PHOTOLYTIC AND MASS SPECTROMETRIC REACTIVITY OF PYRAZOLIDINE DRUGS

By
J. REISCH* and S. K. GRUDZINSKI.
Department of Pharmaceutical Chemistry, University of Ife. Ile-Ife, Nigeria

SUMMARY

Photolysis of pyrazolone and pyrazolidinone compounds has been described. Some of these compounds, e.g., Amidopyrine (Aminophenazone) and Phenylbutazone (Butazolidine), have found application as drugs. Primary photochemical processes occurring in them lead to the opening of the pyrazolidine ring. Secondary reactions that follow, have been explained by assuming a transitional formation of ∝-lactam (aziridinone) ring. This view has been supported by the analogous processes taking place in the mass spectrometer.

INTRODUCTION

An analogy between the fragmentation pattern of a compound in the mass spectrometer and its photochemical degradation was established at the early stage of development of organic mass spectrometry (Nicholson, 1954). In the case of relatively complex molecules, the knowledge of the course of their photolytic decomposition allows predictions as to their mass spectral fragmentation and *vice versa* (Reisch and Grudzinsk, 1980). An investigation into the photoreactivity of pyrazolidine drugs, given below, offers an excellent example of the relationship of these two processes.

PRIMARY PHOTOCHEMICAL PROCESSES OF A PYRAZOLONE MOLECULE

On absorption of an appropriate photon, the molecule assumes, via internal conversion, the lowest vibrational level of singlet excited state (S_1). The deactivation process leads not only to a change in electron distribution in the carbonyl group but also to an increase in ∝-charge on the nitrogen atoms (Fig. 1). The repulsion between the unshared electron pairs of the both nitrogen atoms results in the lengthening of the N-N bonding. As the elongation of the bonding exceeds a value corresponding to the angle of ∝ = 119°, the electron distribution of the excited molecule undergoes a far-reaching change. The carbonyl group assumes again the electronic configuration of the ground state and, all in all, a transfer occurs of the charge of the delocalized system towards the C-4, C-3, N-2 atoms as well as onto the σ-bonding between N-1 and N-2. As a result of this transfer, the repulsion between the nitrogen atoms becomes so strongly augmented that the ring must break open in order to achieve stabilisation of the system. In the reactive state the molecule might be in the form of an open structure that corresponds to the -σ transition. Two border-line structures for the open molecule may be here considered: an ionic form and a diradical form. The actual reactive form is probably a linear combination of these two structures.

In molecules with a suitably favoured structure, for example, in those of 2-methyl-4-amino-1,3-diphenylpyrazolone-5, the linear primary photoproduct may become stabilised to such an extent that it can be isolated (Fig. 2). Should both the starting materia (Pyrazolone) and its isomeric photoproduct give identical mass spectra, one would be only right to conclude that the both primary processes initiated either by photons or by impact electrons proceed along the same pathway (Fig. 2).

SECONDARY REACTIONS OF THE PHOTOLYSIS OF PYRAZOLONES AND PYRAZOLINONES

Some sequel reactions of the photolysis of pyrazolone derivatives may be explained most easily by assuming a transitional formation of ∝-lactam (asiridinone) by ring closure (Reisch, 1974 and 1975). In the same manner can also be interpreted their mass spectral fragmentation patterns (Locock et al., 1974; Reisch and Triebe, in press).

As an example, the process leading to the decomposition of a pyrazolidinedione is shown in Fig. 3. The mass spectral fragmentation characteristic of all pyrazolone derivatives involves the loss of one phenylisocyanate fragment either in the form of a radical ion or as a neutral molecule; the ∝-lactam fragment is being left to survive. In the photolysis, the aziridinone (∝-lactam) is probably formed as an intermediate that reacts further on, due to a necleophilic attack by the solvent. As can be seen in Fig.3, the both processes are fully analogous.

