3-Amino-1-[2-(2-ethoxyethoxy)ethoxy]benzo[*f*]quinazoline

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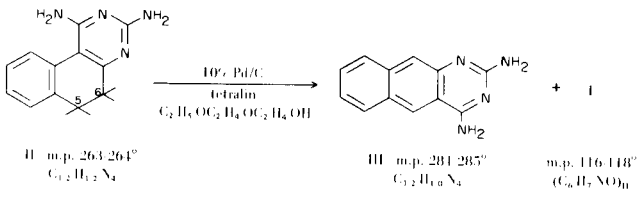
The structure of an anomalous product, isolated as a companion substance during the catalytic dehydrogenation of 1,3-diamino-5,6-dihydrobenzo[*f*]quinazoline, has been elucidated with the aid of chemical and spectral evidence, including mass spectrometric data. The mass spectrometric fragmentation pattern of the compound is in good agreement with the assigned structure.

During the course of a study designed to establish the structure of 1,3-diamino-5,6-dihydrobenzo[*f*]quinazoline (II), a byproduct (I) was isolated (2). Compound II was obtained by fusion of dicyandiamide with 2-tetralone (3) and its structure has been established by synthesis and also by dehydrogenation with selenium dioxide in acetic acid to 1,3-diaminobenzo[*f*]quinazoline (4,5).

Earlier attempts to prove the structure of II by dehydrogenation with palladium charcoal or selenium failed to furnish any 1,3-diaminobenzo[*f*]quinazoline (2). A disproportionation reaction with tetralin and 10% palladium-charcoal in 2-(2-ethoxyethoxy)ethanol gave 2,4-diaminobenzo[*g*]quinazoline (III) by a novel rearrangement (6). Isolation of III as the major product of this dehydrogenation in about 13% yield led us to believe that the structure of II was the linear 2,4-diamino-5,10-dihydrobenzo[*g*]-quinazoline, until later work from these laboratories proved it to be the angular isomer II (4,5). In the above reaction, a small amount (4%) of a colorless companion compound (I), was isolated which melted at a much lower temperature than either II or III. Studies leading to the structure elucidation of I form the basis of this communication.



II m.p. 263-264°
$C_{12}H_{12}N_4$

III m.p. 281-285°
$C_{12}H_{10}N_4$

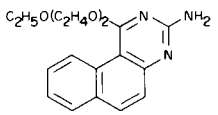
m.p. 116-118°
$(C_6H_7NO)_n$

Elemental analysis indicated empirical formula $(C_6H_7NO)_n$ for I. The starting material II, from which compound I originated in the process of dehydrogenation, has the composition $C_{12}H_{14}N_4$. It was therefore considered likely that the molecular formula for I might be $C_{12}H_{14}N_2O_2$ (n = 2). However, the ultraviolet and infrared spectral properties of I were inconsistent with any of several possible partially reduced, hydroxylated benzoquinazoline structures corresponding to the molecular formula $C_{12}H_{14}N_2O_2$. In acidic ethanol I showed five ultraviolet absorption maxima (246, 262, 300, 247, and 360 nm), characteristic of the various completely aromatic benzo[*g*]- and benzo[*f*]quinazolines prepared in these laboratories (6,7). The infrared absorption spectrum of I in potassium bromide exhibited absorption bands at 3.48 μm (characteristic of symmetrical methylene stretching vibrations) and in the 8.8-9.4 μm region, (possibly indicating C-O-C ether stretching vibrations (8)) but did not in the amide carbonyl region (5.8-6.1 μm) (9). Because of the insufficient quantity of material available, nmr studies could not be carried out.

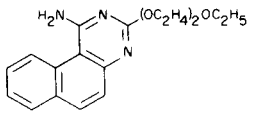
At this stage, a mass spectrometric analysis of I gave a molecular ion peak at m/e 327 and indicated that the molecular formula $(C_6H_7NO)_n$ derived from elemental analysis is actually $C_{18}H_{21}N_3O_3$ (n = 3) rather than $C_{12}H_{14}N_2O_2$ (n = 2). During the disproportionation reaction the parent 1,3-diaminobenzo[*f*]quinazoline system thus appeared to have undergone the loss of one amino group and to have gained the elements of 2-(2-ethoxyethoxy)ethanol by solvolysis.

