298. Structural Studies of Crystalline Enamines

by **Kevin L. Brown**[1]), **Lorenz Damm, Jack D. Dunitz, Albert Eschenmoser, Reinhard Hobi**[2]), and **Christoph Kratky**[3])

Organic Chemistry Laboratory, Swiss Federal Institute of Technology, ETH-Zentrum, CH-8092 Zürich

(3.X.78)

Summary

Crystal structure analyses of five crystalline enamines together with recently published structural data for two other enamines reveal varying degree of pyramidality at the enamine nitrogen atom. The pyramidality appears to be most pronounced in enamines from piperidine and morpholine, less so in enamines derived from prolinoid amines. A pyrrolidine enamine obtained from a derivative of cyclohexane-1,4-dione seems to have a virtually planar enamine group. The implications of these findings for current stereochemical problems in enamine chemistry are discussed.

Introduction. – When one considers the importance of enamines [1] as intermediates in present-day synthetic and enzymatic chemistry, it seems astonishing that so very little is known about the fine details of the structure of the enamine grouping [2]. Indeed, until quite recently it seems to have been taken for granted that the enamine group is more or less planar. This presumption seems not to have been seriously questioned, probably because it appeared to be so nicely consistent with, or even indicated by, the most characteristic and useful feature of enamine chemistry, namely, nucleophilic reactivity at the carbon atom.

Our interest in this problem arose out of attempts to understand the mechanism of enantioselection in intramolecular aldol condensations of type **1** → **2** [3] [4]; these transformations involve the important synthetic principle of introducing chirality by conversion of a prochiral center to a chiral one by means of enantioselective catalysis[4]). In the absence of evidence to the contrary, it seems likely that enamine intermediates are formed during these ring-closure reactions and are implicated in the stereoselection step. Enantioselection involving an enamine intermediate of type **3** would require a mechanism for distinguishing between opposite diastereotopic faces of the enamine grouping. If the enamine nitrogen atom were not

---

[1]) Present Address: Chemistry Division, D.S.I.R., Petone, New Zealand.

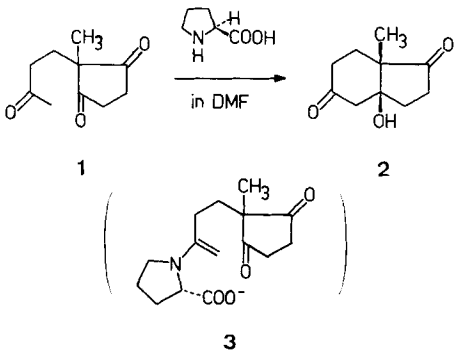
[2]) Present Address: Institut für Pharmakologie und Biochemie der Vet. Med. Fakultät der Universität Zürich.

[3]) Present Address: Institut für Physikalische Chemie, Universität Graz, A-8010 Graz, Österreich.

[4]) For related work in this field compare [5–7] and for a review see [8].

planar but pyramidal, its pyramidality could provide a switch for relaying chiral information from the chiral carbon centre of the optically active catalyst to the nucleophilic enamine carbon atom in a 'through-bond' fashion. Our own experiments designed to identify 'through-space' mechanisms for such transmittance of chiral information have so far been soberingly unsuccessful[5]). A knowledge of the detailed structure of the enamine grouping therefore seemed essential for progress in understanding the role of the chiral catalysts in the above-mentioned type of asymmetric synthesis.

Scheme 1. *Enantioselective aldolization catalysis by proline* (Hajos & Parrish [3]; Eder, Sauer & Wiechert [4])



This paper presents results of X-ray analyses of five crystalline enamines, **4**–**8**, which have been specifically prepared for this purpose [9] [10]. Details of their preparation and of the crystallographic analyses are given later in this paper. During the course of our work, we have become aware of crystal structure analyses of two other enamines, **9** [11] and **10** [12], that have appeared recently. In our discussion we shall draw on these results as well as our own, in order to cover all the crystal structure evidence available to us[6]). Microwave as well as theoretical studies for the simplest enamine, vinylamine, have been carried out in the present context by *Meyer* [14] and *Müller & Brown* [15] respectively.

Discussion of Crystal Structure Results. – Information about the geometry of the enamine group, obtained from the seven available crystal structure analyses, is summarized in *Tables 1* and *2* (for definitions of symbols see *Fig. 1*). For structures **9** and **10** the quantities listed were calculated from published atomic coordinates [11] [12], while the other data are obtained from our own analyses, which are described in detail later in this paper.

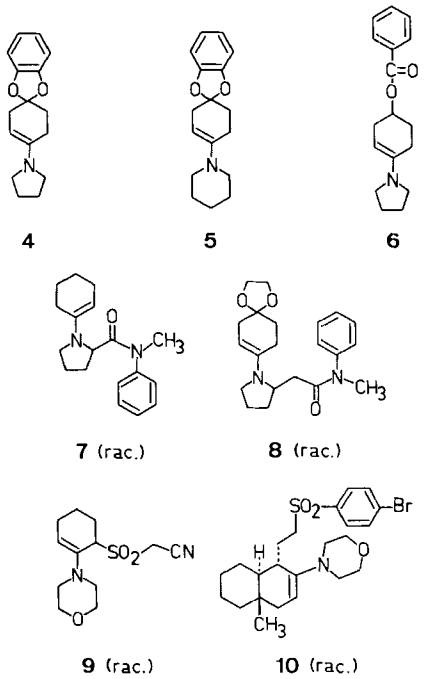
The quality of the data varies widely from one structure to another, with mean estimated standard deviations in atomic position ranging from about 0.003 Å for **4** and **7** (low-temperature analyses) to about 0.02 Å for **10** (heavy-atom structure). Moreover, some of the results may be suspected to be contaminated by systematic

---

[5]) Unpublished work by *Hobi* [9], *Damm* [10], *A. Kümin & A. Eschenmoser.*

[6]) An enamine group occurs in the natural product oxotuberostemonine, whose crystal structure has also been determined [13]. Here the group is part of a fused polycyclic ring system and its geometry is largely determined by ring constraints. We therefore omit it from our survey.

