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Review

The polymorphism of cimetidine

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Abstract: High resolution FT-IR data are given on five known and two uncharacterized modifications of cimetidine. On the basis of the chronological order of publications and the usual nomenclature, an attempt is made to clear up the uncertainty concerning the names of the various modifications. An attempt is made to rationalize the spectroscopic data characterizing the given modifications. The anhydrous and the monohydrate modifications are discussed separately, together with those changes which occur on the dehydration of the monohydrates without melting.

Keywords: *Polymorphs of cimetidine; FT-IR of cimetidine modifications; cimetidine monohydrates; modification transitions.*

Introduction

The widely used histamine H_2 antagonist cimetidine (Fig. 1) shows large-scale polymorphism. The first publication on cimetidine in 1972 [1] was followed by a patent which deals especially with the three modifications (A, B and C) of cimetidine [2]. In addition to the procedure for their preparation, IR spectroscopic and physicochemical data are given. Later research has begun to find further modifications [3–6]. Other authors have dealt with the exact structural determination of these modifications [7–10].

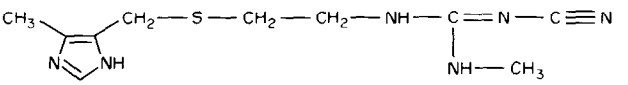

Figure 1
N-Cyano-*N'*-methyl-*N''*-[2-([(5-methyl-1-H-imidazol-4-yl)-methyl]-thio)-ethyl]-guanidine; cimetidine.

In addition, comparisons of the relative bioavailabilities of the different cimetidine products can be found [11–14]. Further publications have indirect connections with the modifications. One of them deals with the modification equilibria arising in solution [15]; another deals with hydrogen bonds formed by solvation [16]. Since in the present work only the solid state polymorphism of cimetidine is considered, such results are beyond the scope of this review, as are those which deal with the structure of some cimetidine salts [17–19] or complexes [20].

The research teams involved in these studies worked in isolation, so that some problems in parallel publication have arisen. To illustrate the confusion, modification "C" can be either anhydrous or the monohydrate, depending on the source of the paper. On the other hand one modification is described as "D" or "Z" depending on the literature source. To these uncertainties a further factor can be added, which arises from the differing origins of the published data. Considering the limited wavenumber accuracy of traditional IR spectrophotometers, it is difficult to compare the different data.

It is worth mentioning that the existence of polymorphic modifications is not mentioned in the recently published analytical profile of cimetidine [21]. In the authors' laboratory the polymorphism of cimetidine has been examined since 1978, as described in this paper.

Review of Earlier Work

Any survey of the polymorphism of cimetidine should begin with the SKF patent [2]. In this work the authors refer to three (A, B and C) modifications. In the appendix of the patent parts of the infrared spectra from 1600 to 600 cm^{-1} are cited as characterizing the A and the B modifications. The authors claim that the 1400, 1385, 1205 and 1155 cm^{-1} bands define the A modification, whereas the band at 1180 cm^{-1} characterizes the B and C modifications. Other common features are also noted. Both modifications are difficult to handle, and they have thixotropic features in aqueous suspension. The authors use the B/C common designation in their description, and some penetrometric data are also given as supporting evidence.

This means that the authors [2] utilize the name "C" without properly characterizing the modification which has very poor properties and does not have water of crystallization. The present authors wish to emphasize this, because all statements which refer to modification C as a monohydrate [10, 19] are incorrect.

As claimed in the SKF patent [2], modification A is the form generally used. This modification had the best reproducibility, so that X-ray crystallography could be applied as early as 1978 by Häddicke *et al.* [7]. These authors do not refer to modification A, but the method of preparation of the crystal analysed leaves no doubt as to which modification was involved. They obtained it from acetonitrile, so that according to the claims of the SKF patent [2] the crystal obtained from non-aqueous media can only be modification A. In addition to this indirect evidence, there is direct evidence too. From the crystallography data the present authors simulated an identical X-ray diffractogram (unpublished results) to that of the modification A presented by the present authors [6] and by Prodič-Kojič [3].