Since the amino groups of 1,3-diaminobenzo[*f*]quinazoline are susceptible to hydrolysis with acid (7), they might likewise be amenable to alcoholysis during a prolonged catalytic reaction (carried out at 198-202° for 38 hours). Compound I, therefore, could be represented by either structure *a* or structure *b*. The ultraviolet and infrared absorption data are in agreement with either *a*

or *b* and the infrared absorption at 8.8-9.4 μm can be attributed to the antisymmetrical C-O-C stretching of the ether linkage (8).

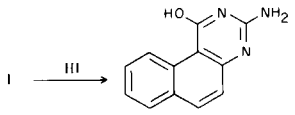


(a)



(b)

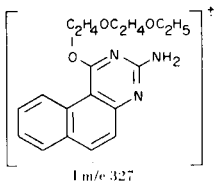
In order to determine the correct position of the ether side-chain in the molecule, I was subjected to ether cleavage. Treatment with constant boiling hydroidic acid afforded a product that was found to be identical with authentic 3-amino-1-hydroxybenzo[*f*]quinazoline (IV), previously reported from these laboratories (6).



IV

On the basis of the foregoing evidence, compound I has been formulated as 3-amino-1-[2-(2-ethoxyethoxy]-benzo[*f*]quinazoline (structure *a*). The mass spectrometric analysis, in addition to furnishing the correct molecular weight of I, gave a fragmentation pattern in agreement with the assigned structure *a*. The major mass ions observed in the mass spectrum of I, together with the possible structures of the fragments responsible for the respective mass ions are shown in Chart 1.

The major ion peaks in the mass spectrum of I (Fig. 1) can be explained on the basis of the fragmentation pattern generally applied to ethers (10). One of the energetically

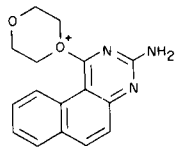


I m/e 327

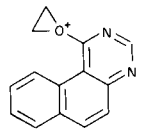
most favored paths in such a fragmentation appears to be α-cleavage to the primary alkyl cations (m/e 238, 282) (Chart 1) and the resonance-stabilized 3-aminobenzo[*f*]-quinazoline ion, R^+ (m/e 194). Additional stabilization for the primary alkyl cations (m/e 238, 282) formed by α-bond cleavage can be achieved by the formation of the cyclic oxonium ions (V-VII) indicated in the following scheme. Five- and six-membered cyclic oxonium ions of this type have been reported (11,12).

A characteristic fragmentation of ethers is decomposition of the primary ether ion to an alcohol ion *via* the loss of a neutral olefin. This might proceed by a concerted process of α-cleavage with hydrogen transfer from a β-carbon atom (13,14).

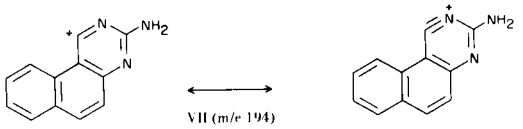
The process requires the presence of an ethyl substituent and is presumed to proceed, according to McLafferty (11), through a four-membered intermediate. In this way the mass ions m/e 211 and 255 may be derived from the ion radical resonance forms Ib and Ic, respectively (Chart 1).



V (m/e 282)



VI (m/e 238)



VII (m/e 194)

The same concerted process of α-cleavage with a hydrogen shift from a beta carbon atom might be presumed to be responsible for the formation of the ion fragment m/e 281 from Ic. In this case a neutral ethyl alcohol molecule is split off.

The most abundant ion peak in the spectrum is at m/e 211. Formation of the latter by a single step fragmentation from the molecular ion (m/e 327) is evident by the appearance of a metastable peak at m/e 137 (calculated for $211^2/327 = 136.2$) (15).

The mass ion m/e 225 may have originated from the ion m/e 283 by way of a six-membered cyclic transition state (16). The presence of mass ion m/e 283, which is derived from Ib by α-cleavage and beta hydrogen transfer with loss of acetaldehyde, is suggested only very faintly in the spectrum, but a metastable peak at m/e 179 furnishes evidence for the formation of mass ion m/e 225 directly from mass ion m/e 283.