Scheme 2. *Crystalline enamines of known crystal structure*



errors of various kinds. In this connection, it must be emphasized that atomic positions derived by X-ray diffraction analysis do not correspond to equilibrium positions but rather to centroids of distributions obtained by averaging the electron density over the intra- and intermolecular vibrations and often over alternative positions with variable occupancies (partial or complete disorder) as well. The separations between such centroids for atoms subject to large-amplitude, highly anisotropic vibrations or to variable site-occupancy may differ markedly from the actual interatomic distances. As an obvious example, the near equality of the observed bond lengths a and b in structure **6** *(Table 2)* is a strong indication that

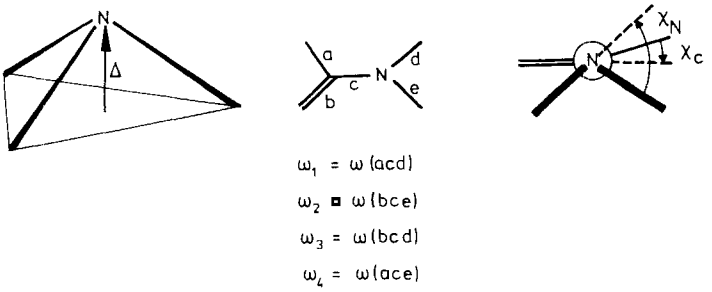


Fig. 1. *Explanation of some of the symbols used in* Tables 1 *and* 2. The angle τ (twist angle) is the mean of ω_1 and ω_2

the cyclohexene ring of this molecule occupies two alternative orientations in the crystal in about equal proportions; in the observed averaged structure the distinction between the double and single bonds is lost. Partial disorder, which is more difficult to detect, may be present in some of the other structures and may affect the 'observed' parameters to a lesser but by no means negligible extent. Moreover, some of the interatomic distances may be subject to systematic shortenings of up to about 0.02 Å, due to the effect of rigid-body librations and internal molecular motions. Methods for applying approximate corrections for these effects have been proposed [16] but are of dubious validity except when the rigid-body model can be expected to hold – which is not the case for the analyses described here.

In spite of these difficulties, it is evident that the geometry of the enamine group is very different from one molecule to another; indeed there are even marked differences between the same molecule (**8**) in different crystalline environments.

From the projections down the respective C–N bonds *(Fig. 2)* we see that the pyramidality at the nitrogen atom varies over the whole range from virtually complete tetrahedralization (sp^3 hybridized N) to virtual planarity (sp^2 hybridized N). The pyramidality is greater for molecules where the N-atom is part of a six-membered ring (piperidine or morpholine, structures **5**, **9** and **10**), smaller for molecules where the N-atom is part of a five-membered ring (pyrrolidine).

A second feature that is apparent from *Figure 2* is the tendency for one of the bonds emanating from the N-atom to eclipse the C=C bond; the maximum value of the torsion angle ω_2(C–N–C=C) observed in any of the structures is only 11° (structure **7**, see *Table 1*).

Figure 2 also shows that although the pyramidality at the central carbon atom of the enamine group is small, it is consistently in the opposite direction to that of the nitrogen atom. This regularity is also apparent from the opposite signs of the χ_N and χ_C values[7]) listed in *Table 1*.

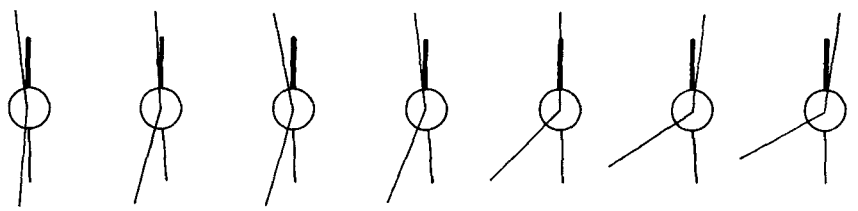


Fig. 2. Newman *projections of enamines* **4–10** *looking down the* $N–C(sp^2)$ *bond.* The C=C bond is maintained in the vertical position throughout

---

[7]) These parameters describe the out-of-plane bending at the N- and central C-atoms respectively and are defined in *Figure 1;* they are related to the torsion angles ω_1, ω_2, ω_3, ω_4 by:

$$\chi_N = \omega_2 - \omega_3 + \pi = -\omega_1 + \omega_4 + \pi$$

$$\chi_C = \omega_1 - \omega_3 + \pi = -\omega_2 + \omega_4 + \pi$$

The twist angle τ *(Fig. 1)* is defined as

$$\tau = (\omega_1 + \omega_2)/2$$

The parameters χ_N, χ_C and τ have been used previously for describing out-of-plane deformations of the amide group [17].

Table 1. *Torsion angles and out-of-plane parameters for crystalline enamines.* For definitions of symbols see *Figure 1* and text

Enamine	ω_1	ω_2	ω_3	ω_4	Δ	χ_N	χ_C	τ
10	−63°	−8°	119°	170°	0.402 Å	53°	−1°	−35°
9	−61.4	−7.0	123.2	168.4	0.370	49.8	−4.6	−34.2
5a[a])	−48.2	−1.1	134.5	176.1	0.325	44.4	−2.7	−24.7
5b[a])	−46.0	0.8	138.3	176.6	0.311	42.5	−4.3	−22.6
8a[a])	−27.3	6.5	157.9	−178.6	0.196	28.6	−5.2	−10.4
7	−17.0	11.4	165.0	−170.6	0.178	26.4	−2.0	−2.8
8b[a])	−20.0	3.0	165.1	177.8	0.120	17.9	−5.1	−8.5
4	−6.0	6.8	175.9	175.1	0.072	10.9	−1.9	0.4
6[b])	−2.0	−2.5	179.6	175.9	0.013	−2.1	−1.6	−2.2

[a]) Two crystallographically independent molecules of **5** and **8**.
[b]) Disordered enamine grouping (see text).

In all the compounds studied the terminal enamine carbon atom carries a hydrogen atom. An out-of-plane bend of a few degrees at this carbon atom, similar to that observed for the central carbon atom, cannot be excluded, but would be detectable only if the hydrogen atom were replaced by a heavier atom or group, such as CH_3.

