International Journal of Pharmaceutics, 35 (1987) 259–262
Elsevier

IJP 01198

Photochemical decomposition of diphenhydramine in water

G.M.J. Beijersbergen van Henegouwen, H.J. van de Zijde, J. van de Griend and H. de Vries

Center for Bio-Pharmaceutical Sciences, Leiden (The Netherlands)

(Received 21 July 1986)
(Accepted 15 October 1986)

Key words: Diphenhydramine; Photodecomposition; Photoallergy, UV light; Demethylation; Rearrangement

Summary

The photodecomposition of diphenhydramine is described: 11 products have been described and a reaction scheme is given. Rearrangement and fission of the side-chain are important routes as well as demethylation of the dimethylamino group. The formation of instable intermediates may be important with respect to photoallergy, reported as a side-effect of diphenhydramine.

Introduction

According to most pharmacopoeias, diphenhydramine in its pharmaceutical preparation should be protected from daylight. Photochemical decomposition results in a decrease of the antihistaminic activity (Murano and Kikkawa, 1952) and products may be toxic.

Side-effects resulting from the exposure of the body to sunlight *after* administration of diphenhydramine have been reported. Emmett (1974) describes a case of photoallergic dermatitis by diphenhydramine. The diagnosis was confirmed by photopatch-testing. This diphenhydramine photoallergy is elicited by UV light in the 290–320 nm range, termed UV-B. (UV-B, a common part of sunlight provokes e.g. sunburn, but is also essential for the photosynthesis of vitamin D_3 in the skin).

In spite of these facts, no literature data are available on the photochemical decomposition of diphenhydramine. Holcomb and Fusari (1974) reported that "under ultraviolet irradiation, the principle decomposition products are benzhydrol and dimethylaminoethanol". However, this appeared to be an interpretation of a Japanese article by Murano and Kikkawa (1952), to which they refer, which does not correspond at least with the abstract (C.A. 1954, 48, 13969 h): "pharmacological properties of Restamin (diphenhydramine) and its hydrolitic products, dimethylaminoethanol and benzhydrol were studied after irradiating them with ultraviolet or infrared rays.".

In the present article, the isolation and identification of a number of photodecomposition products are described. As a result of this, a decomposition scheme was postulated, which was confirmed by additional experimental data.

Materials and Methods

Diphenhydramine-base was obtained by extracting an alkaline solution of the HCl-salt in

Correspondence: G.M.J. Beijersbergen van Henegouwen, Center for Bio-Pharmaceutical Sciences, Gorlaeus Laboratories, P.O. Box 9502, 2300 RA Leiden, The Netherlands.

water with ethylacetate followed by evaporation of the organic solvent.

Silica gel for TLC, 60 GF_{254} (Merck), was used for the column chromatography. TLC was performed on aluminium sheets pre-coated with silica gel GF_{254} (Merck). Organic solvents were 'chemically pure' and used after distillation. Water was demineralized and distilled in an all-glass apparatus before use. Preparative irradiation of diphenhydramine: 1.5 litres of a saturated solution of diphenhydramine-base in water (0.4 g/l) in a cylindrical quartz-vessel (d = 6.5 cm) designed for efficient stirring was irradiated for 90 min in a Rayonet Photochemical Reactor (RPR-208, Southern New England Ultraviolet Co., Middletown, U.S.A.) equipped with 8 lamps RUL 254 nm. Hereafter the water was evaporated and the residue dissolved in the eluent for column chromatography. 3.2 g photodecomposed diphenhydramine in 15 ml ethylacetate/methanol (2 : 1) was brought onto a silica gel column (l = 15 cm and d = 4 cm). Because of the small particle size, an overpressure of nitrogen (10 cm Hg) was applied during the elution with successively 700 ml ethylacetate/methanol (2 : 1) and 500 ml methanol/ammonia (7 : 3).

Fractions of 20 ml were collected, which were analyzed with TLC and GLC. Based on this first chromatographic separation, four fractions were distinguished: fraction I with mainly products E, G, H, I, J and K; fraction II with mainly B and C; fraction III with mainly A and fraction IV with mainly D and F. Further separation of fraction I would have been laborious and was avoided. For 5 of the 6 compounds in the mixture, a reference appeared to be present and the TLC and GLC data permitted identification of all compounds (by amongst others GC-MS).

B and C in fraction II were separated by eluting a column (l = 23 cm and d = 2 cm) with ethylacetate/methanol (2 : 1) under nitrogen pressure (10 cm Hg). Fractions of 10 ml each were analyzed with TLC and GLC. The combined fractions containing either B or C were purified from traces of polymeric material by using the same column but with chloroform/methanol/ammonia (100 : 10 : 10 drops) as an eluent.