CORRELATIONS BETWEEN MASS SPECTRAL FRAGMENTATION AND PHOTOLYSIS IN MEDICINAL PYRAZOLIDINEDIONES

An example will be given now to show how the mass spectrum of a substance can be used so as to reconstruct the course of its photolysis from all fragmentary processes involved, including even those which proceed so rapidly that they cannot be traced by any other analytical methods.

It has been demonstrated quite certainly that pyrazolidinediones are converted by a nucleophilic attack of methanol on the transitionally formed α-lactam into malonic acid dianilides (Fig.4). In methanol these immediate products are light-stable and may be isolated in relatively high yields. If water is used as solvent, the corresponding compound formed is only a by-product of photolysis which presumably is further decomposed by the action of light. Phenylaminomalonic acid dianilides and 2-ketocarboxylic acid anilides are also formed as additional photoproducts. The mechanism of formation of the phenylaminomalonic acid dianilides by a nucleophilic attack of aniline on the α-lactam is rather obvious, but the way by which the aniline has been formed was earlier not at all clear.

It should be noted that in the mass spectrum of hydroxymalonic acid anilide a fragment corresponding to aniline appears in a high yield. Consequently, both photolysis and electron impact-induced fragmentation should correspond to one another. As depicted in Fig.4, the reaction course may have been through an intramolecular hydrogen transfer (Norrish Type III). Hereby formanilide is being formed of which it is known that, on the one hand, it is decarbonylated quantitatively on irradiation (λ = 254 nm) and, on the other hand, it produces the ion (M^+-CO) in a very high yield in the mass spectrometer (Barnett and Roberts, 1972).

For the sake of completeness, it has to be mentioned that only the photolysis or hydroxymalonic acid derivatives follows the Norrish Type III — splitting. The alternative — radical α-splitting (Norrish Type II) — should be here excluded because otherwise both methoxy- and phenylaminomalonic acid dianilides would have also been decomposed by light, which is however not the case (Reisch, 1974 and 1975). On the other hand, electron bombardment makes the α-splitting to dominate in all the three types of derivatives. The Norrish Type III — splitting of hydroxymalonic acid dianilides is merely a side-path in the mass spectrometric degradation.

BIBLIOGRAPHY

Barnett, B.K. and Roberts, T.D.: Chem. Commun., 1972, 758.

Locock, R.A., Moskalyk, R.E., Chatten, L.G. and Lundy, L.M.: J. Pharm. Sci., 63, 1896 (1974).

Nicholson, A.T.C.: Trans. Faraday Soc., 50, 1067, 1954.

Reisch, J.: Gyogyszereszet, 19, 81 (1975).

Reisch, J.: Deutsch. Apotheker Ztg., 51, 2028 (1974).

Reisch, J. and Fitzek, A.: Arch.Pharm. (Weinheim), 307, 211 (1974).

Reisch, J. and Grudzinski, S.K.: Nig.J.Pharm., 11, 5 (1980); ibid., 11, 12 (1980).

