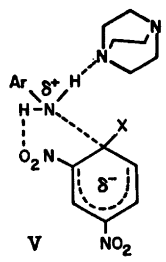

V

group [6] and the other to a DABCO molecule. The feasibility of this model depends on the relative magnitudes of the decreases in $T\Delta S^{\ddagger}$ and in $\Delta H^{\ddagger}$ implied by incorporation of a DABCO molecule. The loss in $T\Delta S^{\ddagger}$ is likely to be about 5 kcal [7] and the strength of the hydrogen bond might well be of similar or greater magnitude; DABCO is quite basic, the amino hydrogens are likely to be quite acidic (because the transition state is probably attained late in the attachment of anisidine nitrogen to aromatic carbon) and the hydrogen bond is expected to be a strong one. (The fact that the reaction of I (X = Cl) with butylamine in benzene is merely second order,[8] which might seem to contradict this model, could be rationalized by postulating for a primary amine of high nucleophilicity an early transition state, in which the amine hydrogens would not be very acidic.)

A second alternative takes account of good evidence [9] that S_NAr reactions of amine nucleophiles may involve three steps: Initial formation of zwitterionic σ-complex II, deprotonation of II by a base to form anionic σ-complex III, and finally leaving group expulsion. Lamm and Lammert discussed it, however, as a two-step process. It is possible that formation of II is a mobile equilibrium and that the deprotonation (k_3) step is rate-limiting. The DABCO molecule would be present in the rate-determining transition state, taking the proton, but there would be no scission of the C–X bond. This model would require that expulsion of the leaving group from III be much faster than reprotonation to II.

There are now known several examples of relatively slow reactions, in water solution, that have rate-determining proton transfer steps.[10] Rate-determining proton transfer steps are even more likely in benzene because hydrogen-bonded networks of solvent to acidic or basic sites, which expedite proton transfer,[11] are not possible.

Because there are plausible alternative interpretations of the results of Lamm and Lammert, they do not constitute a serious challenge to the validity of the element effect as a criterion of mechanism.

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A Novel Fragmentation in the Mass Spectra of Some 3-(2-Hydroxyphenyl)-4-oxo-3,4-dihydroquinazolines

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In our current study on metabolites of the hypnotic drug methaqualone [2-methyl-4-oxo-3-(2-tolyl)-3,4-dihydroquinazoline] we reported the mass spectra of its monohydroxy derivatives.[1] We found that the fragmentation of these compounds was dominated by loss of the

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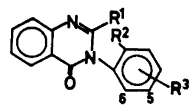
Table 1. Chemical and mass spectral data of the investigated compounds.



No.	R^1	R^2	R^3	Yield[a] %	M.p. °C	Prominent peaks (rel. int. %)
1[b]	CH_3	OH	6-CH_3	94	227.5–228.5	M^+ = 266(36), M^+ – 15(100), M^+ – 42(59)
2	H	OH	6-CH_3	48	203–205	M^+ = 252(100), M^+ – 17(76), M^+ – 28(16)
3	H	OCH_3	6-CH_3	53	133–133.5	M^+ = 266(96), M^+ – 1(61), M^+ – 17(39), M^+ – 31(100)
4	C_2H_5	OH	6-CH_3	68	130–132	M^+ = 280(40), M^+ – 15(12), M^+ – 29(100), M^+ – 56(40)
5	C_2H_5	OCH_3	6-CH_3	54	173.5–174	M^+ = 294(36), M^+ – 15(18), M^+ – 29(100), M^+ – 31(64)
6	H	OH	6-OH	40	152–155	M^+ = 254(100), M^+ – 17(51), M^+ – 28(42)
7	H	OCH_3	6-OCH_3	51	163–165	M^+ = 282(68), M^+ – 31(100)
8	CH_3	OH	6-OH	52	183–186	M^+ = 268(40), M^+ – 15(12), M^+ – 42(100)
9	CH_3	OCH_3	6-OCH_3	35	212–215	M^+ = 296(100), M^+ – 15(50), M^+ – 31(83)
10	C_2H_5	OH	6-OH	45	273–277	M^+ = 282(39), M^+ – 29(32), M^+ – 56(100)
11	C_2H_5	OCH_3	6-OCH_3	10	228–231	M^+ = 310(77), M^+ – 29(100), M^+ – 31(91)
12	CH_3	OH	5-CH_3	54	236–237	M^+ = 266(78), M^+ – 15(60), M^+ – 42(100)

[a] After recrystallization from ethanol or aqueous ethanol. [b] This compound has been described earlier.[1,2]

group in position 2, giving rise to the base peak. In the spectrum of one of these compounds, 3-(2-hydroxy-6-methylphenyl)-2-methyl-4-oxo-3,4-dihydroquinazoline (1), an unexpected and prominent peak at $M^+ - 42$ was observed. High resolution measurement and a metastable peak verified that the corresponding transition was due to the expulsion of a ketene moiety from the molecular ion. However, according to the literature no reasonable explanation for this unusual fragmentation seems to be available. In order to elucidate the mechanism the shift technique was used. Thus a number of suitably substituted 4-oxo-3,4-dihydroquinazolines were synthesized and their mass spectra evaluated. The data are collected in Table 1. In analogy to the behaviour of the monohydroxy derivatives of methaqualone, important peaks corresponding to loss of the 2-substituent appear, *i.e.* $M^+ - C_2H_5$ in the spectra of 4, 5, 10, and 11 and $M^+ - CH_3$ in the spectra of 8, 9, and 12.

All compounds having R^2 = OH (Table 1) also fragment through another important route, related to the loss of ketene from compound 1. Thus the spectra of compounds 2 and 6 exhibit a prominent peak at $M^+ - CO$, compounds 8 and 12 at $M^+ - CH_2CO$ and compounds 4 and 10 at $M^+ - CH_3CHCO$.