In 1979 Prodič-Kojič *et al.* [3] mentioned four modifications of cimetidine. However, they did not correlate their modifications with the SKF patent, and they use the codes CRC 1820/I-IV. It is clear that CRC 1820/I is identical with modification A. Considering the spectral data for CRC 1820/II it can be seen that the characteristic bands at 3500, 3390 and 3300 cm^{-1} derive from the O–H vibrational stretch of one mole of water of crystallization. The authors do not discuss the water content of the sample in this paper, although this is discussed in their next publication [8]. Since CRC 1820/II differs from cimetidine by one mole of water, this should be discussed separately. Unfortunately the sections of the IR spectra given in the paper of Prodič-Kojič *et al.* [3] are reduced in size to such an extent that it is impossible to determine the wavenumbers of the peaks. Consequently, to correlate their CRC 1820/III and CRC 1820/IV modifications with the

SKF data [2] proved to be rather difficult. Hegedüs [6] performed this correlation with the help of X-ray powder diffraction spectra, from which it appears that CRC 1820/III and CRC 1820/IV are identical with the "C" and "B" modifications respectively.

In chronological order the next two contributions were patents describing cimetidine H and cimetidine Z respectively [4, 5]. The designation H refers to the monohydrate, as discussed below. In one patent [5], modification Z is claimed to be easy to handle, sand-like material; it does not have significant absorption at 1180 cm^{-1}, but does show a characteristic doublet of medium intensity at 950 and 940 cm^{-1}.

The X-ray crystallographic data of cimetidine Z are discussed by Párkányi *et al.* [9]. Almost identical data are given in the paper of Shibata *et al.* [10], who designated this modification as D. Although the two teams adopted different starting conditions, the atomic coordinates and torsion angles are within normal error limits. This suggests that modifications Z and D are one and the same material.

In the opinion of the present authors, Shibata *et al.* [10] are mistaken in using the term modification C when writing about Prodič-Kojič's modification CRC 1820/II. As shown above, the modification cannot be a monohydrate, because Bavin *et al.* [2] defined modification C as an anhydrous material 7 years earlier.

Methods and Definitions

Names proposed for the principal modifications are listed below, together with the method of purification adopted:

Modification A: According to the SKF patent [2], this was obtained by recrystallization from isopropanol.

Modification B: This was obtained by slowly cooling a hot aqueous solution of 15% w/w cimetidine.

Modification C: This was prepared from a hot 5% w/w aqueous solution of cimetidine by rapid cooling. This procedure can be made more reliable by seeding with crystals.

Modification D: According to the patent [5], the base was obtained from a 15% w/w aqueous solution of cimetidine acetate at about 20°C.

Modification M1: This was obtained according to the patent [4]. A hot 15% w/w aqueous solution of cimetidine was poured into a five-fold excess of ice.

Modification M2: This was crystallized from a 1.4% w/w aqueous solution of cimetidine, which was allowed to stand at 0°C for seven days.

Modification M3: This was obtained from a 10% w/w aqueous solution of cimetidine acetate, liberating the base at 15°C. However, the reproducibility of this method was found to be poor.

Measurement of IR spectra

A pellet of each modification of 13 mm diameter was prepared by mixing 1.0–1.5 mg of sample with 300 mg of KBr and pressing it with a force of about 10^5 N in an electro hydraulic press.

High resolution FT-IR spectra were recorded on a NICOLET 7000 spectrophotometer. Its wavenumber accuracy was better than 0.01 cm^{-1}, and its resolution was 1 cm^{-1}. Conventional spectra (resolution 4 cm^{-1}, wavenumber accuracy ± 3 cm^{-1}) were recorded on a Perkin–Elmer 257 instrument with the normal slit program and medium scan speed. In all spectra shown in the figures the wavenumber scale expansion is changed at 2000 cm^{-1}.

Results and Discussion

In the following section the above-mentioned anhydrous and monohydrate modifications of cimetidine are discussed, together with the authors' own data and a critical evaluation of the often contradictory data in the literature. On this basis suggestions are made as regards the unambiguous nomenclature of the modifications. A more detailed discussion of this matter is to be found in Ref. [6].

Anhydrous modifications

Modification A was defined exactly in the patent [2], and this name has been widely accepted. Prodič-Kojič is alone in calling this material CRC 1820/I [3]. The infrared spectral data can be seen in Table 1. The spectrum between 4000 and 400 cm^{-1} is shown in Fig. 2.