The observed bond lengths and angles in the enamine grouping also show quite large variations *(Table 2)*. In spite of considerable scatter, some definite trends can be discerned[8]). With decreasing pyramidality at the nitrogen atom, the enamine N–C-bond distance decreases from about 1.42 to about 1.38 Å; the adjacent C–C-single-bond distance decreases from about 1.51 to about 1.48 Å, while the C=C double bond distance stays practically constant at about 1.34 Å. The

Table 2. *Bond lengths and angles in crystalline enamines.* For identification of symbols see *Figure 1*. All values are uncorrected for rigid-body libration effects

En-amine	a	b	c	d	e	ab	ac	bc	cd	ce	de
10	1.54 Å	1.35 Å	1.42 Å	1.49 Å	1.52 Å	122°	114°	124°	113°	117°	108°
9	1.514	1.334	1.426	1.476	1.461	120.1	115.0	124.8	116.3	115.7	109.2
5a	1.503	1.342	1.410	1.456	1.464	120.4	115.1	124.4	117.0	116.9	111.3
5b	1.511	1.337	1.412	1.450	1.449	120.5	115.3	124.1	117.3	117.2	111.9
8a	1.495	1.334	1.395	1.490[a])	1.450	121.6	116.3	121.9	123.2	120.7	110.7
7	1.500	1.349	1.393	1.439	1.458[a])	121.0	116.1	122.8	124.1	120.4	110.9
8b	1.483	1.348	1.385	1.509[a])	1.463	121.0	116.4	122.4	124.8	122.1	111.0
4	1.480	1.366	1.380	1.451	1.457	121.9	116.5	121.6	126.0	121.4	111.8
6	(1.427)	(1.412)	1.381	1.435	1.435	121.9	(118.8)	(119.3)	(124.7)	(123.5)	111.8
Mean[b])	1.503	1.345	1.400	1.464		121.2	115.6	123.3	120.2	118.9	110.7
Range[b])	0.06	0.032	0.046	0.085		1.9	2.5	3.2	13	6.4	3.9

[a]) Bond to atom carrying substituent in the pyrrolidine ring.
[b]) Excluding bracketed values (disordered structure).

[8]) In examining these and other trends, structure **10** should be down-weighted because of its much lower precision. Structure **4** may be affected by the same kind of disorder as **6** (two alternative orientations of the cyclohexene ring) although to a much smaller degree (not more than 10%).

observed trend in N–C distance is in qualitative agreement with the calculations by *Müller & Brown* [15] for vinylamine, which give a distance of 1.416 Å for their nonplanar equilibrium structure and of 1.391 Å for their planar transition state.

As far as bond angles are concerned, those at the central carbon atom (ab, ac, bc in *Table 2*) show only small and unsystematic variations, which are probably not significant. The angles at the nitrogen atom *must* change with the degree of pyramidality at this atom, the angle sum being 360° for the planar N-atom and about 338° for the most pyramidal N-atom observed (structure **10**). The required decrease in angle with increasing pyramidality occurs mainly for the exocyclic C–N–C angles. The endocyclic angle stays more or less constant at about 111°, except for the morpholine structures **9** and **10**, where it is a couple of degrees smaller.

Concerning the Nitrogen Inversion Path in Enamines. – Reaction paths for several prototypal chemical reactions have been derived over the last few years by examining how the structural parameters of certain molecules or parts of molecules change in response to perturbations connected with different crystal or molecular environments [18]. The basic idea is to try to arrange a group of related structures, frozen in particular environments, into a sequence that corresponds, in a general sense, to the course of structural changes expected to occur during the reaction. Although the enamines **4–8** were not selected with this purpose in mind, they happen to furnish data from which a reasonably clear description of the enamine nitrogen inversion process can be derived. Indeed, the sequence of observed conformations shown in *Figure 2* can be regarded as a set of snapshots taken at various stages during this process.

As can be seen from *Figure 2* (see also *Tables 1* and *2*), the changes in the relative atomic positions involve mainly changes in the two torsion angles ω_1 and ω_3, or, equivalently, in the two alternative out-of-plane parameters[7]) χ_N and τ. The reaction path is then essentially two-dimensional, with only minor changes in the other structural parameters. *Figure 3* shows the corresponding two-dimensional distribution of sample-points; the quantities plotted are actually $\theta = \tau$ and $\varphi = \chi_N/2$, for ease of comparison with the theoretical results of *Müller & Brown* [15], who used these parameters to describe the nitrogen inversion process in vinylamine. (For perfect eclipsing of an N–C bond with the C=C bond, $\theta = -\varphi$.)

Our distribution of sample-points *(Fig. 3)* follows a smooth curve with a modest amount of scatter, and we interpret this curve as delineating the main features of the nitrogen inversion path in a typical pyramidal enamine. Perturbations associated with the particular molecular and crystal environments are evidently sufficient to displace the position of the energy minimum by appreciable amounts along this path but by much smaller amounts normal to the path. The potential energy variation of the conceptually isolated enamine group must then be relatively flat along the correlation curve and much steeper in directions normal to it. From the structural data alone we cannot say more about the energy variation along the reaction path (the calculations by *Müller & Brown* [15] yield a value of about 1.5 kcal mol^{-1} for the inversion barrier in vinylamine).

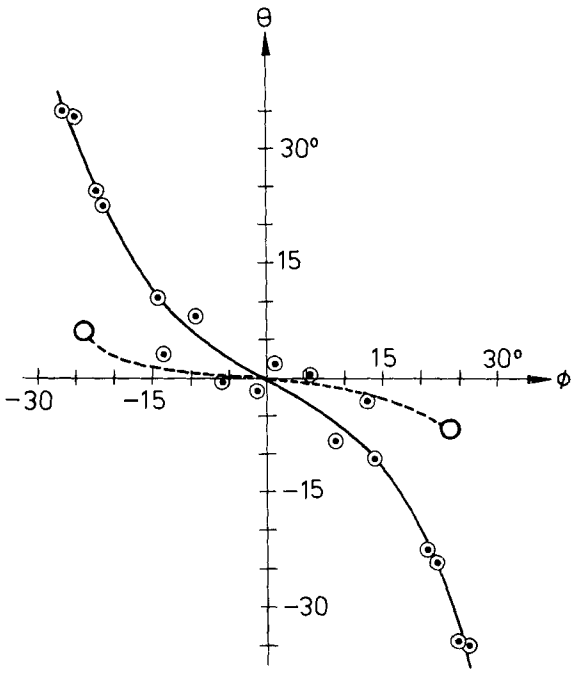


Fig. 3. *Distribution of $\theta = \tau$ versus $\phi = \chi_N/2$ for crystalline enamines.* The dashed curve shows the path for nitrogen inversion in vinylamine as calculated by *Müller & Brown* [15]

Crystal Structure Analyses. – Before the individual structure analyses are described in detail, we draw attention to some common features. The compounds **4**–**8** are sensitive to moisture; manipulations on the crystals (cutting, mounting *etc.*) were therefore carried out in a dry-box or in a glove bag continuously flushed with dry nitrogen. For diffractometry, single crystals cut from larger specimens (mostly poorly developed irregular plates or agglomerates) were enclosed in glass capillaries for **4** and **6**–**8** or sealed in epoxy resin for **5**. Measurements were carried out with an ENRAF-Nonius CAD4 diffractometer equipped with a graphite-monochromator (Mo*Ka* radiation, $\lambda = 0.71069$ Å). The crystals of **4** and **7** showed a rapid decline in diffracted intensity with increasing *Bragg*-angle (large thermal motion) at room temperature; to improve the quality of the data, these crystals were maintained at low temperature (100 K for **4**, 183 K for **7**) during data collection.