Reisch, J. and Triebe, J.: Arch.Pharm. (Weinheim), in press.
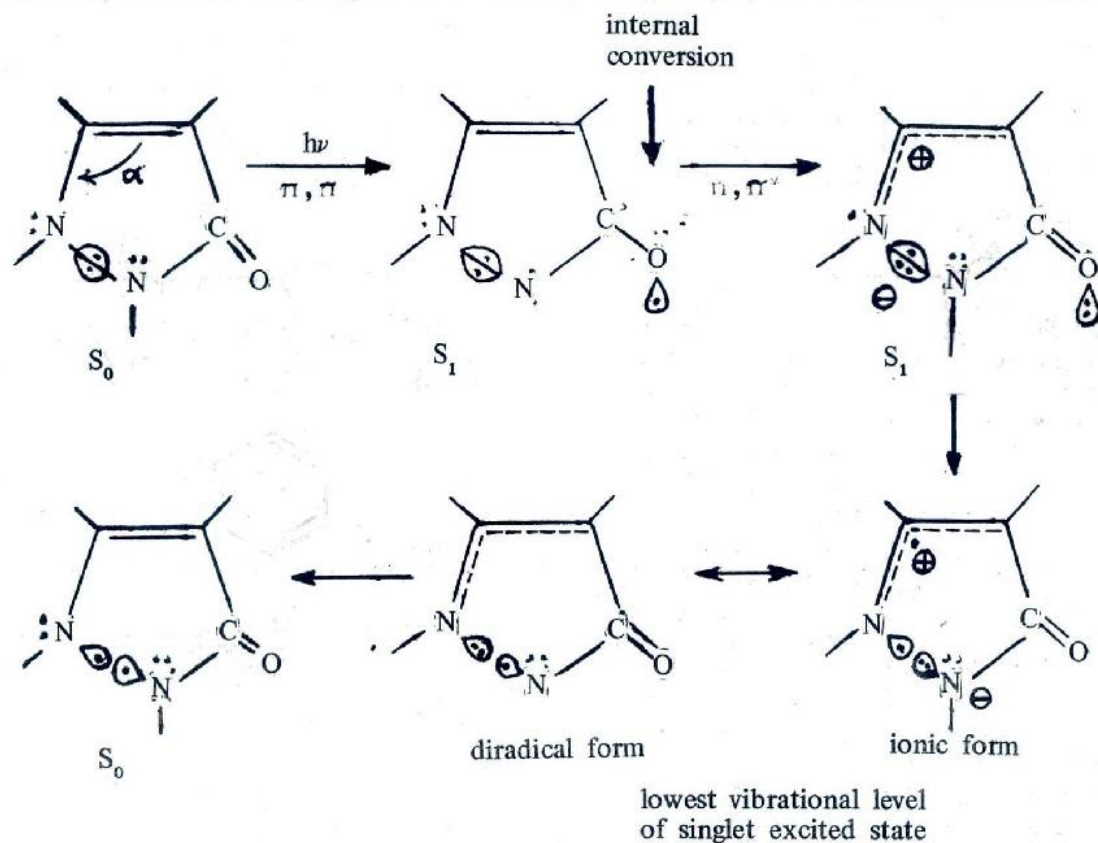
Fig.1: Deactivation process of an excited pyrazolone molecule.

(Note: According to the manner of presentation proposed by L. Salem, the σ-electrons are depicted as half-wings of the corresponding orbital, and the -electrons as dots or a double bond).