Modification B was also defined in the patent [2]. This material is referred to as CRC 1820/IV in Prodič-Kojič's paper [3]. The infrared spectrum of this material can be seen in Fig. 3, the spectral data being tabulated in Table 1.

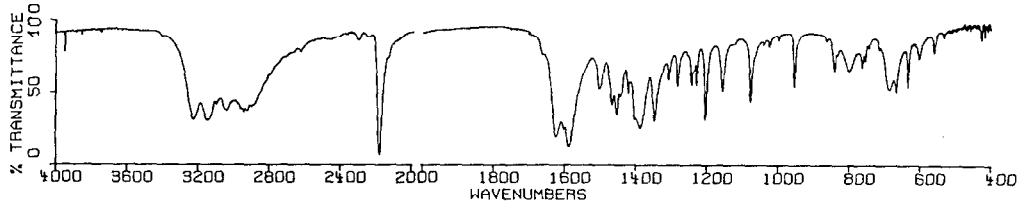

Figure 2
Infra-red spectrum of modification A.

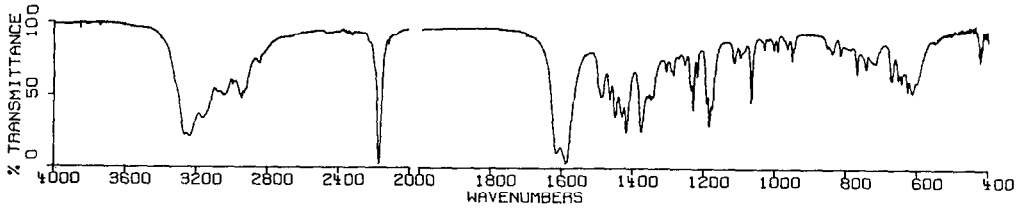

Figure 3
Infra-red spectrum of modification B.

Modification C has not yet been clearly defined. Although Shibata quotes Prodič-Kojič's CRC 1820/II as modification C [10, 19], this is an error, as noted above. To define modification C various data have to be considered. In the patent [2] the band at 1180 cm^{-1} is mentioned, but this is common to both the B and C modifications. On the other hand, the physical and especially the rheological properties of the material should be examined. Modification C, produced as described above, is a material like cotton wool, with long needle crystals, which settle quite slowly; it also shows thixotropic features. Neither in the SKF patent [2] nor in Prodič-Kojič's paper [3] is there a method for the preparation of this modification. In addition, Prodič-Kojič, who designates this material CRC 1820/III, emphasizes that its production is not reproducible. The spectrum which he gives in the paper is evidence for this statement, because the most significant

Table 1
High resolution Fourier transform infra-red data of the cimetidine modifications A, B, C and D*

A	B	C	D
3401	3265	3320	3295 s
3226 s	3237 s	3276 s	3213 s
3142 s	3165 s	3162	3188
3098	3077	3086	3097
3051	3043	3045	3055
3038	2998	2996	—
2995	2985	2959	2985
2943	2948 s	2950	2944
2898	2933	2932	2911 s
—	2849	2847	2855
2621	2466	—	2360
—	—	2465	2345
2298	2326	2328	2319
2237	—	2234	2239
2178 s	2174 s	2166 s	2155 s
—	2121	2078	—
1662	—	—	—
1623 s	1614 s	1615 s	1614 s
1588 s	1587 s	1587 s	1587 s
1502	1488	1487 s	1492 s
1466	1464	—	1469
1454 s	1449	1450 s	1451 s
1443	1430	1433 s	1433 s
1422	1417 s	1418 s	—
1403	1375 s	—	—
1388 s	1358	1375 s	1377 s
1347 s	1349	1347	1348 s
—	1343	—	—
1308	1306	1298	1307 s
1283	1288	1288	1280
—	1270	—	1261
—	1253	1247	1248
1243	1236	—	1234
1228	1230 s	1229 s	—
1204 s	1218	1217	1205 s
—	1192 s	—	—
—	1184 s	1182 s	1181
1156 s	1176 s	—	1170
1124	1115	1113	1150
—	1097	1094	1099
1077 s	1066 s	1066 s	1082
1024	1030	1031	1071 s
—	1020	—	1025
—	1004	1004	—
999	993	—	—
—	965	976	954 s
954 s	952	948 s	943 s
864	855	—	892
842	839	839	860
832	816	—	815
800	790	—	—
764	769	771 s	755 s
755	—	—	709
743	743	746	681
716	716	715	660 s
688 s	671	675	625 s
667 s	653	645	618
635 s	644	625 s	579
603	628	590	574
560	615	—	507
534	600	558	479
428	—	—	434
418	422	422 s	418

