CLOBAZAM: CHEMICAL ASPECTS OF THE 1,4 AND 1,5-BENZODIAZEPINES

H. KUCH

Medizinische Abteilung, Hoechst AG, D-6230 Frankfurt/Main 80, Postfach 80 03 20, West Germany

- 1 The structures and chemistry of the 1,4- and 1,5-benzodiazepines are compared. These two groups of drugs differ in respect to basicity, lipophilicity and electronic charge distribution.
- 2 The 1,4-benzodiazepine diazepam has a weakly basic imine group in contrast to the acid methylene protons of clobazam.
- 3 The imine function of diazepam is more lipophilic than the carboxamide group of clobazam with its rather hydrophilic character.
- 4 Diazepam and clobazam differ in electronic charge distribution and hence in the location of the chemically reactive centres, the imine partial structure in diazepam and the malonic acid portion of clobazam.

SINCE the introduction of chlordiazepoxide and diazepam in the early 1960s, a large number of minor tranquillizers of similar structural design have been developed by pharmaceutical companies all over the world, and thus the chemistry of minor tranquillizers has become more and more synonymous with that of the 1,4-benzodiazepines (Sternbach, 1971).

A new anxiolytic, clobazam, has been synthesized by Rossi *et al.* (1969) in the laboratories of Maestretti in Milan (a subsidiary of Roussel Uclaf) and subsequently developed in a joint venture by Hoechst and Roussel Uclaf.

Clobazam is the first anxiolytic drug which belongs to the class of the 1,5- rather than the 1,4-benzodiazepines; therefore, these introductory remarks will mainly focus on a few selected chemical aspects of the two series of compounds trying to point out both structural characteristics and differences in reactivity.

If we compare, for example, the structural formulas of diazepam⁽¹⁾ and clobazam⁽²⁾ (Figure 1), there is obviously no big difference at a superficial

Figure 1 Structural formulas of (1) diazepam (1,4-benzodiazepine derivative) and (2) clobazam (1,5-benzodiazepine derivative).

glance, and as far as the three-dimensional molecular models are concerned, both structures seem to be totally superimposable.

Taking a closer view, however, we notice that in clobazam one of the nitrogen atoms of the seven-membered diazepine ring has been shifted towards the benzene ring and is now located in position 5. What does this imply besides a change in nomenclature?

Of course, it is the synthetic chemist who is primarily affected by these alterations. He has to take into account that different starting materials are required and different reaction schemes are to be followed in the preparation of both series of compounds. To obtain 1,4-benzodiazepines of the diazepam type, for example, appropriately substituted 2-aminobenzophenones must be condensed with reactive derivatives of the amino acid glycine (Figure 2) (Sternbach *et al.*, 1962), whereas a general access into the 1,5-benzodiazepines is achieved by the reaction of 2-nitrodiphenylamines with the corresponding derivatives of malonic acid (Figure 3) followed by reductive ring closure (Rossi *et al.*, 1969).

On further examination of the two molecules (Figure 1) we become aware of yet another structural change in the '4,5 region', namely the replacement of the C=N double bond in diazepam by an amide group in the case of clobazam.

It is well known that nearly all minor tranquillizers of the 1,4-benzodiazepine series have a C=N double bond or imine function in this position, and that this contributes substantially to their biological activity. If the double bond is saturated (for instance, by hydrogenation), the anticonvulsant and muscle relaxant properties of the resulting compounds are markedly reduced (Sternbach *et al.*, 1968). This does not hold true in the 1,5-benzodiazepine series, where the presence of the imine function does not seem to be essential for psychotropic activity.

Compared with the neutral carboxamide the imine group is weakly basic in character and somewhat more hydrophobic. It is much more reactive than an

Figure 2 Synthesis of diazepam (1).

acid amide and thus susceptible to a variety of chemical transformations.

For example, hydrolytic cleavage of a ketimine to yield the parent compounds, ketone and amine, is readily achieved by mild treatment with dilute acids. In the case of carboxamides the corresponding cleavage reaction generally requires prolonged boiling with concentrated mineral acids (Figure 4).

It is evident that under these circumstances 1,4-benzodiazepines of the diazepam type are much more prone to ring-fission of the seven-membered heterocycle than are clobazam and related compounds; and we may thus see why, among the metabolites of certain 1,4-benzodiazepines, ring-opened compounds like aminobenzophenones have also been detected (Beyer, 1971), whereas the metabolic transformation of clobazam does not affect the diazepine ring (Volz *et al.*, 1979).

Another remarkable feature of the imine partial

structure of the 1,4-benzodiazepines is its susceptibility to oxidation (Figure 5). Desmethyldiazepam⁽³⁾, for instance, can be converted by the action of peracetic acid into its N-oxide⁽⁴⁾ (Bell *et al.*, 1962), a compound which is closely related to chlordiazepoxide, the very first benzodiazepine on the market. N-oxides like ⁽⁴⁾, when treated with acetic acid anhydride, undergo a Polonovsky-type re-arrangement to yield the corresponding 3-acetoxy compound⁽⁵⁾ (Bell & Childress, 1962) which by mild alkaline hydrolysis can be easily converted into oxazepam, another well known minor tranquillizer and also one of the main metabolites of diazepam.

