[7] $(CH_3)_3C^{\cdot} + CH_3^{\cdot} \rightarrow (CH_3)_4C$

(13) the combination reaction 7 is slightly more favorable than the disproportionation reaction involving the same radicals.

With increasing pressure the competition for methyl and tertiary-butyl radicals in other condensation reactions increases (including some polymerization processes), therefore the production of neopentane diminishes. Such behavior would not be expected for isopentane and n-pentane which are formed by hydrogen abstraction from isobutene by isopentyl or *n*-pentyl radicals.

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Quaternization of quinazoline with methyl iodide

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Contrary to previous reports, the methylation of quinazoline with methyl iodide has been shown to produce both 1-methylquinazolinium iodide and 3-methylquinazolinium iodide. These quaternary salts are formed in the ratio of 5:1 in favor of the latter isomer.

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There are a number of reports in the literature (1-4) that suggest that the quaternization of quinazoline with methyl iodide gives exclusively the 3-methylquinazolinium ion 1. Formation of the 1-methylquinazolinium ion 2 in this reaction



has never been observed. This conclusion is based upon the oxidation of the pseudo-base 3, which 1 readily forms in aqueous solutions, to 3,4-dihydro-3-methyl-4-oxoquinazoline 4 by alkaline potassium ferricyanide.



We have used n.m.r. spectroscopy to study the products of the methylation of quinazoline by methyl iodide, and wish to report that, contrary to previous reports in the literature, appreciable methylation of the N-1 atom does occur, although the main product is the 3-methylquinazolinium ion.

Results and Discussion

The n.m.r. spectrum (in trifluoroacetic acid) of the product from the methylation of quinazoline with methyl iodide is shown in Fig. 1. Two peaks

CANADIAN JOURNAL OF CHEMISTRY. VOL. 48, 1970 4-62 CF₃COOH Sideband 8-55 9-97 9-45 4-74

FIG. 1. The n.m.r. spectrum, in trifluoroacetic acid, of the product from the methylation of quinazoline with methyl iodide.

δppm

7

6

8

(δ 4.62, 4.74) which can be assigned to *N*-methyl groups are apparent, and have relative intensities of 5:1. The n.m.r. spectrum of the same reaction product in dilute aqueous acid solution (0.1 *N* HCl in D₂O) is shown in Fig. 2. Dual peaks, with relative intensities 5:1, appear at three places in this spectrum: δ 8.32, 8.45; 6.21, 6.34; and 3.53, 3.69. In aqueous acid solutions the 3-methyl-quinazolinium ion is known to exist as the cation **6** of the pseudo-base which is formed by hydroxide addition to C-4 (4). The dual peaks in

10

9



the spectrum in Fig. 2 are readily assigned to protons in similar environments to those on C-2 and -4 and N-methyl protons respectively in a structure such as 5. They compare well with the peaks at δ 8.42 (C(2)—H) and 6.38 (C(4)—H) in

the n.m.r. spectrum of the covalently hydrated quinazoline cation 7 (5).

5

4

The similarities of the chemical shifts of these major and minor sets of peaks suggest that they arise from very similar chemical structures. We assign these structures as the covalent hydrates, 6 and 8, of the 3-methylquinazolinium ion (major isomer) and 1-methylquinazolinium ion (minor isomer) respectively. Evidence in support of this structural assignment is presented in the following paragraphs.

When an aqueous solution of the mixture of N-methylquinazolinium ions was carefully titrated with aqueous potassium hydroxide, a white precipitate started to appear at pH 8.5. After the addition of one equivalent of alkali the precipitate was collected. The n.m.r. spectrum of this product in dilute aqueous acid indicated that only the major isomer was present, since the peaks for the minor isomer that were initially present (Fig. 2) were no longer observed. Oxidation of the original mixture of pseudo-bases with alkaline potassium ferricyanide gave a product that had an n.m.r. spectrum in which two peaks were assignable to N-methyl groups (δ 3.52 (major) and 3.80 (minor) in DMSO- d_6). Oxidation of 3 has previously been shown to give 4(3).

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FIG. 2. The n.m.r. spectrum, in 0.1 N HCl in D_2O , of the product from the methylation of quinazoline with methyl iodide.