* The data are in cm^{-1}. s = significant peak.

peaks of the spectrum of modification A can also be found in it. According to the present authors' experience the reproducibility of modification C is fair; it is, however, advisable to use seeding crystals to obtain a uniform product. The infrared spectrum of this modification is shown in Fig. 4, the spectral data being listed in Table 1.

Modification D. Because of the proven identity of cimetidine D with Z (see above) the designation "D" is suggested as being in accordance with the nomenclature rules. Shibata states [8] that the reproducibility of this material cannot be guaranteed. In contrast, the reproducibility of the preparation method proposed by the present authors is quite good. The infrared spectrum of this modification is shown in Fig. 5, the spectral data being listed in Table 1.

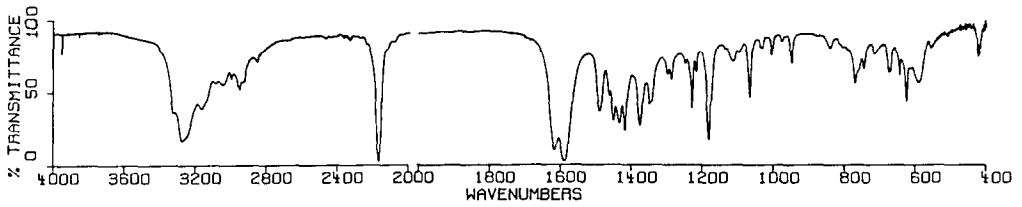

Figure 4
Infra-red spectrum of modification C.

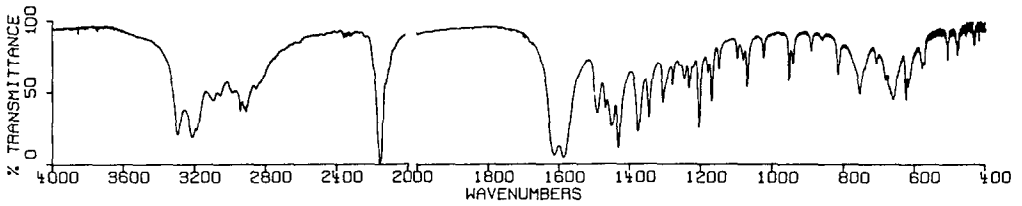

Figure 5
Infra-red spectrum of modification D.

Monohydrate modifications

As mentioned above, the material described as "cimetidine H_2O" also shows polymorphism. In discussing this it is helpful to use M1, M2 . . . to designate the different modifications. The sign M shows that in this case monohydrates are considered. To the best of the authors' knowledge, "cimetidine H_2O" has three polymorphs. Only one of them is described in the literature [3, 4, 6, 8, 10].

Cimetidine M1. The patent [4] describes this modification as cimetidine H, which Prodič-Kojič describes as CRC 1820/II. Prodič-Kojič did not consider the interesting possibility that the hydrate can be dehydrated in the KBr pellet itself. He presented an infrared spectrum, which is really a 1:1 mixture with cimetidine A, as evidenced by the presence of the peaks at 1205, 1155 and 1075 cm^{-1}. In contrast to Prodič-Kojič the patent [4] gives a very simple and reliable procedure to generate the cimetidine M1 modification, as briefly described above.

The infra-red spectrum of cimetidine M1 differs from that of Prodič-Kojič [3]. The former was recorded immediately after preparing the pellet because of the above-mentioned dehydration. The identity of the materials was established by Hegedüs with

the help of X-ray diffraction data [6]. Prodič-Kojič *et al.* give the crystallographic analysis data of their monohydrate [8]. From these data the powder diffractogram of CRC 1820/II was simulated and compared with that of cimetidine M1 (unpublished work). The identity is unequivocal. The high resolution IR absorption data of modification M1 are presented in Table 2, and illustrated in Fig. 6.