identical fragmentation
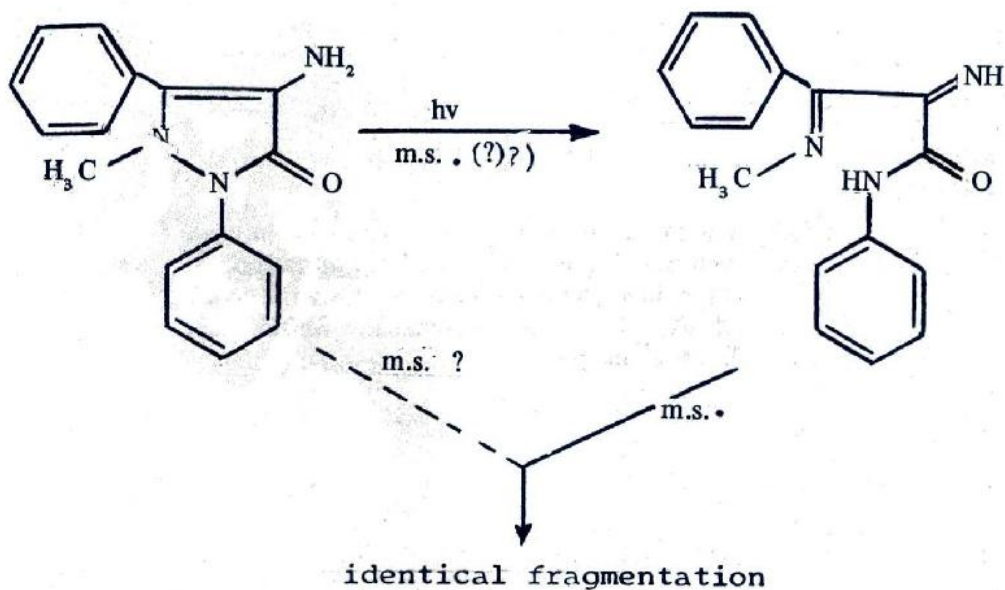
Fig.2: Primary process of the photolysis of 2-methyl-4-amino-1, 3-diphenylpyrazolone-5 (Reisch and Fitzek, 1974).
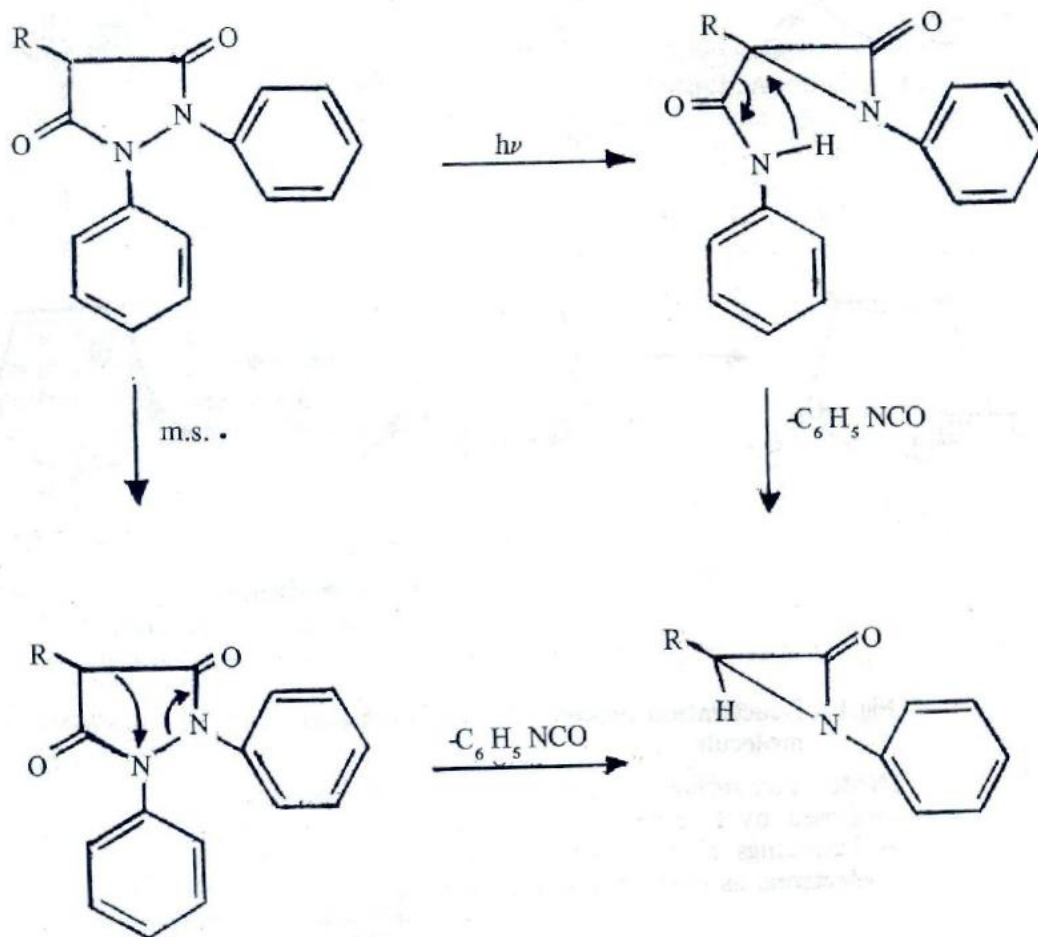
135

