (100 ml.) was treated with dry, freshly distilled diethylamine (10 ml.). Next day, diethylamine hydrobromide was filtered off. Evaporation of the benzene liquors gave a thick syrup which was boiled for 10 min. with concentrated hydrochloric acid (10 ml.) and water (40 ml.). After addition of alkali, the *diamine* was isolated in ether and distilled, to give a light yellow oil (6·5 g.), b.p. 120—125°/0·7 mm. (Found: C, 78·4; H, 10·3; N, 11·5. $C_{16}H_{24}N_2$ requires C, 78·7; H, 9·9; N, 11·5%).

1,2-Dihydro-2,2-dimethyl-4-morpholinomethylquinoline.—This was prepared in the same way as the foregoing compound, except that acetone was used instead of benzene as the solvent for the first stage. The intermediate N-*acetyl-compound* [20·3 g. from acetyl-bromo-compound (35·3 g.)] was isolated as off-white prisms, m.p. 87—89° (Found: C, 72·1; H, 8·3; N, 9·3. $C_{18}H_{24}N_2O_2$ requires C, 72·0; H, 8·0; N, 9·3%) and yielded the *diamine* (16·6 g.), m.p. 127—129°. An analytical sample of the latter formed very pale yellow prisms, m.p. 127—129°, from ethanol (Found: C, 74·4; H, 8·8; N, 10·8. $C_{16}H_{22}N_2O$ requires C, 74·4; H, 8·6; N, 10·9%).

1,2-Dihydro-2,2-dimethyl-4-(4-methylpiperazin-1-ylmethyl)-quinoline (II).—(a) *From 1-acetyl-4-bromomethyl-1,2-dihydro-2,2-dimethylquinoline.* The acetyl-bromo-compound (10·95 g.) and *N*-methylpiperazine (25 ml.) in benzene (100 ml.) reacted at room temperature and after 1 hr. the condensation product was isolated and distilled to give a light yellow oil (5·4 g.), b.p. 168—174°/0·9 mm. Hydrolysis with boiling hydrochloric acid (16%) yielded the triamine as a yellow oil, which formed a *trihydrochloride* (4·3 g.), m.p. 162—165° (decomp.) (Found: C, 49·2; H, 7·8; Cl, 24·9; N, 10·0. $C_{17}H_{28}Cl_3N_3,2H_2O$ requires C, 49·0; H, 7·7; Cl, 25·5; N, 10·1%).

(b) *From 4-bromomethyl-1,2-dihydro-2,2-dimethylquinoline hydrobromide.* To a stirred solution of 1-methylpiperazine (20 ml.) in benzene (100 ml.) the powdered hydrobromide (19·5 g.) was added in portions at 20—25° during 30 min. Next day, 1-methylpiperazine hydrobromide (21·5 g.) was filtered off; the benzene liquors were washed with water and evaporated. The residue was distilled and the triamine (7·2 g.) was collected as a yellow oil, b.p. 138—140°/0·05 mm. from which the trihydrochloride (8·2 g.), m.p. 161—164° (decomp.) was prepared. I.r. spectra confirmed the identity of the products from (a) and (b).

1-(1-Acetyl-1,2-dihydro-2,2-dimethylquinolin-4-ylmethyl)-pyridinium Bromide (III).—The *N*-acetyl-bromo-compound (2·95 g.) in acetone (5 ml.) was mixed with pyridine (0·9 ml.). After 4 hr. the colourless *salt* (1·55 g.), m.p. 148—152°, was filtered off; it recrystallised from a small amount of ethanol, as off-white prisms, m.p. 171—173°, which became green with time (Found: C, 60·5; H, 5·8; Br, 22·1; N, 7·4. $C_{19}H_{21}BrN_2O$ requires C, 61·1; H, 5·6; Br, 21·6; N, 7·5%). The same compound (i.r.) was obtained by adding to 1-acetyl-1,2-dihydro-2,2,4-trimethylquinoline (21·5 g.) in pyridine (100 ml.) a solution of bromine (5·4 ml.) in carbon tetrachloride (25 ml.) during 2 hr. at 20°. The pyridine hydrobromide was filtered off and, the excess of pyridine was removed under reduced pressure; the residue was treated with acetone to give the crude brownish quaternary salt (23·4 g.), m.p. 150—162°. A sample crystallised as off-white prisms, m.p. 173—175°, from ethanol (Found: C, 60·4; H, 5·8; N, 7·0. Calc. for $C_{19}H_{21}BrN_2O$: C, 61·1; H, 5·6; N, 7·5%).