Table 2
High resolution Fourier transform infra-red data of the cimetidine modification M1*

3501 s	1449 s	1007
3386 s	1432	958 s
3299 s	1416 s	943
3208	1367	878
3170	1308	817 s
3130	1283	756
3086	1256 s	731
3041	1234	720
2966	1205	686
2943	1179	660
2900	1169	645
2617	1164 s	636 s
2470	1126	625
2360	1106	604
2152 s	1099	580
1592 s	1085	573
1571 s	1071	476
1485	1059	426
1465	1024	

*The data are in cm^{-1}. s = significant peak.

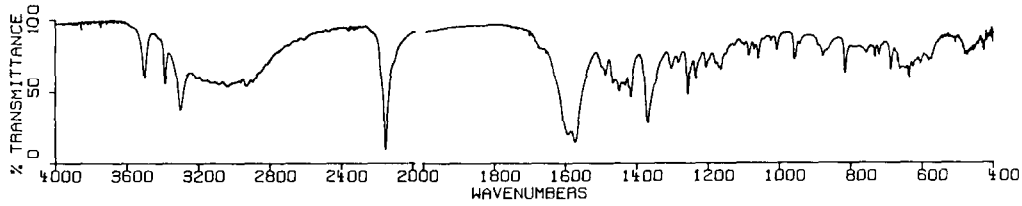

Figure 6
Infra-red spectrum of modification M1.

Modifications cimetidine M2 and M3

These modifications have been described only by Hegedüs [6] who labelled them D and ZH respectively. These modifications are of poor reproducibility and do not have good technological properties. For these the medium-resolution infra-red spectra are presented in Figs 7 and 8, the spectral data being listed in Table 3.

The cimetidine monohydrate modifications can lose their water of crystallization without melting, thereby changing their crystal form. Such transitions have already been mentioned as occurring in the KBr pellet. Moreover, cimetidine M1 is transformed spontaneously to cimetidine A on storage for several months at room temperature [3, 6]. Cimetidine M2 can be transformed into cimetidine C at 90°C, while cimetidine M3 yields cimetidine D at room temperature [6].