The structures were solved (**6** and **8** not without difficulty) with the help of direct methods (MULTAN program [19]) and refined by least-squares analysis (full matrix for **6** and **7**, blocked matrix for **5** and **8**, block diagonal for **4**) with anisotropic thermal parameters for C-, N- and O-atoms, isotropic for H-atoms, which were located from difference maps calculated at various stages.

All five crystal structures show indications of disorder (unexplained peaks in difference maps, unreasonably large, anisotropic vibrational ellipsoids for some atoms, unreasonable interatomic distances), which were at best only partially interpretable in terms of simple disorder models.

Crystallographic data are listed in *Table 3*, atomic positional and vibrational parameters in *Tables 4–8*. Mainly as a result of disorder, these parameters are not as accurate as one might wish. Bond lengths and angles are not tabulated, except for the enamine grouping *(Table 2)*; this information can be calculated from the positional coordinates if desired. In general, they are in reasonable agreement with commonly accepted values, although there are a few exceptions, mostly attributable to the disorder present in our crystals.

Crystallographic and General Structural Aspects of Enamine **4**. A difference synthesis calculated at an intermediate refinement stage ($R = 0.103$, H-atoms included in model structure, all atoms isotropic) showed two residual density peaks of 0.7–0.8 e.Å^{-3} in the region of the β-carbon atoms of the

pyrrolidine ring, as well as a large number of minor peaks close to other atoms. The location of the two major peaks suggested a disorder model in which the pyrrolidine ring occurs in two possible envelope conformations, each having one of the β-carbon atoms displaced by about 0.5 Å from the plane of the nitrogen and the α-carbon atoms. The refinement was then continued with two possible sites and variable partial occupancy factors for each of the β-carbon atoms, assuming a fixed $B(\text{iso}) = 2.0$ Å^2 for these atoms. In the final refinement cycle, the occupancy factors were held constant and B(iso) was allowed to vary. All other non-hydrogen atoms were refined with anisotropic vibration parameters.

A second difference synthesis calculated at the close of the refinement still showed numerous residual density peaks and troughs up to ± 0.3 e.Å^{-3}, but no systematic pattern could be recognized in them. They are probably due to a combination of genuine bonding deformation density [20], experimental error and inadequacies in the final structural model.

The molecular conformation is shown in *Figure 4*. Apart from the slight pyramidality at N (hardly discernable in *Fig. 4*) the main features, none of which merit more detailed discussion, are: (a) the atoms of the aromatic ring and of its fused acetal ring lie approximately in one plane (within 0.07 Å, the aromatic ring itself within 0.01 Å), which is nearly orthogonal to the mean plane of the two other rings; (b) the pyrrolidine ring has an envelope conformation; (c) the cyclohexene ring has a half-chair conformation.

In the packing diagram *(Fig. 5)* hydrogen atoms have been omitted for the sake of clarity. However, the approximate positions of these atoms, which are involved in the intermolecular contacts, can readily be estimated from simple stereochemical considerations based on the heavy-atom skeleton. All intermolecular H ... X(X≠H) distances less than 2.9 Å involve the O-atoms of the acetal ring or the enamine N-atom; the shortest (2.52 Å)[9]) is a contact between the axial O- and an *ortho*-phenylene-H-atom, and the other three (2.73–2.77 Å) are O(axial) ..... H(pyrrolidine), O(equatorial) .... H-(cyclohexene) and N ... H(*meta*-phenylene) contacts. It may be noted that in the N ... H contact, the H is on the same side of the enamine group as the developing N lone pair. On the evidence of this structure alone it might be tempting to ascribe the slight pyramidality at N to incipient hydrogen bonding[10]). However, comparison with the structures of the other crystalline enamines discussed here shows that there is no simple relationship between degree of pyramidality at N and N ... H contact distance, or indeed, any other packing factors that we can identify.

As can be seen from *Figure 5*, the long axis of the molecule is nearly perpendicular to the *b*-axis of the crystal, the direction of greatest thermal expansion *(Table 3)*. The expansion coefficient is much smaller in the *a*-direction and is practically zero or even slightly negative in the *c*-direction. Measurements of the lattice dimensions at intermediate temperatures show that, on warming from 100 K, the *c*-axis initially decreases, passes through a minimum (~7.970 Å) at about 240 K and then increases very slowly to the RT value.

Enamine **5**. No special difficulties were encountered in this analysis. The final difference synthesis shows small residual peaks (0.15 e.Å^{-3}) that might indicate the presence of a small proportion (less than 5%) of molecules containing an inverted chair conformation of the piperidine ring. However, least-squares analysis with alternative sites and variable occupancy parameters for the atoms concerned led to no improvement relative to an ordered model.

The two crystallographically independent molecules have virtually identical structures; corresponding bond lengths involving non-hydrogen atoms agree within 0.015 Å, bond angles within 1° and torsion angles within 4°. Both molecules show abnormally large vibration parameters for C(9) and C(10) of the piperidine ring (see *Table 5* and *Fig. 6*), which may again indicate disorder in this part of the molecule, or genuine large-amplitude vibration, or both.

In spite of the striking similarity between the overall shapes of molecules **4** and **5** (compare *Fig. 4* and *6*), the crystal structures appear to be quite unrelated. The change from the high-symmetry orthorhombic space group *Pccn* to the low-symmetry triclinic one brings about major changes in the relative positions and orientations of neighbouring molecules, *i.e.*, in the molecular arrangement (compare *Fig. 5* and *7*). In particular, any role ascribable to putative hydrogen bonding must be even

[9]) All X–H distances mentioned in this section and in the following ones have standard deviations of about 0.05 Å.