It should be mentioned that although the triple peaks at m/e 281, 282 and 283 are not intense, they are significant enough to throw light on the possible mode of fragmentation of the side chain ether.

The most intense peak in the mass spectrum of IV (Fig. 2) is that of the molecular ion at m/e 211. Four peaks of weak (less than 10%) to moderate (10-25%) relative intensity, at m/e 194, 182, 169, and 140, appear in both spectra (Figs. 1 and 2). The first of these has already been ascribed to the resonance-stabilized 3-amino-benzo[*f*]quinazolinium ion (R^+, Chart 1). The remaining three peaks may also be assumed to have originated from

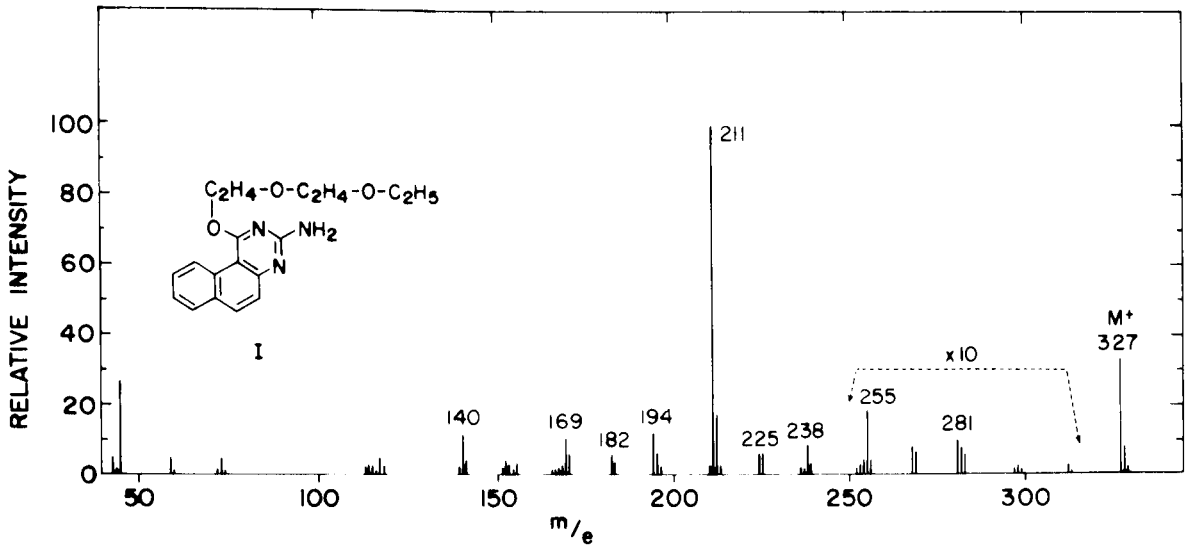


Fig. 1. Mass Spectrum of 3-Amino-1-[2-(2-ethoxyethoxy)ethoxybenzo[*f*]quinazoline (I), 70 eV.