1-Acetyl-1,2-dihydro-2,2-dimethyl-4-thiocyanomethyl-quinoline.—The acetyl-bromo-compound (14·7 g.) and

Reactions of 3,6,8-tribromo-4-bromomethyl-1,2-dihydro-2,2-dimethylquinoline (V = R^1CH_2Br) with nucleophilic reagents, R^2M (where M = H, Na, or K), according to the equation $R^1CH_2Br + R^2M \longrightarrow R^1CH_2R^2 + MBr$

R^2M	Reaction solvent	Yield on (V) (%)	M.p. of product	Found (%) C	H	Br	N	S	Formula of product	Required (%) C	H	Br	N	S
NH_3 [a]	EtOH–Me_2CO–H_2O	71	130—132°	33·9	3·1	55·5	6·6		$C_{12}H_{13}Br_3N_2$	33·9	3·1	56·5	6·6	
Me_2NH [b]	EtOH	88	82—83	37·2	3·7	52·8	6·0		$C_{14}H_{17}Br_3N_2$	37·1	3·7	53·0	6·2	
Et_2NH	Me_2CO	72	57—60	39·7	4·1		5·6		$C_{16}H_{21}Br_3N_2$	39·9	4·4		5·8	
Piperidine	Me_2CO	94	82—84	41·4	4·3		5·7		$C_{17}H_{21}Br_3N_2$	41·4	4·4		5·5	
Morpholine	Me_2CO	75	135—138	38·9	3·7		5·4		$C_{16}H_{19}Br_3N_2O$	38·8	3·9		5·7	
p-EtO·C_6H_4·NH_2	Me_2CO	84	135—136	44·2	3·6	44·0	5·0		$C_{20}H_{21}Br_3N_2O$	44·0	3·9	44·0	5·1	
p-Me_2N·C_6H_4·NH_2	Me_2CO	72	164—165	44·4	4·0	44·3	7·5		$C_{20}H_{22}Br_3N_3$	44·1	4·1	44·1	7·7	
2-Aminopyridine [c]	Me_2CO	75	220—230	34·4	3·1	56·0	6·8		$C_{17}H_{17}Br_4N_3$	35·0	2·9	54·9	7·2	
1-Methylpiperazine [d]	Me_2CO	70	107—108	40·3	4·4	47·4	8·3		$C_{17}H_{22}Br_3N_3$	40·1	4·3	47·2	8·3	
Et_2N·$[CH_2]_2$·NH_2 [d,e]	Dioxan	52	68—71	41·3	5·3	45·8	8·1		$C_{18}H_{26}Br_3N_3$	41·2	5·0	45·8	8·0	
MeONa	MeOH	97	150—151	35·8	3·2	54·5	3·0		$C_{13}H_{14}Br_3NO$	35·5	3·2	54·5	3·2	
EtONa	EtOH–H_2O	77	78—79·5	37·3	3·7	52·4	3·1		$C_{14}H_{16}Br_3NO$	37·0	3·5	52·9	3·1	
Me_2N·CS·SNa	Me_2CO	86	164—165	34·0	3·4	45·3	5·1	11·8	$C_{15}H_{17}Br_3N_2S_2$	34·1	3·2	45·5	5·3	12·1
B.T.T.[f]	Me_2CO	96	121—122	39·8	2·7	41·7	4·7	11·1	$C_{19}H_{15}Br_3N_2S_2$	39·6	2·6	41·7	4·9	11·1
D.T.T.T.[g]	Me_2CO	95	171—172	38·8	2·6	36·4	2·4	19·2	$C_{21}H_{16}Br_3NS_4$	38·8	2·5	36·9	2·2	19·7
KSCN	Me_2CO	96	123—124·5	33·9	2·6	51·3	5·8	6·6	$C_{13}H_{11}Br_3N_2S$	33·4	2·4	51·4	6·0	6·9
p-AcNH·C_6H_4·ONa [h]	Me_2CO	83	216—217	41·4	3·5		5·3		$C_{20}H_{19}Br_3N_2S_2$	42·9	3·4		5·0	