Thus this oxidized product should be a mixture of 4 and 9. The methyl group in 9 has been



reported (6) to have a chemical shift of δ 3.8 in DMSO- d_6 . On this basis, the minor oxidation product can be assigned to 9 and the major product must therefore be 4. This was confirmed by oxidation of the precipitated pure pseudo-base to give a product which has only one peak (δ 3.52 in DMSO- d_6) in its n.m.r. spectrum that is assignable to an N-methyl group.

Since 4 is derived from the major product of the methylation of quinazoline, this indicates that this major product is 1 (previously reported to be the only product) and therefore 2 is the minor product. The presence of 9 in the oxidation products also eliminates the remote possibility that the two pseudo-bases contributing to the spectrum in Fig. 2 are stereoisomers of 6 arising from a slow inversion of N-3. Such stereoisomers would give rise to the same oxidation product, 4. The possibility that the dimethylated quinazoline dication 10 is the minor product of the reaction can be ruled out on the basis of the



oxidation experiments discussed above and the following evidence. The pseudo-base **3** was treated with methyl iodide to give **11**. The n.m.r. spectrum of **11** in trifluoroacetic acid has peaks at δ 3.70 (singlet, 3H), 3.87 (singlet, 3H), 7.69 (center of multiplet, 5H) and 8.35 (singlet, 1H), while in D₂O the peaks are at δ 3.58 (singlet, 3H), 3.73 (singlet, 3H), 6.28 (singlet, 1H), 7.62 (center of multiplet, 4H), and 8.50 (singlet, 1H). There is a close correspondence between the spectra in these two solvents except for the peak at δ 6.28 in D₂O which seems to move downfield in trifluoroacetic acid and occurs along with the benzene ring protons in the multiplet centered at δ 7.69. This downfield shift can be explained by

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a conversion of **11** into **12** in trifluoroacetic acid, with the downfield shift of C(4)—H resulting from the replacement of the hydroxyl group on C-4 by the more strongly electron-withdrawing trifluoroacetoxy group. The spectrum in trifluoroacetic acid is not consistent with what would be expected for the dication **10**. For **10**, the peaks for the protons on C-2 and -4 should be even further downfield than those for the protons on the same two carbon atoms in **1** (δ 9.45 and 9.97 in Fig. 1). Finally, oxidation of **11** did not give a product with an *N*-methyl peak at δ 3.80 as was observed for the minor oxidation product in the mixture of pseudo-bases.

It is interesting that the 1-methylquinazolinium ion forms the pseudo-base cation 8 rather than 13 which would result from nucleophilic addition at the more electron-deficient C-2. The formation of 8 can be explained by its enhanced stability due to amidinium-type resonance stabilization (7) which is not possible in 13. This type of resonance stabilization has also been invoked to explain the stabilities of the cation of the pseudobase of the 3-methylquinazolinium ion, 6, and of the covalently hydrated quinazoline cation, 7.



Methylation of a nitrogen heterocycle containing more than one azine nitrogen atom is expected to occur predominantly at the most basic nitrogen atom in the absence of opposing steric effects. Owing to the ready formation of a covalent hydrate by the quinazolinium ion (7), it is not possible to ascertain experimentally the site of protonation in quinazoline. Estimates have been made of the relative basicities of N-1 and -3 in quinazoline on the basis of an empirical equation that has been developed to generate estimates of pK_a values for substituted quinolines and isoquinolines (8). These considerations suggest that N-3 is probably only slightly more basic than N-1 and that the non-hydrated quinazolinium ion is probably a mixture of N(3)- and N(1)-protonated species in which the former predominates. Theoretical calculations of the electron density distribution in the quinazoline molecule also indicate that there is probably little difference in the basicities of the N-1 and -3 atoms in guinazoline (9–11). Thus, one would predict that N-3 should be only slightly favored over N-1 as the methylation site, and that methylation may possibly produce a mixture of the isomeric *N*-methylquinazolinium ions. Our experimental results are in accord with such a rationalization of this reaction.

It is noteworthy that the presence of substituents on C-4 can alter the preferred site of methylation from N-3 to -1 (3). This further confirms that there is little difference in the susceptibilities of N-1 and -3 to methylation, since the preferred site of attack may be readily influenced by the electronic and/or steric effects of substituents.

Experimental

The n.m.r. spectra were recorded on Varian T-60 or A-60 spectrometers using sodium 2,2-dimethyl-2-silapentane-5-sulfonate as internal reference.

