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QUINOLINES —— A NEW HYDROXYMETHYLATION REACTION

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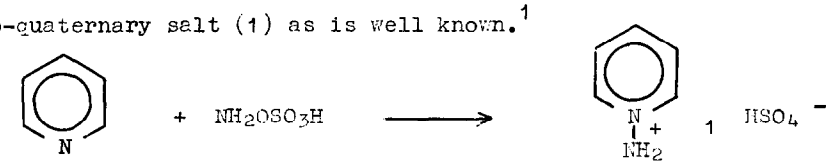
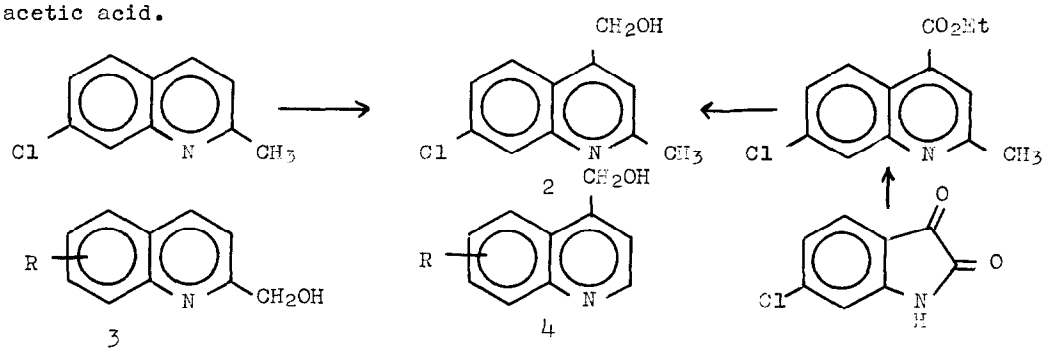
The interaction of hydroxylamine-O-sulphonic acid (HSA) with azines such as pyridines, quinolines and isoquinolines in aqueous solution leads to the N-amino-quaternary salt (1) as is well known.[1]



In the present work, difficulty was experienced in the N-amination of some quinolines owing to their insolubility in the aqueous acid medium, so that similar experiments were conducted using methanol as solvent. This was first attempted with 7-chloro-2-methylquinoline, unexpectedly the product obtained was 7-chloro-4-hydroxymethyl-2-methylquinoline (2) and the unchanged quinoline, which was separated by chromatography on alumina deactivated by acetic acid.



The structure of 2 was proved by p.m.r. and mass spectrometry, and by unambiguous synthesis from 6-chloroisatin via 4-carboxy-7-chloro-2-methyl--quinoline and its ethyl ester. The p.m.r. spectrum of 2 (in trifluoroacetic acid) had signals at 1.9 τ (3-proton multiplet, 3-H, 5-H, 8-H), 2.1 τ (1-proton quartet, 6-H), 4.3 τ (2-proton singlet, CH_2) and 6.85 τ (3-proton singlet, CH_3).

The reaction has been found general (Table 1) for quinolines substituted

in the carbocyclic ring and having either a 2- or 4- position vacant. For quinoline, and its 7-methyl derivative, a mixture of the 2- and 4-hydroxymethyl compounds was formed (ratio 2:1 respectively in each case), which were again separated by chromatography. The 2-hydroxymethyl compounds (3) were eluted with chloroform, whereas the 4 required methanol, and this probably reflects the intramolecular hydrogen-bonded character of the former.

TABLE 1

Products from the Reaction of Some Substituted Quinolines with HSA in Methanol.[a]

Reactant Quinoline (Substituents)		Yield[b] (%)	Conversion (%)	P.m.r. Absorptions Aromatic	CH_2	(τ)[c] OH	m.pt.
None	(3)	55	44	1.90 - 2.75	5.05	4.70	62-3°
	(4)	25		1.35 - 2.60	4.80	4.70	96-7°
2-Methyl-		85	40	1.60 - 1.90[d]	4.27[d]	-[d]	85-6°
4-Methyl-		68	76	1.90 - 2.80	5.15	4.87	76-7°
2,8-Dimethyl		92	50	2.40 - 2.90	5.10	5.86	102-3°
7-Chloro-2-methyl		95	60	1.70 - 2.10[d]	4.30[d]	-[d]	185-6°
6-Bromo-2-methyl		93	42	1.95 - 2.60	4.88	4.88	164-5°

a. Molar Ratios:- Quinoline:HSA = 1:3, in about 10% $^{w}/_{v}$ in methanol.

b. Yields based upon unrecovered quinoline.

c. In $CDCl_3$.

d. In CF_3CO_2H.

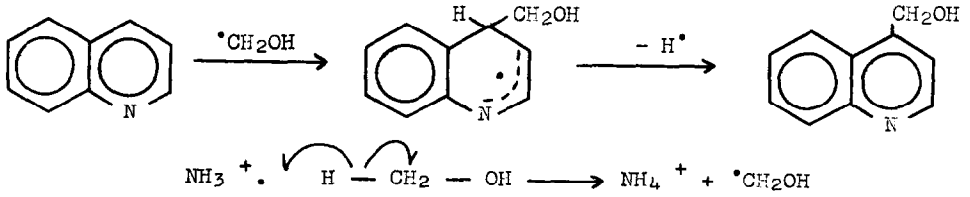
Under conditions similar to those of Table 1, the reaction with 3-bromoquinoline gives a 2- or 4-hydroxymethyl derivative whose orientation has yet to be determined; the reaction with 3-nitroquinoline fails, so that this is probably an electronic effect.

4-Methylquinoline-N-oxide under identical conditions gave a mixture which could not be separated but whose p.m.r. spectrum showed two $-CH_2-$ absorptions near 5τ; one of these was probably due to 3 (R=4-CH_3) while the other was consistent with the corresponding N-oxide. When the solid N-amino quaternary salt of 4-methylquinoline was preformed by reaction with aqueous

HSA, basified and heated with a solution of HSA in methanol, 3 (R=4-CH_3) was obtained. 1,4-Dimethylquinolinium methosulphate was recovered unchanged after reaction with methanolic HSA.

The N-amination process in aqueous solution is best interpreted as electrophilic attack by $\overset{+}{N}H_2$ on the ring nitrogen atom, but in the presence of ferrous ions there is also evidence of homolytic fission of the N-O bond of HSA leading to $\overset{+}{N}H_3$. The hydroxymethylation reaction is unaffected by the presence or absence of ferrous ions, but the conversion is much lower when HSA is replaced by hydroxylamine sulphate and ferrous sulphate. The failure of the hydroxymethylation reaction with 3-nitroquinoline and the quaternary salt is a clear indication that the reaction is not nucleophilic, and this is supported by the difficulty in defining a suitable nucleophilic species for such a reaction. The observed orientation in the quinoline ring is inconsistent with electrophilic attack on either the free quinoline, or its protonated or N-aminated derivatives, but could indicate substitution on the N-imine, by analogy with the corresponding N-oxide. If the latter is the case, then attack by $CH_2\overset{+}{O}H$ formed by removal of a hydride ion from methanol

is conceivable; we have found however that the reaction fails when the following reagents are heated with methanolic quinoline or quinoline-N-imine dimer a) HSA + CH_2O, b) CH_2O+ HCl. The dimeric N-imine is known to react as the monomer is solution.[3] We consider that the substitution reaction is most probably a radical reaction, the reagent being $\cdot CH_2$-OH. The same intermediate has recently postulated[4] for the conversion of pyridazine-N-oxides to 4-hydroxymethylpyridazines in 0.02 to 7.0% yields.



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