[a] Large excess of ammonia. Hydrochloric acid added to reaction mixture to precipitate the hydrochloride, m.p. 240—241° (Found: C, 30·7; H, 3·5; Br, 51·0; N, 5·8. $C_{12}H_{14}Br_3ClN_2$ requires C, 31·2; H, 3·1; Br, 52·0; N, 6·1%). [b] Already reported.[1] [c] One molecular proportion of 2-aminopyridine used, product was 3,6,8-tribromo-1,2-dihydro-2,2-dimethyl-4-(2-pyridylaminomethyl)quinoline hydrobromide. [d] Large excess of diamine used. [e] Details in text. [f] B.T.T. is sodium benzothiazole-2-thiolate. *S*-Alkylation (as shown by i.r. and u.v. spectra) occurs. [g] D.T.T.T. is sodium 4-phenyl-3-thioxo-1,2-dithiole-5-thiolate.[3] [h] Potassium carbonate (in excess) was used as an acid acceptor. Product was deacetylated, with sodium hydroxide in aqueous ethanol, to the p-*aminophenoxymethyl compound*, m.p. 192—193 (Found: C, 41·8; H, 3·4; Br, 47·3; N, 5·8. $C_{18}H_{17}Br_3N_2O$ requires C, 41·8; H, 3·3; Br, 46·4; N, 5·4%) and this was converted with dicyandiamide to the p-*biguanidinophenoxymethyl compound*, m.p. 179—180° (Found: C, 40·3; H, 3·8; Br, 38·7; N, 14·0. $C_{20}H_{21}Br_3N_6O$ requires C, 39·9; H, 3·5; Br, 39·9; N, 14·0%).

[1] J. P. Brown, *J. Chem. Soc.* (*C*), 1968, 1077.

potassium thiocyanate (7 g.) in acetone (120 ml.) gave a green resinous product from which pale yellow prisms (4·3 g.), m.p. 102—105° of the *thiocyano-compound* were obtained on addition of a little ethanol (Found: C, 66·0; H, 5·6; N, 10·1; S, 11·7. $C_{15}H_{16}N_2OS$ requires C, 66·5; H, 5·9; N, 10·3; S, 11·7%).

1-*Acetyl*-4-*benzothiazol*-2-*ylthiomethyl*-1,2-*dihydro*-2,2-*dimethylquinoline*.—The acetyl-bromo-compound (29·4 g.) and sodium benzothiazole-2-thiolate in acetone (100 ml.) gave the sulphide (29·5 g.), m.p. 132—133°. An analytical sample formed off-white prisms, m.p. 133—134°, from ethanol (Found: C, 66·7; H, 5·3; N, 7·1; S, 16·0. $C_{21}H_{20}N_2OS_2$ requires C, 66·3; H, 5·3; N, 7·4; S, 16·9%). Attempted deacetylation gave only resinous material.

