Tetrahedron Letters No.25, pp. 2931-2934, 1968. Pergamon Press. Printed in Great Britain.

STABLE α-AMINO ETHERS - PYRAZINE AND PYRIMIDINE DERIVATIVES

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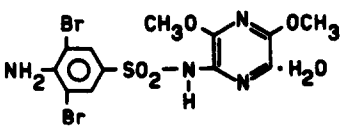
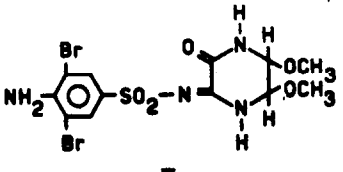
(Received in UK 2 February 1968; accepted for publication 22 March 1968)

α-Amino ethers of the kind $-\overset{|}{\underset{}{C}}(NHR)(OR')$ have been little studied [2] because they can easily give rise to azomethines by elimination of R'OH. Among the most interesting examples, mention should be made of the work of the school of Prof. A. Albert with regard to the covalent addition of alcohols to the C = N bond of some selected polyazanaphthalenes to give "alcoholates" which are in effect, cyclic, relatively stable, α-amino ethers [3]. However, this reaction has never been observed in simple diazines [4] and a greater instability of the "alcoholates" was to be expected in these cases. In the present communication we will present evidence of the structure of cyclic, stable, α-amino ethers, which can formally [5] be formed by covalent addition of methanol to some pyrazine and pyrimidine derivatives. The re-aromatization of these compounds, by alkaline treatment, will also be briefly illustrated.

PYRAZINE DERIVATIVES. Bromination of 3-methoxy-2-sulfanylamidopyrazine in methanol gave the product $C_{12}H_{14}Br_2N_4O_5S$, m.p. 240°, as reported by Wojahn [6], to which the formula I had been assigned [6]. However, the absence of water, as determined by the Karl Fischer precedure, made us reconsider the proposed structure and we now assign to this product the formula II, on the grounds of the following spectral and chemical evidence.



I

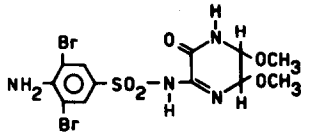


II

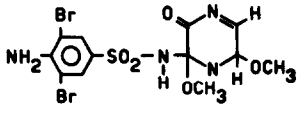
The NMR spectrum [7] shows a singlet at τ 2.1 (2H) which is due to two equivalent aromatic protons, two singlets at τ 6.67 (3H) and τ 6.69 (3H) which are due to two non-equivalent $O-CH_3$ groups, a signal centered at τ 3.85 (2H) which disappears on treatment with D_2O and which is attributed to the NH_2 group. The most interesting feature of the NMR spectrum, however, is the presence of an unresolved signal centered at τ 5.29 (1H) and a doublet of doublets centered at τ 5.47 (1H). On addition of D_2O these signals become two doublets .

(J=1.8 cps) centered at τ 5.29 and τ 5.47. These signals are tentatively assigned to two vicinal protons, further coupled with a mobile proton (NH) as shown in formula II.

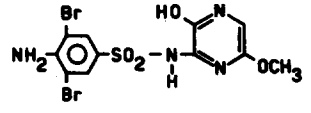
Hydrochloric acid (6N) hydrolysis (3 hr at reflux) gave, besides the expected 3,5-dibromo-sulfanylamide, glyoxal, which was isolated in almost quantitative yield as the bis-2,4-dinitrophenylhydrazone. It is therefore apparent that the NMR signals at τ 5.29 and τ 5.47, previously discussed, must be due to a couple of vicinal protons and this limits the final choice to structures II, III and, possibly, IV.



III



IV



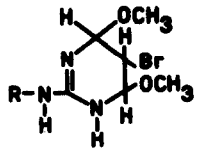
V

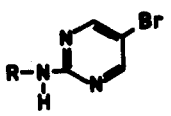
The UV spectrum in EtOH shows a maximum at 300 mμ (ε = 15,000) and a second broad one at 250-270 mμ; the addition of NaOH determines a strong hypsochromic shift (λ_{max} = 255 mμ) yielding a spectrum which is similar to that of 3,5-dibromosulfanylamide. The UV spectrum is consistent only with the extensively conjugated formula II; by addition of alkali, the tautomeric equilibrium, which in EtOH is largely in favour of the sulfonimide structure, is shifted towards the sulfonamide structure III [8].

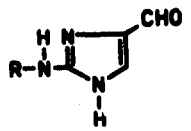
The data previously reported allow the assignment of formula II to the compound $C_{12}H_{14}Br_2N_4O_5S$ prepared according to Mojahn [6], and which formally derives from a 2-(3,5-dibromosulfanylamido)-3-hydroxy-x-methoxypyrazine by addition of a molecule of methanol [9]. The reverse reaction, namely the elimination of methanol to give a fully aromatic pyrazine nucleus, was found to be relatively easy, as expected.

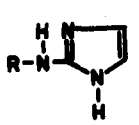
By treating II at 90° (3') with NaOH 2N both the product of hydrolytic cleavage, namely 3,5-dibromosulfanylamide and a 2-(3,5-dibromosulfanylamido)-3-hydroxy-x-methoxypyrazine are formed in about 1:1 ratio. The last compound was shown to be 2-(3,5-dibromosulfanilamido)-3-hydroxy-5-methoxypyrazine (V) by converting it, with diazomethane in alkaline solution (to minimize N_1 methylation), to 2-(3,5-dibromosulfanylamido)-3,6-dimethoxypyrazine which was catalytically dehalogenated to give 2-sulfanylamido-3,6-dimethoxypyrazine, identified by comparison with an authentic sample [10].