These data indicate the origin of the atoms involved. The fragmentation implies interaction between the group at C-2 in the quinazoline ring and the phenolic group R^2. For the case when ketene is lost, the reaction may tentatively be formulated as outlined in Fig. 1.

The mechanism of the fragmentation can be concerted or involve a skeletal rearrangement.

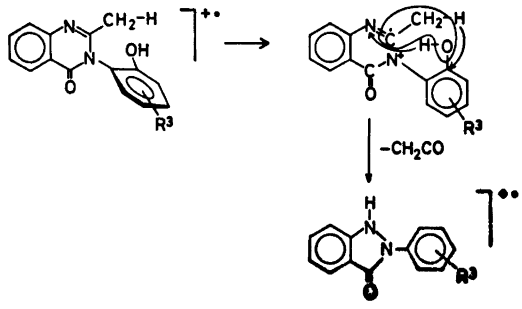


Fig. 1.

In compounds having a 2,6-disubstituted aromatic ring at N-3 this ring and the oxoquinazoline nucleus obviously are not coplanar. This implies that an initial cleavage of the quinazoline ring must occur in order for the interaction to take place (*cf.* Fig. 1). However, on the basis of the present evidence it is not feasible to speculate further on the details of the fragmentation. The driving force can be assumed to originate in the liberation of a neutral fragment. Besides, an energetically favourable steric arrangement must take place in order to make the reaction possible. This assumption is supported by the fact that only compounds having a hydroxyl group in *ortho*-position (R^2 = OH) are exposed to the fragmentation.[1]

Experimental. Melting points were determined in open capillary tubes in an electrically heated

metal block, using calibrated Anschütz thermometers. Infrared spectra were run in KBr discs using a Perkin-Elmer Infracord Model 157G with a grating monochromator. Infrared spectra were routinely recorded and are in agreement with the expected structures. Mass spectra were recorded on an AEI MS-30 mass spectrometer. The ionizing energy was maintained at 70 eV and the temperature of the source at 200°C.

Synthesis. Compounds having a methoxy group (*i.e.* compounds No. 3, 5, 7, 9, and 11) were prepared as follows. *N*-Formylanthranilic acid, *N*-acetylanthranilic acid, or *N*-propionylanthranilic acid (0.01 mol) was condensed with 2-methoxy-6-methylaniline [3] or 2,6-dimethoxyaniline [3] (0.01 mol) in the presence of phosphorus trichloride (0.005 mol) as earlier described.[2] Compounds 2, 4, 6, 8, 10, and 12 were prepared from the corresponding methoxy derivatives by boiling with an excess of 48 % hydrobromic acid for 1.5 h.

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On the Stereochemistry of the Interaction between Nucleic Acids and Basic Protein Side Chains

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Interactions between nucleic acids and basic proteins play an important role in cell chemistry and it would appear to be of interest to establish the stereochemistry of these interactions at the atomic level. We thought that some information might be obtained by X-ray analysis of single crystals of salts between phosphate diesters and various organic bases simulating arginine and lysine side chains. Such complexes may serve as models for the contacts occurring in nucleoproteins between phosphate groups and basic amino acids. The compounds studied are the diethyl phosphates of propylguanidine (I), arginine (II) and putrescine (III). A good model should preferably contain no hydrogen bond forming groups other than those present at the contacts, and compound (II) is therefore less satisfactory than the others. The crystal structures of the three compounds have been reported elsewhere.[1-3] In the present note the patterns of hydrogen bonding will be discussed and related to the structure of complexes between DNA and polyarginine, protamine, and polylysine.

The bonding between arginine and phosphate diesters. Arginine forms salts with phosphate diesters and bonding occurs between $(RO)_2PO_2^-$ and the guanidinium cationic group $-(NH)C(NH_2)_2^+$. In Fig. 1 the surroundings of the guanidinium group in model compounds (I) and (II) are shown. Extensive hydrogen bonding occurs, the stereochemistry of which may be described as follows:

(1) The guanidinium group forms five N−H···O hydrogen bonds to oxygen atoms in neighbouring molecules. These bonds are not far from linear and lie roughly in the plane of the guanidinium group, as is to be expected. The tendency for this general pattern of hydrogen bonding is also evident in crystal structures of inorganic salts of arginine.[4] In the present structures, especially (I), in which the guanidinium group is bonded only to diester phosphate groups, some additional characteristic stereochemical features are observed:

(2) One of the five hydrogen bonds both in (I) and (II) involves an ester oxygen atom and is much weaker (length 3.08 Å and 3.09 Å, respectively) than the others, which lie within the normal range for N−H···O bonds (mean length about 2.85 Å). The direction of this bond is roughly that of the bisecting line of the P−O−C angle. Such a hydrogen bond has apparently not been observed previously.

(3) Four of the hydrogen bonds occur in two pairs of nearly parallel bonds to oxygen atoms in the same anionic group. The N···N distances in the guanidinium group (*ca.* 2.3 Å) are not far from the O···O distances in phosphates (*ca.* 2.5 Å) and carboxylates (*ca.* 2.25 Å), making it stereochemically favourable for pairs of nearly parallel bonds to be formed. The pairs are of two types, a "strong" pair involving two normal bonds to the two *oxo* oxygen atoms in the same phosphate group, and a "weak" pair of one normal and one weak bond to one *oxo* and one ester oxygen atom, respectively. The pairs are at an angle of about 120° with one another. In compound (II) the "strong" pair is formed to the carboxyl group rather than to the phosphate, but the "weak" pair exists in both structures. It may be concluded that a guanidinium group may form a strong link between two phosphate diester groups by pairs of hydrogen bonds, and that