4-(2-*Diethylaminoethylaminomethyl*)-1,2-*dihydro*-2,2-*dimethylquinoline and its* 6-*Bromo*-, 3,6-*Dibromo*-, *and* 3,6,8-*Tribromo-derivatives*.—The hydrobromide of the mono-bromination product (I; R = Br) (66·8 g.) was added to a solution of 2-diethylaminoethylamine (108 ml.) in benzene (400 ml.) at 25°. The reaction product was distilled and treatment of the fraction boiling at 120—200°/0·3 mm. with light petroleum (b.p. 40—60°) gave the crystalline *triamine* (20·9 g.), m.p. 51—53° (Found: C, 75·8; H, 10·2; N, 14·6. $C_{18}H_{29}N_3$ requires C, 75·3; H, 10·1; N, 14·6%). The 6-*bromo-analogue* was similarly made from the dibromo-compound (IV; R = H) (41·2 g.); the product was not distilled. Addition of light petroleum (20 ml.) gave off-white needles (16·8 g.), m.p. 76—78° which formed needles, m.p. 84—85°, from light petroleum (Found: C, 58·5; H, 7·8; N, 10·5. $C_{18}H_{28}BrN_3$ requires C, 59·0; H, 7·7; N, 11·5%). The 3,6-*dibromo-analogue* was similarly made from the tribromo-compound (IV; R = Br) (49·1 g.) and formed pale yellow needles (18 g.), m.p. 98—99° (Found: C, 48·5; H 5·8; Br, 36·1; N, 9·5. $C_{18}H_{27}Br_2N_3$ requires C, 48·5; H, 6·1; Br, 36·0; N, 9·4%). The 3,6,8-*tribromo-analogue* was made from the tetrabromo-base (V) (16·3 g.) in dioxan (100 ml.) and the diamine (10 ml.) and formed pale yellow prisms (9·2 g.), m.p. 68—71° from light petroleum (Found: C, 41·3; H, 5·3; Br, 45·8; N, 8·1. $C_{18}H_{26}Br_3N_3$ requires C, 41·2; H, 5·0; Br, 45·8; N, 8·0%). In an experiment using tetrabromo-base (9·8 g.) and diamine (11 ml.) in acetone (200 ml.), a mixed product (2·7 g.), m.p. 79—82° was obtained, which from light petroleum gave flat, pale yellow prisms (1·4 g.), m.p. 102—105° of NN-*di*-(3,6,8-*tribromo*-1,2-*dihydro*-2,2-*dimethylquinol*-4-*ylmethyl*)-N'N'-*diethyldiethyldiamine* (Found: C, 38·5; H, 4·1; Br, 51·4; N, 5·7. $C_{30}H_{36}Br_6N_4$ requires C, 38·4; H, 3·9; Br, 51·5; N, 6·0%).

Di-(3,6,8-*tribromo*-1,2-*dihydro*-2,2-*dimethylquinol*-4-*ylmethyl*)*methylamine*.—The tetrabromo-compound (V) (4·9 g.) in acetone (60 ml.) and methylamine (1·5 g.) in ethanol (50 ml.) and water (5 ml.) gave the *triamine* (2·6 g.), m.p. 205—208°. An analytical sample formed pale yellow prisms, m.p. 211—212°, from ethanol (Found: C, 35·5; H, 3·1; Br, 56·2; N, 4·9%; *M* (Rast), 826. $C_{25}H_{25}Br_6N_3$ requires C, 35·4; H, 3·0; Br, 56·7; N, 5·0%; *M*, 847).

Reaction of 3,6,8-*Tribromo*-1,2-*dihydro*-2,2,4-*trimethylquinoline* (V) *with Ethanolamine*.—A mixture of tetrabromo-compound (V) (20 g.) and ethanolamine (100 ml.) was kept at 20° for 2 hr. and then heated at 95° for 1 hr. Three days later, a solid (3·6 g.), m.p. 169—170°, was filtered off. Recrystallisation from methyl ethyl ketone gave prisms, m.p. 176—178° (Found: C, 35·6; H, 3·5; Br, 53·1; N, 6·0. $C_{14}H_{17}Br_3N_2O$ requires C, 35·8; H, 3·6; Br, 51·2; N, 6·0%). After removal of this product, dilution of the ethanolamine liquors with water gave a sticky solid (11·6 g.), m.p. 94—95°. Recrystallisation from light petroleum (600 ml.) gave pale yellow prisms (8·5 g.), m.p. 97—98°. A second recrystallisation from benzene gave very pale yellow prisms (5·5 g.), m.p. 106—107° (Found: C, 36·4; H, 3·6; Br, 49·7; N, 6·1. $C_{14}H_{17}Br_3N_2O$ requires C, 35·8; H, 3·6; Br, 51·2; N, 6·0%).