[10]) For comparison, the structure of **9** shows an intramolecular C–H ... N interaction with an H ... N distance of 2.47 Å, regarded as indicative of weak hydrogen bonding [11].

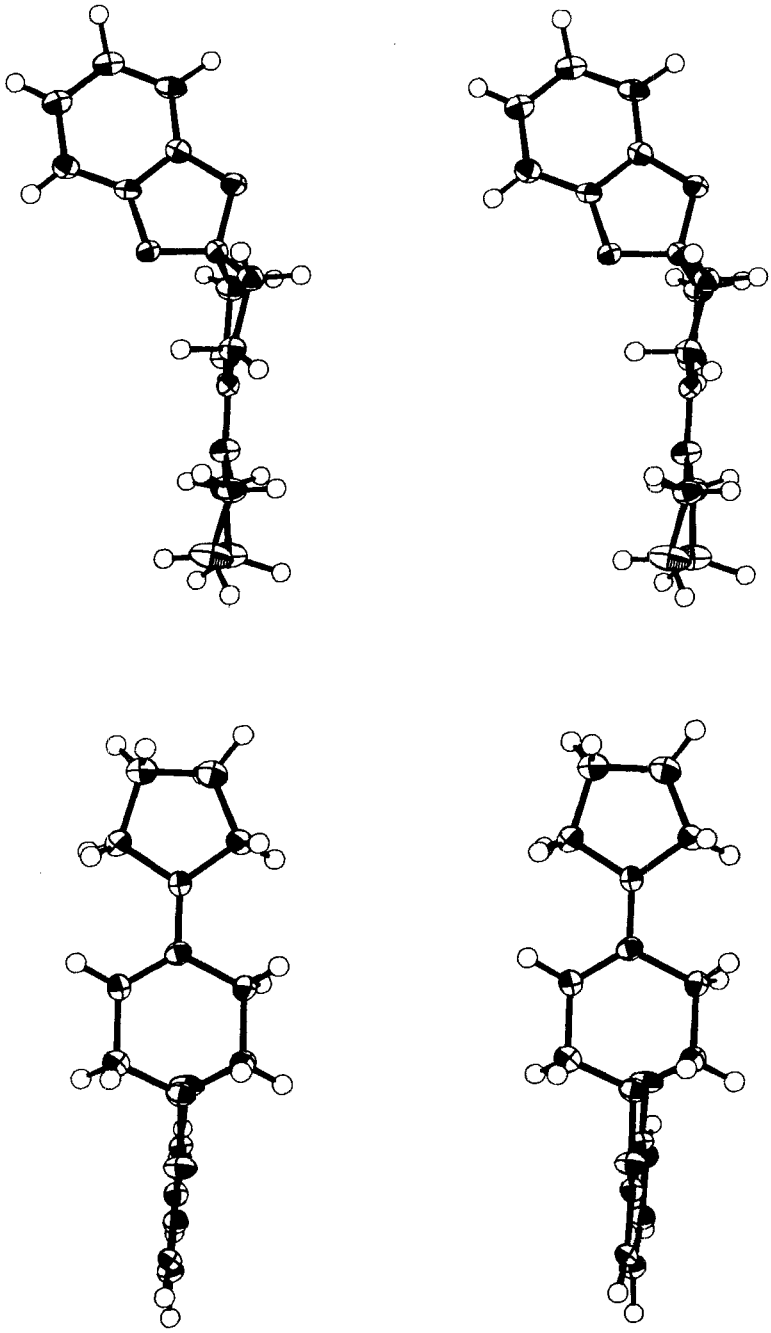


Fig. 4. *Molecular structure of enamine* **4** (two views)

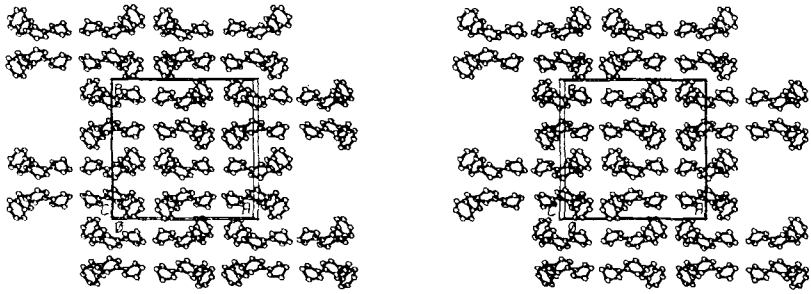


Fig. 5. *Crystal packing of enamine* **4** (hydrogen atoms omitted)

less important in this structure than in **4**. Of the two crystallographically independent molecules, one makes no N ... H or O ... H contacts of less than 2.9 Å, although there is an N ... H contact of 2.91 Å. The other molecule makes O ... H contacts of 2.69 Å and 2.88 Å, and an N ... H contact of 2.78 Å. In both short N ... H contacts, the H (*ortho*-phenylene) is on the same side of the enamine group as the developing lone pair, but it is even closer (~2.65 Å) to the central enamine C- than to the N-atom, in both cases. There are several other C ... H contacts that are marginally less than 2.9 Å.

Racemic Enamine **6**. Although the bimolecular unit cell is much the smallest of those encountered in this series, the structure analysis was one of the more difficult. For simplicity, the centrosymmetric space group $P\bar{1}$ was assumed. After several trials with MULTAN had failed to produce a reasonable *E*-map, it was concluded from packing considerations that the sign of the outstandingly strong (020) reflexion ($E=3.37$) must be negative, in contradiction to the previous MULTAN indications. Symbolic addition procedures (6 symbols) then led ultimately to a set of signs that gave an *E*-map in which 18 of the 20 non-hydrogen atoms in the molecule were clearly recognizable. Positions of the two remaining atoms were obtained from a subsequent difference synthesis.