Methylation of Quinazoline

(A) Quinazoline (1 g) was dissolved in ethanol (5 ml). Methyl iodide (1 ml) was added and the solution was refluxed for 4 h. The solvent was evaporated and the viscous residue dissolved in chloroform. The chloroform solution was extracted with dilute aqueous hydrochloric acid and the aqueous extracts were evaporated to yield a mixture of the hydroiodides of the pseudo-bases of the *N*-methylquinazolinium ions as a yellow viscous oil which solidified on standing; m.p. 89°.

Anal. Calcd for $C_9H_{11}N_2OI$: C, 37.4; H, 3.48; N, 9.69; I, 43.8. Found: C, 38.2;¹ H, 3.64; N, 9.64; I, 44.0.

(B) Quinazoline (1 g) and methyl iodide (1 ml) were allowed to stand at room temperature overnight. The excess methyl iodide was evaporated and the residue worked-up as described above.

The ratio of 1-methyl- to 3-methylquinazolinium ions in the trifluoroacetic acid solution was the same, within experimental error, for the products from quaternization in ethanol solution (method A) and the neat methyl iodide (method B).

3,4-Dihydro-4-hydroxy-3-methylquinazoline

Aqueous potassium hydroxide (1 M) was added dropwise to an aqueous solution (1 M) of the mixture of products from the quaternization reaction, until the pH reached 9.5. The white precipitate which had formed was filtered off and redissolved in water (2 ml) to which 1 drop of hydrochloric acid had been added. The pseudo-base was then reprecipitated by addition of potassium hydroxide solution; m.p. 161–162°, lit. m.p. 162–163° (1), 164–165° (2), 158° (3), 167–168° (4). Mass spectrum: molecular ion peak at 162; most intense peak at M-17 (loss of OH).

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.7; H, 6.21; N, 17.3. Found: C, 65.7;¹ H, 6.22; N, 17.2.

Methylation of 3,4-Dihydro-4-hydroxy-3-methylquinazoline The pure pseudo-base (0.05 g) and methyl iodide (1 ml)

¹Difficulty in obtaining satisfactory carbon analyses for this class of compound has been reported previously (12).

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were refluxed in ethanol (3 ml) for 24 h. The reaction product was worked-up as described for the methylation of quinazoline.

Incubation of the pseudo-base cation with methyl iodide in ethanol, under the same conditions that were used for the methylation of quinazoline, did not result in the methylation of N-1.

Oxidation Experiments

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The pseudo-base was treated with a solution of potassium ferricyanide (1 M) in aqueous potassium hydroxide (1 M) for 10-15 min. The oxidation products were extracted into chloroform; these extracts were dried over magnesium sulfate and the solvent removed on the rotary evaporator. Treatment of either the pseudo-bases or their oxidation products with strong alkali for excessive periods of time resulted in their decomposition products being present in the chloroform extracts.

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Electron spin resonance studies of radiation damage. Part IV.^{1,2} The effect of photobleaching on the trapped radicals in gamma irradiated 2-methyltetrahydrofuran glasses at 77 °K

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The concentration of trapped radicals was found to decrease during the course of photobleaching trapped electrons in gamma irradiated 2-methyltetrahydrofuran glasses at 77 °K.

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The electron spin resonance (e.s.r.) spectra of irradiated gamma 2-methyltetrahydrofuran glasses at 77 °K consists of a narrow singlet 4 G wide due to a trapped electron and a broad septet of linewidth 10 G and hyperfine spacing of 20 G due to a trapped radical (1-3). The reported e.s.r. studies have been in agreement apart from one exception, namely, the effects of photobleaching. Smith and Pieroni (4) reported that photobleaching led to the complete removal of the singlet together with one third of the radical septet; however, Shirom and Willard (5) report no change in the intensity of radical spectrum within $\pm 2\%$ and Dainton and Salmon (2) report "no significant change took place in the background spectrum" (i.e. the radical) when the electron singlet was photobleached. We thought these differences were sufficiently important to re-investigate the photobleaching of these glasses.

Methyltetrahydrofuran, MTHF, was purified by the usual methods (2), but the final stages involved treatment with naphthalene and a sodium mirror on a vacuum line followed by distillation to a storage vessel containing a sodium mirror only. After several months there has been no deterioration of this mirror. Greaseless and O-ring free stopcocks were used throughout the vacuum system. Samples were prepared by distillation from the storage bulb to thin walled spectrosil e.s.r. tubes which had been flamed out at red heat. These were gamma

¹For Part III, see ref. 8.

²AECL No. 3699.