The i.r. spectra of the two compounds, when observed in dilute carbon tetrachloride solution, indicate the presence of a hydroxy-group. The compound m.p. 97—98° (1 g.) was boiled for 5 min. with acetic anhydride (0·7 g.) to yield a *diacetyl derivative* (1·1 g.), m.p. 133—135°. A sample formed off-white needles, m.p. 137—139° from light petroleum (b.p. 100—120°) (Found: C, 39·0; H, 3·7; N, 5·0. $C_{18}H_{21}Br_3N_2O_3$ requires C, 39·1; H, 3·8; N, 5·1%). The i.r. spectrum indicates the presence of ester and amide carbonyl groups and of a secondary amino-group. The product m.p. 176—178° (0·079 g.) similarly gave a substance (0·073 g.) m.p. 130—155°. Recrystallisation from light petroleum (b.p. 100—120°) gave very pale yellow prisms m.p. 161—163° (Found: C, 37·1; H, 3·7; N, 4·3, 4·3, 4·6, 4·6. $C_{16}H_{19}Br_3N_2O_2$ requires C, 37·6; H, 3·7; N, 5·5%). The i.r. spectrum indicates the presence of ester carbonyl and secondary amino-groups.

The low-melting reaction product is therefore considered to be 3,6,8-*tribromo*-1,2-*dihydro*-4-(2-*hydroxyethylaminomethyl*)-2,2-*dimethylquinoline*. The by-product was not obtained when the experiment was twice repeated with different samples of the tetrabromo-compound and may well have arisen from an impurity in the first sample. Heating ethanolamine with the tribromo- (IV; R = Br) or pentabromo-compound,[1] or with two products analysing as tetrabromo-compounds, which have now been obtained by bromination of the dihydroquinoline (I; R = H) in other solvents, did not give the by-product.

1,4-*Bis*-(3,6,8-*tribromo*-1,2-*dihydro*-2,2-*dimethylquinol*-4-*ylmethyl*)*piperazine*.—A solution of the tetrabromo-compound (V) (14·7 g.) in acetone (200 ml.) was mixed with a solution of piperazine (2·6 ml.) in acetone (5 ml.) at 50°. The reaction mixture was allowed to cool and next day the solid was filtered off, washed with acetone, and kept in water to dissolve piperazine dihydrobromide. The residue (9·9 g.), m.p. 258—260° could not be satisfactorily recrystallised (Found: C, 37·2; H, 3·3; Br, 53·9; N, 5·7. $C_{28}H_{30}Br_6N_4$ requires C, 37·3; H, 3·3; Br, 53·2; N, 6·2%).

Reaction of 3,6,8-*Tribromo*-4-*bromomethyl*-1,2-*dihydro*-2,2-*dimethylquinoline* (V) *with* 2-*Dimethylaminoethanol*.—The powdered tetrabromo-compound (24 g.) and 2-dimethylaminoethanol (20 ml.) were mixed, and then stirred and heated at 95° for 2 hr. The clear solution was cooled, and a solution of sodium hydroxide (4 g.) in water (250 ml.) was added. The semisolid was washed with water by decantation and then treated at room temperature with ethanol (15 ml.). A sticky solid (22·8 g.), m.p. 221—223°, was filtered off. This *quaternary salt*, presumably (VI) or (VII), separated from water as off-white plates, m.p. 230° (decomp.) (Found: C, 38·8; H, 4·5; Br, 45·6; N, 5·7. $C_{16}H_{21}Br_3N_2O$ requires C, 38·7; H, 4·2; Br, 48·3; N, 5·6%). The aqueous solution of the compound contained ionic bromine and no precipitate was obtained on adding alkali.

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