Compared with the impressive reactivity of the imine function, which has been demonstrated by a few selected examples only, the carboxamide structure must be regarded as being chemically nearly inert. From this the question arises whether there are other features in clobazam and related 1,5-benzodiazepines

Figure 3 Synthesis of clobazam (2).

Figure 4 Hydrolytic cleavage of ketimines and amides.

that might still attract the interest of organic chemists.

Again, an answer may be drawn from Figure 1, looking this time at the partial structure of positions 3–5 of both diazepam and clobazam. It is easily recognized that we are dealing with the elements of an α -amino acid, for example, glycine, in diazepam, whereas in the clobazam formula the contribution of malonic acid is obvious. Malonic acid and related compounds are well known to possess a reactive methylene group which is activated by the neighbourhood of the two flanking carbonyl functions.

Consequently it may be expected that clobazam too exhibits similar reactivity with respect to its CH_2 group in position 3, indeed, that is exactly the case (Figure 6). Bases like sodium hydride for instance are capable of abstracting a proton from carbon 3 of clobazam⁽²⁾ and the resulting anion can subsequently be alkylated to furnish the respective 3-alkyl derivatives⁽⁷⁾ (Weber *et al.*, 1972).

In general, active methylene compounds undergo a base catalyzed addition to activated unsaturated systems, the so-called Michael reaction. Such an addi-

Figure 5 Synthesis of oxazepam (6).

Figure 6 Substitution reactions of clobazam at carbon atom 3.

tion is shown in the lower part of Figure 6 where clobazam adds to the $\text{C}=\text{C}$ double bond of methyl acrylate to yield the corresponding propionic acid ester⁽⁸⁾.

When carrying out these base-catalyzed reactions it is important for the chemist to always choose the proper catalyst. If, for example, sodium ethylate is used to remove one of the acid protons, a completely different type of reaction results (Figure 7). The ethylate anion preferentially attacks the carbonyl group, thus breaking the $\text{N}-\text{C}$ bond; subsequently ring

contraction with formation of a benzimidazolone system⁽⁹⁾ takes place and ethyl acetate is eliminated simultaneously (Weber *et al.*, 1972).

To summarize, we note that for the cursory observer both structure and chemistry of the 1,4- and 1,5-benzodiazepines look pretty much the same. By the actual examples of diazepam and clobazam, however, it has been demonstrated that striking differences between the two series become apparent to the more sympathetic examiner.

Figure 7 Ring contraction of 1,5-benzodiazepin-2,4-diones.

References

- BELL, S.C., SULKOWSKI, T.S., GOCHMAN, C. & CHILDRESS, S.J. (1962). 1,3-Dihydro-2H-1,4-benzodiazepine-2-ones and their 4-oxides. *J. org. Chem.*, **27**, 562–566.
- BELL, S.C. & CHILDRESS, S.J. (1962). A rearrangement of 5-aryl-1,3-dihydro-2H-1,4-benzodiazepine-2-one 4-oxides. *J. org. Chem.*, **27**, 1691–1695.
- BEYER, K.-H. (1971). Die Biotransformation der Benzodiazepinderivate. *Deutsche Apotheker-Zeitung.*, **111**, 1503–1606.
- ROSSI, S., PIROLA, O. & MAGGI, R. (1969). Sintesi di 1,2,4,5-tetraidro-2,4-dicheto-3H-1,5-benzodiazepine. *La Chimica e L'Industria*, **51**, 479–483.

- STERNBACH, L.H., FRYER, R.I., METLESICS, W., REEDER, E., SACH, G., SAUCY, G. & STEMPEL, A. (1962). Quinazolines and 1,4-benzodiazepines. VI. Halo-, methyl-, and methoxy-substituted 1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-ones. *J. org. Chem.*, **27**, 3788–3796.
- STERNBACH, L.H., RANDALL, L.O., BANZIGER, R. & LEHR, H. (1968). Structure-activity relationships in the 1,4-benzodiazepine series. In *Drugs Affecting the Central Nervous System*, **2**, 237–264. Ed. Burger, A. New York: Marcel Dekker.
- STERNBACH, L.H. (1971). 1,4-Benzodiazepines. Chemistry and some aspects of the structure–activity relationship. *Angew. Chem. int. Edit.*, **10**, 34–43.
- VOLZ, M., CHRIST, O., KELLNER, H.-M., KUCH, H., FEHLHABER, H.-W., GANTZ, D., HAJDÚ, P. & CAVAGNA, F. Kinetics and metabolism of clobazam in animals and man. *Br. J. clin. Pharmac.*, **7**, 41S–50S.
- WEBER, K.-H., BAUER, A. & HAUPTMANN, K.-H. (1972). Benzodiazepine mit psychotroper Wirkung, III. N-Aryl- und N-Heteroaryl-1H-1,5-benzodiazepin-2,4-[3H, 5H] -dione. *Liebigs Ann. Chem.*, **756**, 128–137.