D and F in fraction IV were separated with the same column as B and C in fraction iI, except that in this case only chloroform/methanol/ammonia (100 : 20 : 20 drops) was used.

Thin-layer chromatography. Ethylacetate/methanol (2 : 1) and chloroform/methanol/ammonia (100 : 20 : 20 drops) were used as eluting solvents.

Gas-liquid chromatography. A Packard-Becker 420 gaschromatograph was used equipped with a glass column (l = 180 cm and i.d. = 2 mm) filled with 3% OV-225 in Chromosorb WHP 100-120 mesh and a hydrogen flame ionization detector. Working conditions: nitrogen carrier gas, flow-rate 18 ml/min; injection block temperature 250°C, detector temperature 250°C, column temperature traject 180–230°C in 30 min. (Separated with increasing retention time: K, C, J, F, I, A, D, B, E, H and G.)

Spectrometry. PMR-spectra of products in $CDCl_3$ + TMS were recorded with a Jeol-JNM-PS-100. Mass spectra of pure compounds were obtained with AEI-MS-902, whereas for a mixture an LKB-2091-2130 GC-MS-Computer system was used.

Results and Discussion

Compounds A up to and including I can be considered as derivatives from diphenylmethane (K, Fig. 1). Their mass spectra show typical fragments m/e 167, 165, 152, 77 and 51 which are also found in that of K. In the spectrum of B were also found m/e 224 (M^+-CH_2OH); m/e 88 (M^+-$(C_6H_5)_2CH$) and m/e 58 ($CH_2=N^+(CH_3)_2$) formed by e.g. m/e 225-$(C_6H_5)_2CH$. However, m/e = 183, benzhydrol fragment, present in the spectrum of diphenhydramine (A) was not observed.

In the PMR-spectrum of B the signals are assigned as follows: singlet at 2.6 ppm (3H) from N–C$\underline{H}_3$; triplet at 2.9 ppm (2H) from N–C$\underline{H}_2$–CH_2OH; triplet at 3.8 ppm (2H) from N–CH_2–C$\underline{H}_2$OH; doublet at 3.4 ppm (2H) from $(C_6H_5)_2$CH–C$\underline{H}_2$; triplet at 4.6 ppm (1H) from $(C_6H_5)_2$C$\underline{H}$–CH_2 and a multiplet at 7.8–8.0 ppm (10H) from aromatic ring protons. It is supposed that B is formed from photoexcited A by a concerted intramolecular rearrangement as represented in

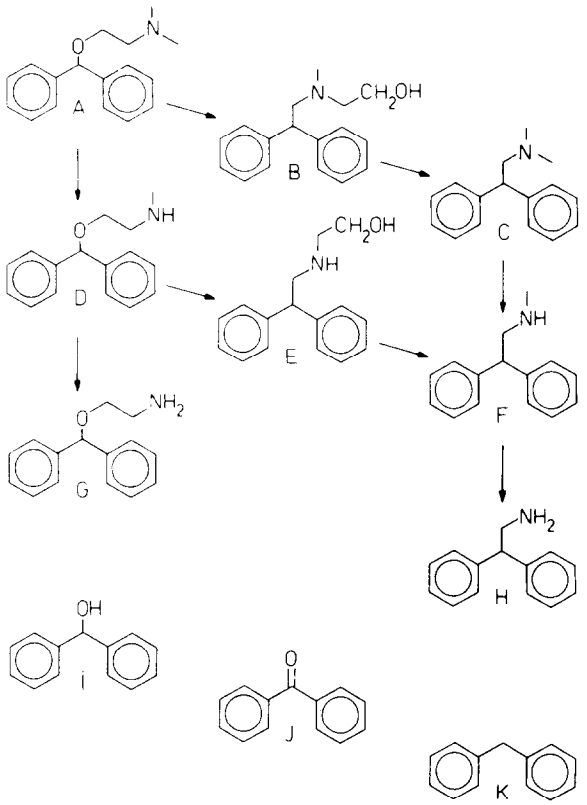

Fig. 1. Photodegradation of diphenhydramine in water.

Fig. 2. The structure of B was further evidenced by irradiating the pure compound in solution: C, F and H were the main photoproducts. Photohydrolysis of B into C may proceed via the simultaneous formation of formaldehyde.

In the mass spectrum of C were observed m/e 225 (M^+) and m/e = 58 ($CH_2=N^+(CH_3)_2$), beside the typical fragments for a diphenylmethane derivative. In the PMR-spectrum of C the signals are assigned as follows: singlet at 2.8 ppm (6H) from $N(C\underline{H}_3)_2$; a doublet at 3.6 ppm (2H) from $(C_6H_5)_2\,CH-C\underline{H}_2$; a triplet at 4.8 ppm (1H) from $(C_6H_5)_2C\underline{H}-CH_2$ and a multiplet at 8.0–8.2 ppm (10H) from aromatic ring protons. Irradiation of pure C in solution led to demethylation of the dimethylamino group with F and H as the only products: further evidence for the structure of C.