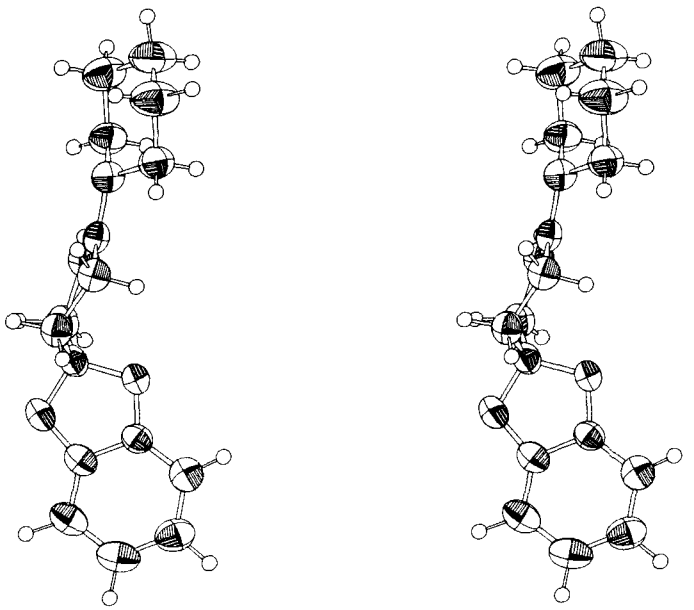


Fig. 6. *Molecular structure of enamine* **5**

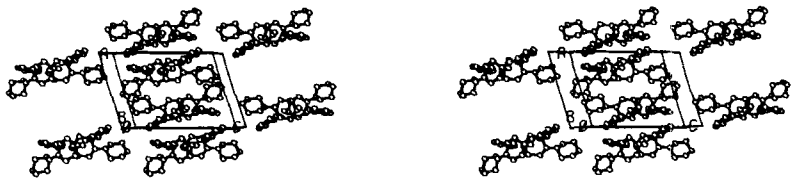


Fig. 7. *Crystal packing of enamine* **5** (hydrogen atoms omitted)

Refinement in space-group $P\bar{1}$ led to a molecule with an approximate plane of symmetry passing through the N- and the central C(1)-atom of the enamine group, and through the atoms of the benzoyl group. In particular, the two ring bonds emanating from C(1) appeared to be almost equal in length (bonds a and b in *Table 2*), whereas the actual bond lengths must, of course, differ by about 0.15 Å or more (single *vs.* double bond). It was apparent that the crystal structure was either disordered (in space group $P\bar{1}$) or else only pseudo-centrosymmetric (space group $P1$ with two crystallographically independent molecules). Refinement in space group $P1$ led to quite unreasonable structural parameters (*e.g.* bond lengths of 1.2–1.6 Å in the phenyl groups!); this in itself is no evidence against the correctness of the non-centrosymmetric space group, since it may be due to ill-conditioning of the least-squares normal equations [21]. Nevertheless, it seemed more useful to continue the refinement in the initially assumed space group $P\bar{1}$, with the proviso that the centrosymmetric structure so obtained could always be interpreted as a superposition of an actual pseudo-centrosymmetric structure and its enantiomorph, or alternatively in terms of disorder. It is virtually impossible to distinguish between these alternatives; for convenience, we have adopted the latter description.

Besides the anomalous bond lengths, additional evidence for disorder (or for the lower-symmetry space group) is found in the anomalously large, anisotropic vibrational parameters of the β-carbon atoms of the pyrrolidine ring and of the carbonyl oxygen atom, as well as in the occurrence of unexplained residual density peaks (up to 0.35 e.Å^{-3}) in the final difference synthesis. The pyrrolidine ring appears to be virtually planar *(Fig. 8)*, but the shape of the vibrational ellipsoids of the β-carbon atoms suggests disorder between two alternative twist conformations.

The enamine grouping in **6** appears to be planar *(Table 1)*, and the question arises whether this apparent planarity is also an artifact attributable to disorder in the crystal structure. If the enamine nitrogen were markedly pyramidal (as in **5**) with one N–C bond eclipsing the double bond, the other N–C bond would necessarily protrude out of the C=C–N plane. Disorder should then lead to markedly anisotropic vibrational ellipsoids for the pyrrolidine α-carbon atoms, similar to that observed for the β-carbon atoms, which is by no means what is actually observed *(Fig. 9* and *Table 6)*. We therefore tend to think that if the enamine group of **6** is indeed pyramidal, it is only slightly so.

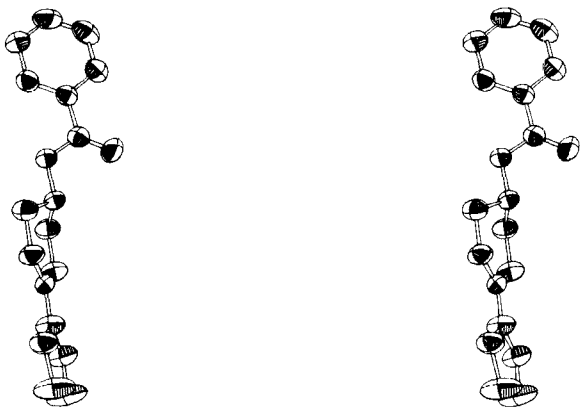


Fig. 8. *Molecular structure of enamine* **6** (hydrogen atoms omitted)

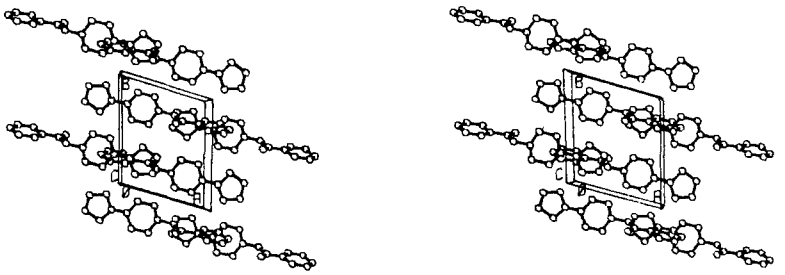


Fig. 9. *Crystal packing of enamine* **6** (hydrogen atoms omitted)

The molecules consist of two nearly planar units that are nearly perpendicular to one another *(Fig. 8)*. They pack in layers perpendicular to the *b*-axis of the crystal *(Fig. 9)* such that enamine groups of one molecule lie between phenyl groups of its neighbours. There are no X ... Y contacts less than 2.9 Å (the shortest is an N ... H (phenyl) contact of 2.98 Å).