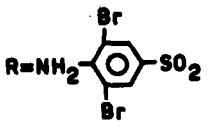
PYRIMIDINE DERIVATIVES. Addition of 5 moles of Br_2 to a methanol solution of 2-sulfanylamidopyrimidine (1 mole) gave a compound $C_{12}H_{15}Br_3N_4O_4S$ which decomposes at ca 200°, resolidifies and finally melts at ca 250°. We assign formula VI to this compound on the basis of the NMR, UV and IR [11] spectral data.


VI


VII


VIII


IX



The NMR spectrum [7] shows a singlet at τ 2.19 (2H) which we assign to the two equivalent protons of the aromatic ring, a signal centered at τ 4.10 (2H) that disappears on treatment with D_2O and which is assigned to the NH_2 group; a singlet at τ 6.70 (6H) which we assign to the two OCH_3 groups. The most significant features of the spectrum are a triplet at τ 5.43 (1H) and a multiplet (2H) which on addition of D_2O becomes a doublet at τ 5.23 (J = 1,5 cps). The former signal is assigned to the CHBr proton coupled with the two vicinal CH-OCH_3 protons; the latter signal is assigned to the two CH-OCH_3 protons coupled with the CHBr proton and further coupled with an exchangeable proton (NH; only one tautomer formula shown (VI)).

The UV spectrum shows a maximum at 266 mμ (shoulder at 310 mμ) and this value confirms the proposed sulfonamide structure [8].

The behaviour of VI toward alkali was unexpected and it is well worth mentioning. In analogy with the former example, a brief treatment of II in aqueous NaOH should have yielded either the stable pyrimidine derivative VII by loss of MeOH, or 3,5-dibromosulfanyalamidoguanidine by hydrolytic cleavage of the amino ether bond. Neither compound was found to be present by TLC; instead a compound $C_9H_8Br_2N_4O_2S$, which gave a positive Pauly test, was obtained in 80% yield. To this compound we have assigned the formula IX on the basis of the following spectral data.

The NMR spectrum shows a singlet at τ 2.18 (2H, aromatic); a singlet at τ 3.28 (2H) which we assign to the two equivalent protons of the heterocyclic ring and two signals, one at τ -1.36 (1H) and one at τ 4.22 (2H) which disappear on addition of D_2O. We assign the former to the imidazole NH and the latter to the NH_2 group. The UV spectrum (λ_{max} 265 mμ) and the IR spectrum are also in accord with the proposed formula.

When VI was treated with anhydrous alkali (NaOMe 2N, 80°, 5 mins.) two different compounds were formed in about 1:2,5 ratio, which were isolated by fractional crystallization. The more abundant one, m.p. 285°, was the expected VII [12] as shown by the elemental analysis and the NMR spectrum which presents the following signals: singlet at τ 2.02 (2H, aromatic), singlet τ 1.47 (2H, equivalent heterocyclic protons), singlet at τ 3.80 (2H, NH_2; exchange in D_2O). To the second product, m.p. 245°, we have assigned the formula VIII on the basis of the elemental analysis, a positive Pauly test, the formation of a 2,4-dinitrophenylhydrazone and the NMR spectrum which shows the following signals: τ 2.18 (2H,

aromatic); τ 2.25 (1H, heterocyclic proton); τ 0.58 (1H formyl proton). The UV spectrum (λ_{max} 296 and 270 mμ) and the IR spectrum (CO conjug. at 1670 cm^{-1}) are also in accord with the proposed formula.

Very little can be said at present about the mechanism of formation of VIII and IX; an open chain intermediate which can either give VIII by loss of HBr and MeOH, or give IX by retro-aldolization (loss of HCOOH) followed by elimination of HBr, is probably involved. We can, however, exclude VIII as an intermediate in the formation of IX, since VIII has been recovered unchanged after treatment with aqueous NaOH, under the conditions used for the synthesis of IX.

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4) A. Albert and J. L. F. Armarego, Advances in Heterocyclic Chemistry (A. R. Katritzky ed.) Academic Press, New York (1965). Vol. 4, p. 18.

5) We stress the "formal" aspect, because the products were formed, not by direct addition, but by a more complex route involving the addition of both BrOMe and MeOH to the diazine nucleus.

6) J. Esche and H. Mojahn, Arch. Pharmaz. 299, 147 (1966).

7) The spectra, in DMSO-d_6, were performed on a Varian A60A spectrometer (TMS int. st.)

8) Yu. M. Scheinker and I. K. Kuznetsova, Zhurnal Fisičeskoi Chimii, 31, 2656 (1957) - Yu. M. Scheinker, I. Ya. Postovskii, N. M. Voronina and V. V. Kushkin, Zhurnal Fisičeskoi Chimii, 31, 1745 (1957).

9) Little can be said at present about the mechanism of formation. Bromination of 3-methoxy-2-sulfanylamidopyrazine in CD_3OD gave a compound whose NMR spectrum did not show any CH_3O signal, as expected, but which still showed the same signals due to the vicinal protons. This fact excludes the direct bromination of the pyrazine nucleus and suggests instead a 1,4-addition of HOBr or MeOBr.

10) W. Barbieri, L. Bernardi, F. Luini and G. Palamidessi, Il Farmaco (in press).

11) The IR spectrum shows a strong ether band at 1035 cm^{-1}, in accord with formula II.

12) A compound of this structure has previously been obtained[13] by dehydration of a so-called 2-(4'-amino-3',5'-dibromophenylsulfo)-amino-4-hydroxy-5-bromo-4,5-dihydropyrimidine monohydrate to which we have recently[10] assigned the correct structure of 2-(4'-amino-3',5'-dibromophenylsulfo)-amino-4,6-dihydroxy-5-bromo-3,4,5,6-tetrahydropyrimidine.

13) H. Mojahn, Arch. Pharmaz., 288, 321 (1955).