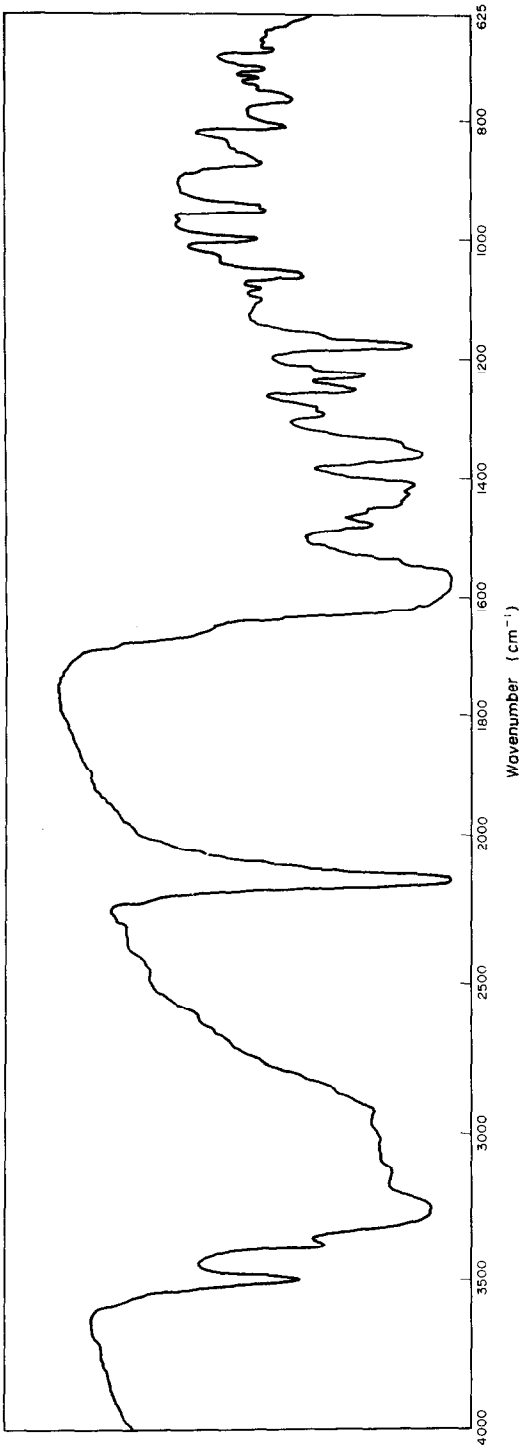

Figure 7
Infra-red spectrum of modification M2.

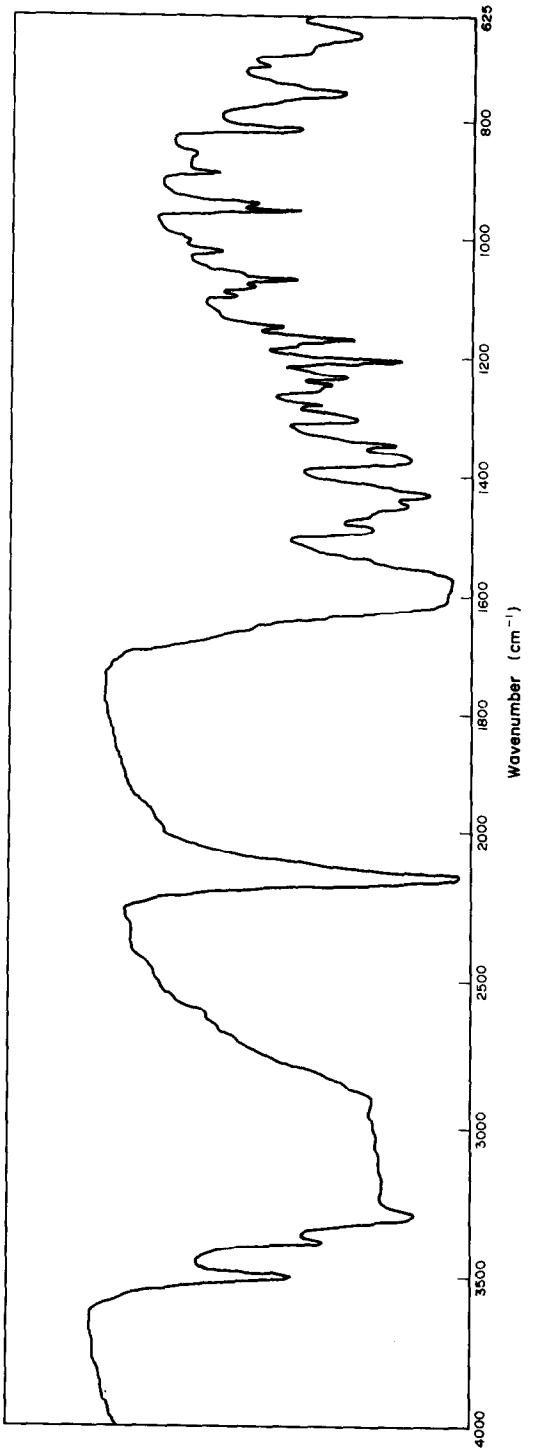

Figure 8
Infra-red spectrum of modification M3.

Table 3
Medium resolution infra-red data of cimetidine monohydrate modifications*

Cimetidine M2		Cimetidine M3	
3495 s	1179 s	3500 s	1207 s
3385 s	1103	3390 s	1170 s
3260 s	1082	3300 s	1150
2920	1064 s	2900	1095
2155 s	1002	2150 s	1070 s
1610	953 s	1610	1025
1570 s	945	1575 s	952 s
1480	873 s	1490	941
1430	811	1450	892
1412 s	767 s	1430 s	860
1365 s	730	1378 s	818 s
1295	717	1348	754 s
1280	683	1307	710
1253	625	1280	660 s
1227		1235	

*The data are in cm^{-1}. s = significant peak.