Racemic Enamine **7**. A difference synthesis calculated at an intermediate refinement stage ($R = 0.135$, all non-hydrogen atoms included in model structure, isotropic temperature factors) showed peaks corresponding to most of the H-atoms and in addition, two prominent peaks (~ 1.2 e.Å^{-3}) in the vicinity of the cyclohexene ring, opposite the double bond. The cyclohexene ring has a half-chair conformation, and the additional peaks were interpreted as indicating the presence of a minor amount (*ca.* 20%) of the inverted ring conformation. Subsequent refinement with partial occupancy factors (80:20) for the disordered atoms led to reasonable geometry and vibrational parameters for both major and minor components. A final difference synthesis showed residual peaks of ~ 0.2 e.Å^{-3}, mostly midway between pairs of bonded atoms and attributable to bonding deformation density [20].

The molecular structure is shown in *Figure 10* (the enantiomer corresponding to the natural (*S*)-proline residue is chosen). The substituted α-carbon atom of the pyrrolidine ring is syn-periplanar to the C=C double bond [ω(C=C–N–C_α) $\sim 11°$]; the substituent is *trans* to the developing lone pair on the enamine nitrogen atom and has a pseudo-axial orientation with respect to the pyrrolidine ring. This ring has a conformation intermediate between twist and envelope and appears to be somewhat less puckered than the pyrrolidine ring in enamine **4** ($\varphi_m = 32°$ in **7**, 42° in **4**: φ_m is the maximum ring torsion angle attainable in a pseudo-rotational circuit [22]). The phenyl group is planar to within 0.01 Å, the *N*-methyl amide group within 0.1 Å. The carbonyl oxygen atom of the latter group is synclinal to the enamine nitrogen atom (torsion angle O–C–C–N, 42°: O ... N distance, 2.82 Å), the rotation from the expected synplanarity [23] being such as to bring the O-atom closer to the centre of the pyrrolidine ring, where it contacts a pseudo-axial H-atom of the α-methylene group at a distance of 2.74 Å. This motion happens to bring the *p*-orbital axis of the electrophilic carbonyl C-atom towards alignment with the *p*-orbital axis

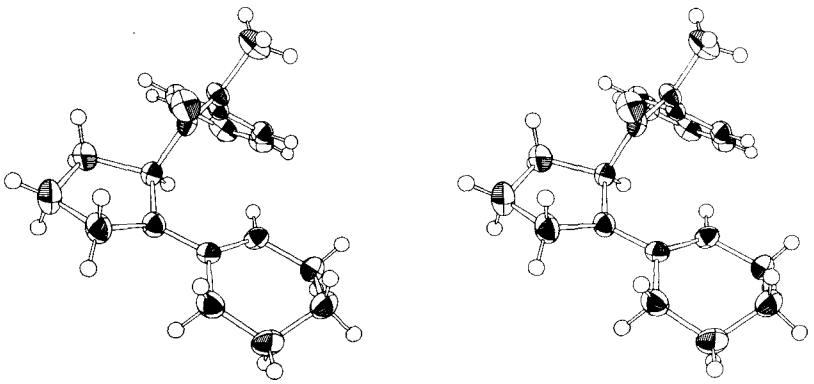


Fig. 10. *Molecular structure of enamine* **7** (the enantiomer with (*S*)-configuration is shown)

of the nucleophilic β-carbon atom of the enamine group. In this connection, it may be noted that the 11° departure of the enamine torsion angle ω_2 from zero (the largest in the whole series; see *Table 1*) also helps to co-align these orbital axes. Bond lengths and angles throughout the molecule are in satisfactory agreement with accepted values.

Apart from two intermolecular O ... H (phenyl) contacts of 2.46 and 2.65 Å the packing *(Fig. 11)* involves mainly *van der Waals* contacts between the protruding rings of neighbouring molecules. There are no intermolecular N ... H contact distances less than 2.9 Å; the shortest is 3.11 Å, and there are several inter-ring C ... H contacts shorter than this.

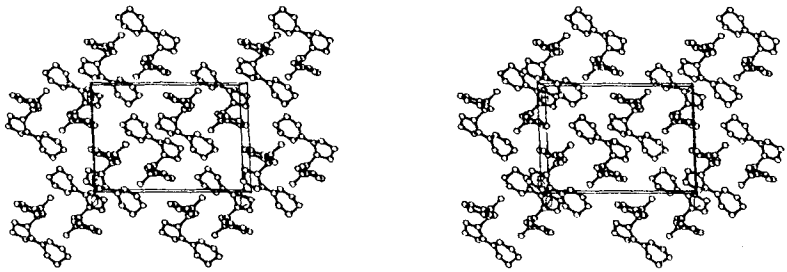


Fig. 11. *Crystal packing of enamine* **7** (hydrogen atoms omitted)

Racemic Enamine **8**. With 52 non-hydrogen atoms in the asymmetric unit, this is the most complex crystal structure in the present series, and the refinement (blocked matrix) converged only very slowly. Difference maps calculated at various stages gave indications of disorder in several parts of the structure; the β-carbon atoms of the pyrrolidine rings, the carbon atoms of the ethylene acetal rings, and the carbonyl oxygen atoms seem to be especially affected. Because of the large number of parameters required to describe the ordered structure, the introduction of additional atomic sites to take account of disorder was considered to be impracticable. The omission of disorder parameters takes its toll in the unreasonably large vibrational amplitudes obtained for several atoms *(Table 8)* and in the high noise level of the final difference synthesis, which contains peaks as high as 0.35 e.Å^{-3}. The H-atoms of the methylene groups in the acetal ring are not included in the final structural model because of indefiniteness of the corresponding density peaks, and the large vibrational amplitudes obtained for some of the other H-atoms show that these are barely definable from the available diffraction data.

The two molecules in the asymmetric unit show small differences in the conformation of the pyrrolidine and acetal rings. There is also a significant difference in the degree of pyramidality at the enamine nitrogen; in one molecule (**8a**) the displacement of the N-atom from the plane of its three bonded neighbours is 0.20 Å, in the other (**8b**) the corresponding displacement is 0.12 Å, with estimated