Fig.3: Analogies between the electron impact-
induced fragmentation and the photolysis of
medicinal pyrazolidinediones (m.s.: Locock
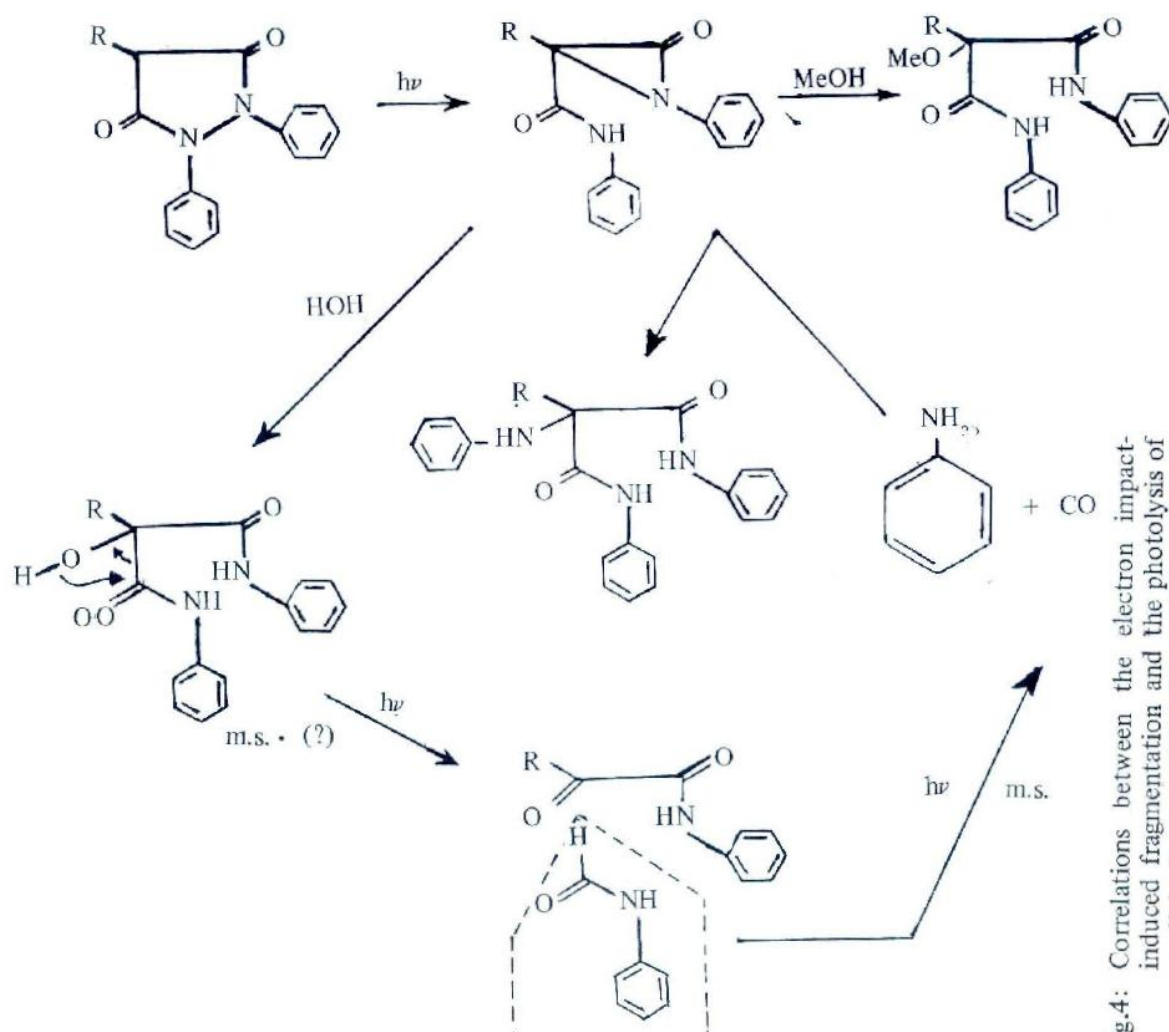et al., 1974; photochemical: Reisch and
Triebe, in press).

Fig.4: Correlations between the electron impact-induced fragmentation and the photolysis of medicinal pyrazolidinediones (m.s.: Locock et al., 1974; photochemical: Reisch and Triebe, in press).