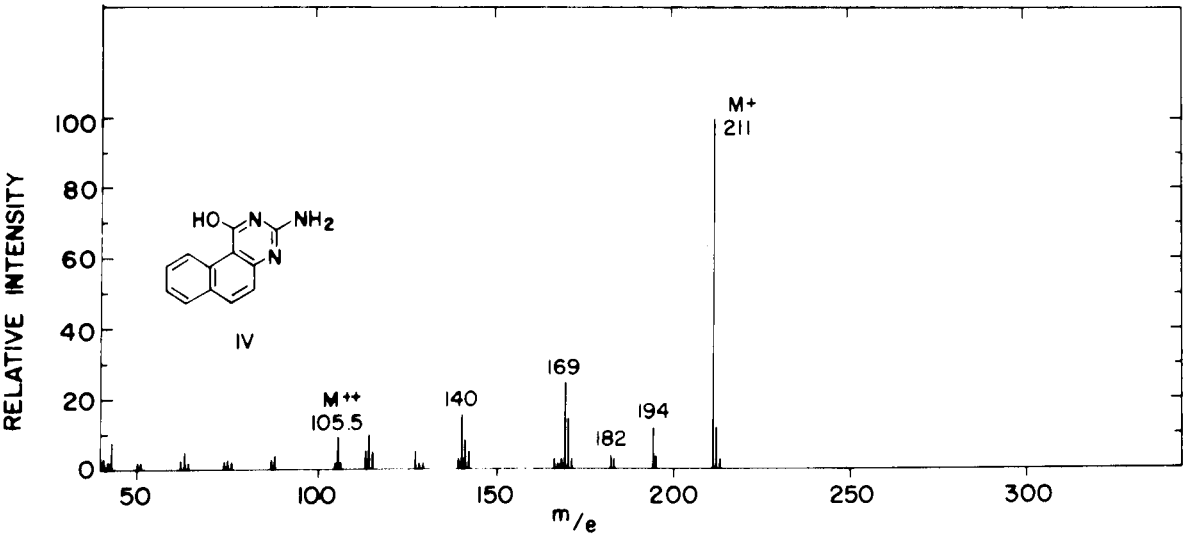
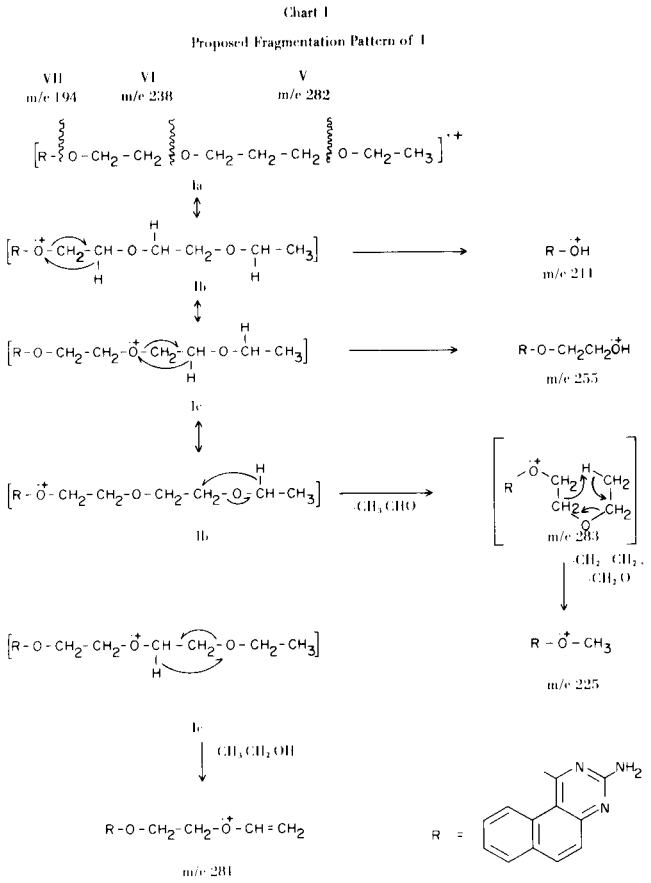
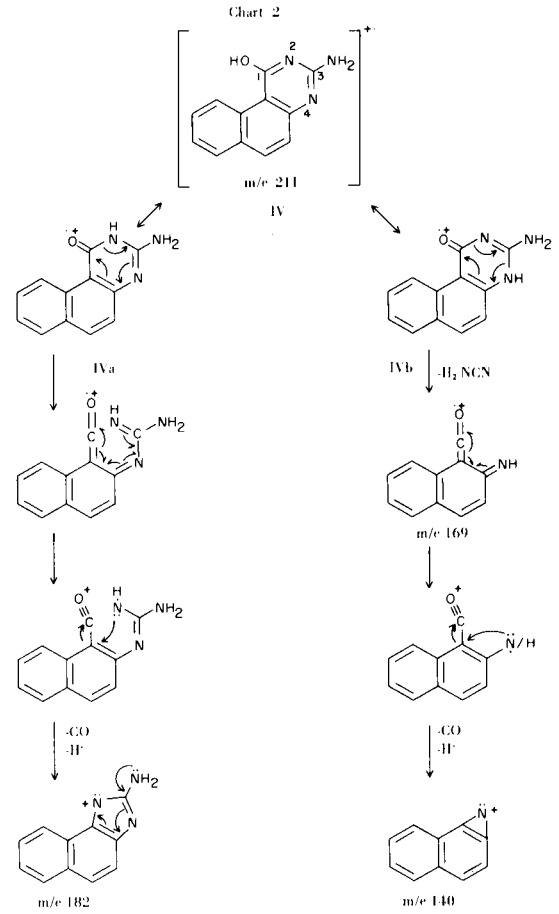