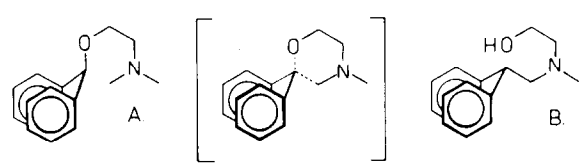

Fig. 2. Intramolecular rearrangement of photoexcited diphenhydramine (A) into B.

In the mass spectrum of F the parent peak m/e = 211 (M^+) was visible, beside two other prominent peaks m/e-167 ($M-CH_2NHCH_3$) and m/e = 44 ($CH_2=N^+HCH_3$). Further the fragments typical for a diphenylmethane derivative were observed. These last peaks were also seen in the mass spectrum of H, but beside these only a prominent peak from m/e = 167 ($M^+-CH_2NH_2$) and from m/e = 197 (M^+) were present. The identity of H was further confirmed by comparison of the TLC, GLC and mass spectral data with that of a product obtained by synthesis (Freeman et al., 1947).

The mass spectrum of D had much in common with that of diphenhydramine (A) itself and it was concluded that it was formed from A by loss of a methyl group from the demethylamino group. The structure of D was confirmed by comparison of the mass spectrum and of the TLC and GLC data with those of an authentic sample of 2-diphenylmethoxy-*N*-methylamine (desmethyl-diphenhydramine).

The fact that demethylation appeared to be a common route in the photodecomposition, A → D and C → F → H, led us to expect that one of the photoproducts would be 2-diphenylmethoxyethylamine (nor-diphenhydramine). TLC and GLC data of an authentic sample indeed corresponded with those of product G. Further evidence for its structure was obtained by irradiation of D which gave G. A remarkable fact is that upon irradiation of G no compound is formed that has structural resemblance to E. This supports the mechanism according to which B (and E) are supposed to be formed (Fig. 2), which is not possible with G lacking a methyl group at the *N*-atom.

Beside G, also E, F and H were irradiation products from D. In the mass spectrum of E were present, beside the typical fragments for a diphenylmethane derivative, m/e = 210 (M^+-CH_2OH) and m/e = 44 ($CH_2=N^+HCH_3$). A benzhydrol fragment m/e = 183, present in the spectrum of D

was not found. That also F and H were irradiation products from D is further evidence for the structure of E in which the side chain has been turned with respect to the situation in D.

Benzhydrol (I), benzophenone (J) and diphenylmethane (K) can be found as a product of all irradiations described. The lapse after which the concentration of these products became detectable depended not only on the duration of the irradiation but also on the starting compound.

If a solution of the HCl salt in water was irradiated instead of that of diphenhydramine base the same products were formed but it took about 24 h to reach the same degree of decomposition. Obviously this reflects the importance of the *N*-atom in the first steps of the photodecomposition of diphenhydramine, the formation of B (Fig. 2) and the demethylation of the dimethylamino group to D (Fig. 1). Both steps are facilitated if the electron pair on the *N*-atom is available and not delocalized as in a bond with a proton.

The photodecomposition proceeds via the formation of unstable intermediates, probably radicals. Demethylation, loss of a CH_2OH fragment in a number of decomposition steps and the formation of polymeric materials are an indication of this. It is further supported by the fact that product formation proceeds even if the irradiation was stopped.

The results of the present study give an idea of which products may be found in a pharmaceutical preparation. With respect to the photoallergy reported, the mechanism of the photoreaction may be of more importance: the formation of unstable intermediates facilitates a reaction with essential biomacromolecules, e.g. proteins, which is considered to be an essential step for the onset of photoallergy.

References

Emmett, E.A., A case of photoallergic dermatitis to a topically applied diphenhydramine preparation was observed, and the diagnosis was confirmed by photopatch testing. *Arch. Dermatol.*, 110 (1974) 249–252.

Freeman, S.K., Ringsk, Wm.F. and Spoerri, P.E., *N*-Aralkyl derivatives of 4(1)-pyridone and the chelidamic acid. *J. Am. Chem. Soc.*, 69 (1947) 858–859.

Holcomb, I.J. and Fusari, S.A., *Analytical Profiles of Drug Substances*, Academic, New York-London, 1974, p. 199.

Murano, T. and Kikkawa, M., Pharmacological studies on the decomposition of Restamin by ultraviolet irradiation. *J. Osaka City Med. Center*, 1 (1952) 114–120.