Summary

The present survey of the modifications of cimetidine indicates that polymorphism occurs on a large scale. There are four anhydrous and three monohydrate modifications. The anhydrous modifications are designated A to D respectively. The monohydrates can be designated as M1, M2 and M3. A rare peculiarity of cimetidine is that all the modifications can be obtained from water except modification A.

This paper presents high resolution FT-IR spectral data in order to characterize those modifications which have good reproducibility and are of technological significance. Some further data of technological importance are also given on the anhydrous modifications in Table 4.

Acknowledgements: Experts at the Central Research Institute for Chemistry of Hungarian Academy of Sciences are acknowledged for recording the FT-IR spectra. Cooperating colleagues at Gedeon Richter Ltd are also thanked for their help.

Table 4
Some properties of the anhydrous cimetidine modifications

Property	A	B	C	D
Medium of crystallization	Non-aqueous medium	Water 70–80°C	Water 50–60°C	Water 10–20°C
Physical form	Microcrystals	Amorphous	Long needles	Sand-like
Filtered weight / Dried weight	1.4	2.6	2.3	1.4
Volume weight ($g\,l^{-1}$)	410	280	320	680
Reproducibility of polymorphic modification	Very good	Good	Poor	Very good
Most significant IR bands (cm^{-1})	1204, 1156, 1077, 954	1230, 1192, 1184, 1176	1182, 1066, 948	2155, 1071 954, 943

References

[1] J. W. Black, W. A. Duncan, G. J. Durant, C. R. Ganellin and M. E. Parsons, *Nature (London)* **236**, 385 (1972).
[2] British Patent Specification No. 1,543,238 (1976).
[3] B. Prodič-Kojič, F. Kajfez, B. Belin, R. Toso and V. Sunjač, *Gazz. Chim. Ita.* **109**, 535–9 (1979).
[4] Belgian Patent Specification No. 893,610 (1981).
[5] Belgian Patent Specification No. 894,464 (1981).
[6] B. Hegedüs, Ph.D. Thesis (Technical University Budapest) (1982).
[7] E. Häddicke, F. Frickel and A. Franke, *Chem. Ber.* **111**, 3222–3232 (1978).
[8] B. Kojič-Prodič, Z. Ružič-Toroš, N. Bresciani-Pahor and L. Randaccio, *Acta Crystallogr.* **B36**, 1223–1225 (1980).
[9] L. Párkányi, A. Kálmán, B. Hegedüs, K. Harsányi and J. Kreidl, *Acta Crystallogr.* **C40**, 676–679 (1984).
[10] M. Shibata, H. Kokubo, K. Morimoto, K. Morisaka, T. Ishida and M. Inoue, *J. Pharm. Sci.* **72**, 1436–1441 (1983).
[11] E. Ortega, J. Querol and J. Graza, *Curr. Ther. Res.* **28**, 692–697 (1980).
[12] Z. Kopitar, P. Cvelbar, B. Vrhovac and M. Grims, *Pharmacia* **19**, 33–39 (1981).
[13] E. Ortega and M. Corona, *Curr. Ther. Res.* **32**, 457–463 (1982).
[14] P. Cvelbar, Z. Kopitar, A. Lenardic, V. Jakovlevic and M. Stanulovic, *Jugosl. Physiol. Pharmacol. Acta* **18**, 245–254 (1982).
[15] Japan Patent Application No. 80/7559 (1980).
[16] R. C. Mitchell, *J. Chem. Soc. Perkin Trans.* **2**, 915–918 (1980).
[17] Japan Patent Application No. 82/35345 (1982).
[18] K. Burns, K. Prout and G. J. Durant, *J. Chem. Soc. Perkin Trans.* **2**, 1239–1242 (1983).
[19] M. Shibata, M. Kagawa, K. Morisaka, T. Ishida and M. Inoue, *Acta Crystallogr.* **C39**, 1255–1257 (1983).
[20] F. T. Greenaway, L. M. Brown, J. C. Dabrowiak, M. R. Thompson and V. W. Day, *J. Am. Chem. Soc.* **102**, 7782–7784 (1980).
[21] P. M. G. Bavin, A. Prost and J. E. Zarembo, in *Analytical Profiles of Drug Substances* (K. Florey, Ed.), Vol. 13, pp. 127–181, American Pharmaceutical Association (1984).

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