Fig. 2. Mass Spectrum of 3-Amino-1-hydroxybenzo[*f*]quinazoline (IV), 70 eV.

the molecular ion of IV, although there is no evidence of the presence of appropriate metastable ions in our spectra to confirm this argument (17). On the basis of information derived from mass spectral studies of pyrimidines (18) and purines (19), a hypothetical mechanism for some of these fragmentation processes is proposed in Chart 2.

A comparison of the mass spectra of 1-, 3-, and 7-methyl derivatives of guanine has established the fact that the most characteristic mode of decomposition of a guanine molecular ion is the initial expulsion of a neutral cyanamide fragment which originates uniquely from N-1 and C-2 and the amino group in the pyrimidine ring of guanine (19). The comparable functions in the 3-amino-1-hydroxybenzo[*f*]quinazoline system IV are N-2, C-3, and the amino group attached to the C-3 atom. Expulsion of cyanamide from the mesomeric form, IVb, which may be the prevailing tautomer in the vapor phase of IV (19), can be explained by a retro Diels-Alder mechanism which results in the formation of a moderately intense peak at m/e 169. Successive loss of CO and a hydrogen atom in either order from this species may readily form the fragment at m/e 140. A nucleophilic attack of the lone pair of electrons on the nitrogen on the positively charged





carbon atom, from which the CO group has been lost, may result in the closure of an aziridine ring. A similar aziridinium ion has been postulated for a comparable ion radical intermediate in the fragmentation of thymine (18).

An alternate and less prominent mode of fragmentation of the molecular ion IV *via* IVa may be visualized by the initial elimination of a carbonyl group and a hydrogen atom to give rise to the minor peak at m/e 182. Loss of CO from the molecular ion is a far less important process in guanine (where the aromatic imidazole is fused to an isocytosine) than it is for isocytosine itself (19).

EXPERIMENTAL (20)

Isolation of 3-Amino-1-[2-(2-ethoxyethoxy)ethoxy]benzo[*f*]quinazoline (I).

The following operations were all conducted under nitrogen. 1,3-Diamino-5,6-dihydrobenzo[*f*]quinazoline (1.0 g., 4.71 mmoles) was dehydrogenated by means of a disproportionation reaction (2) with tetralin (20 ml.) and 10% palladium-charcoal (0.5 g.) in refluxing 2-(2-ethoxyethoxy)ethanol (45 ml.) for 38 hours at 198-202° (internal temperature). After solvent removal *in vacuo*, the crude reaction product was initially purified by vacuum sublimation. During the first stage of this process (75-140°/0.5-0.7 mm.) a colorless distillate [(1.4 g., containing unchanged starting material (II, 0.25 g.)] was collected. Further sublimation for 24 hours at 180-190° gave two distinct bands of sublimate: the less volatile yellow crystalline sublimate (99.1 mg., 13.2%; m.p. 277-278°) was identified as 2,4-diaminobenzo[*g*]quinazoline (III) (6).

The more volatile, nearly colorless, sublimate was dissolved in 25 ml. of ethanol:benzene (1:1) and filtered free of a small insoluble residue. The filtrate was reduced to approximately 3 ml. and kept overnight at -10°. After removal of a small amount of yellow solid, the volume was further reduced to 1 ml. and the filtrate was kept overnight again at -10°. A nearly colorless solid, collected and washed with a minimal volume of cold ethanol/ether (80 mg., m.p. 112-120°), gave 32 mg. of I (m.p. 113-115°) after crystallization from absolute ethanol. Fractional crystallization (ethanol) of other residues and evaporated mother liquors from the more volatile sublimate afforded an additional 17 mg. of I: total, 49 mg. (4.2% yield based on unrecovered starting material). Two further crystallizations of these combined solids from a minimal volume of absolute ethanol afforded colorless prismatic needles; 25 mg. (2.1%) of pure I; m.p. 116-118°; λ max in nm: (ϵ x 10^{-3}) (ethanol, *p*H 1) 239 (23.0, infl), 246 (27.2), 262 (61.4), 278 (16.9, infl), 300 (16.9), 288 (11.8, infl), 347 (3.00), 360 (3.00); λ max (potassium bromide) in μm: 3.84 (CH_2) and 8.8-9.4 (C-O-C) but no absorption at 5.8-6.1 for amide (8,9).

Anal. Calcd. for $(C_6H_7NO)_n$: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.88; H, 6.59; N, 12.92.

Analytically pure I was used both for the ether cleavage and for mass spectrometric determinations.

3-Amino-1-hydroxybenzo[*f*]quinazoline (IV) from I.

A mixture of I (9 mg., 2.75 μmoles) and constant boiling hydroidic acid (b.p. 127.5°) (1.5 ml.) was refluxed for 40 minutes. The cooled reaction mixture was poured over chopped ice (5 g.) and the resultant aqueous suspension was neutralized with 0.1 *N* sodium bicarbonate to *p*H 8. The dark brown precipitate (5.0 mg.) was collected and dried at 60° *in vacuo*. This solid was dissolved in 5 ml. of water containing 0.5 ml. of concentrated hydrochloric acid. The resultant dark blue solution was boiled for 5 minutes and became clear and colorless. Filtration and concentration to about 3 ml. afforded long needles on cooling. The crystals of IV·hydrochloride were collected by centrifugation and dried: yield, 1.95 mg. (27%); m.p. above 360°. Another crop (1.1 mg., 15%) of product was recovered from the mother liquor on concentration and centrifugation: total yield 3.05 mg. (42%). Treatment with dilute ammonia yielded IV free base (m.p. above 310°), which was identified as 3-amino-1-hydroxybenzo[*f*]quinazoline by infrared comparison with an authentic sample (21); λ max in nm (ε x 10^{-3}) (ethanol, *p*H 1) 212 (32.50), 225 (21.80, infl.), 233 (22.0, infl.), 255 (38.70), 263 (41.40), 300 (4.6, infl.), 313 (5.99), 333 (4.10), and 374 (3.38); λ max (potassium bromide) in μm: 5.86 (C=O), but no absorption at 3.84 (CH_2).

Acknowledgment.

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(1) This investigation was supported in part by research grant C6516 and research career development award K3-CA-22,151 from the National Cancer Institute, National Institutes of Health, U.S. Public Health Service.

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(17) In ref. 16, p. 4569, footnote 5, the authors state, "Ionic fragmentation processes do not always give rise to metastable peaks, however, and failure to observe these peaks does not prove that such reactions do not occur."

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(20) The mass spectra were determined with an AEI MS9 mass spectrophotometer equipped with a direct inlet system and operating at 70 eV. Ultraviolet spectra were measured with a Carey Model 11 spectrophotometer at *p*H 1 in ethanolic 0.1 *N* hydrochloric acid. Infrared spectra were taken in potassium bromide or potassium chloride disks with a Perkin-Elmer Model 137B spectrophotometer (sodium chloride prism). Melting points were determined in capillary tubes in a modified Wagner-Meyer apparatus [E. C. Wagner and J. F. Meyer, *Ind. Eng. Chem., Anal. Ed.* **10**, 584 (1938)] and are corrected. The analysis was performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

(21) The identity of the sample was established by comparison and contrast of both the ultraviolet and the infrared absorption characteristics with authentic (7) 3-amino-1-hydroxybenzo[*f*]-quinazoline and 1-amino-3-hydroxybenzo[*f*]quinazoline, respectively.