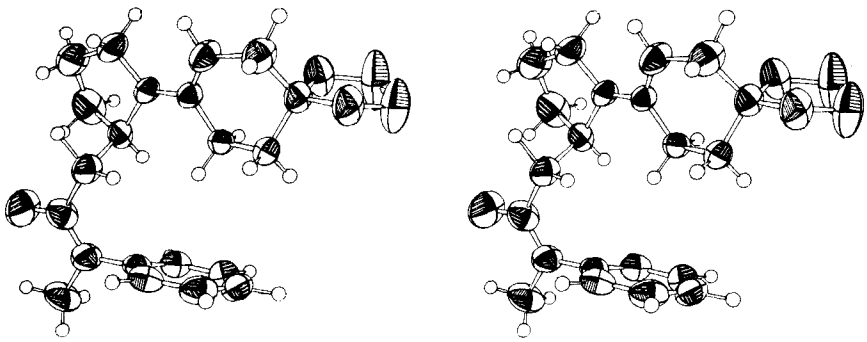


Fig. 12. *Molecular structure of enamine* **8** (the enantiomer with (*R*)-configuration is shown)

standard deviation of about 0.01 Å in both values. Nevertheless, the overall shapes of two symmetry-independent molecules are so similar that *Figure 12*, which actually refers to molecule **8a**, can be considered to apply to both (in the stereo-drawing, *Fig. 12*, the enantiomer corresponding to a (*R*)-homoproline residue is chosen). In contrast to the proline derivative **7**, the substituted α-carbon atom of the pyrrolidine ring is now anti-periplanar to the C=C double bond [ω(C=C–N–C_α) ~ 160°], but the substituent is still *trans* to the developing lone pair on the enamine nitrogen atom and pseudo-axial with respect to the pyrrolidine ring (as in **7**). The important difference in steric relationship between the substituent in the pyrrolidine ring and the double bond of the enamine group is shown schematically in *Figure 13* for the prolinoid and the homoprolinoid enamines **7** and **8** (both drawn in the *S*-configuration).

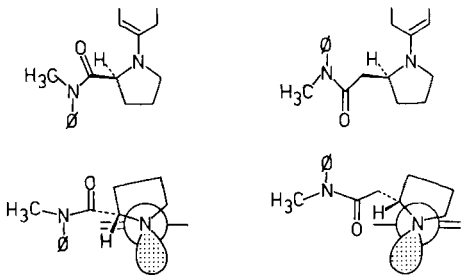


Fig. 13. *Steric relationships between the enamine double bond and the carboxamide substituent in* **7** *and* **8**. Note that the substituent is *syn* to the double bond in **7**, *anti* in **8**

In the homoproline derivative **8**, the carbonyl group swings away from the pyrrolidine ring, rather than towards it, as in **7**. The pyrrolidine rings of the two independent molecules of **8** are slightly more puckered ($\varphi_m = 37°$) than that of **7** and again have conformations intermediate between twist and envelope. The phenyl groups of both molecules are planar to within 0.01 Å, but the *N*-methyl amide groups are distinctly non-planar (deviations up to 0.13 Å). With a few exceptions (in the disordered portions of the molecules), bond lengths and angles agree well with accepted values.

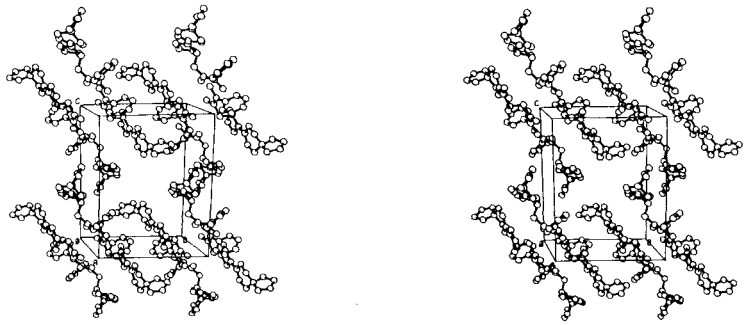


Fig. 14. *Crystal packing of enamine* **8** (hydrogen atoms omitted)

Figure 14 shows the packing arrangement, which is rather intricate. In contrast to **7**, the enamine nitrogen atoms of both symmetry-independent molecules are engaged in intermolecular N ... H contacts (2.61 Å and 2.66 Å, both with *m*-phenyl H-atoms). There are also O ... H contacts of 2.48 Å and 2.53 Å between acetal oxygen atoms and *o*-phenyl H-atoms, and of 2.68 Å and 2.55 Å between carbonyl oxygen atoms and *N*-methyl H-atoms. The carbonyl oxygen atom of molecule **8b** (though not of **8a**) makes a second, even shorter contact of 2.38 Å with an *o*-phenyl H (of a symmetry related **8b** molecule). The pattern of intermolecular contacts is thus quite different from that of **7**, in spite of the similarity in chemical structure.

Table 3. *Crystallographic data (standard deviations in brackets) and details of measurement: N(M)* is the number of independent reflexions measured, *N(S)* the number with measured intensity significantly above background at the 2σ or 3σ level, and *R* is the final agreement index

Crystal	**4**		**5**	**6**	**7**		**8**
	$C_{16}H_{19}NO_2$		$C_{17}H_{21}NO_2$	$C_{17}H_{21}NO_2$	$C_{18}H_{24}N_2O$		$C_{21}H_{28}N_2O_3$
Temperature	RT.	100K	RT.	RT.	RT.	183K	RT.
a(Å)	18.718	18.514 (10)	10.348 (6)	8.982 (2)	11.041	10.942 (7)	9.818 (8)
b(Å)	18.545	17.937 (30)	10.617 (7)	9.818 (2)	9.144	9.101 (5)	12.194 (3)
c(Å)	7.977	7.998 (13)	14.603 (10)	9.878 (2)	15.680	15.485 (6)	16.526 (4)
α(°)	90	90	101.14 (3)	74.70 (2)	90	90	88.54 (2)
β(°)	90	90	106.40 (3)	114.92 (2)	91.73	92.10	81.13 (4)
γ(°)	90	90	94.69 (5)	110.80 (2)	90	90	76.78 (4)
V(Å^3)	2769	2656	1494	732	1582	1541	1903
Z	8		4	2	4		4
Space Group	*Pccn*		$P\bar{1}$	$P\bar{1}$	$P2_1/n$		$P\bar{1}$
M.W.	257.33		271.36	271.36	284.40		356.47
D_x	1.23	1.29	1.21	1.23	1.19	1.23	1.24
θ_{max}(Mo$K\alpha$)	–	28°	25°	28°	–	27°	24°
$N(M)$	–	3203	5471	3465	–	3354	6320
$N(S)$	–	1681 (2σ)	2304 (3σ)	1502 (2σ)	–	1716 (2σ)	2764 (2σ)
R	–	0.057	0.038	0.074	–	0.045	0.063

Some Chemical Implications. – It has been inferred [24] from NMR. spectroscopic and chemical evidence that pyrrolidine enamines exhibit a higher degree of p-π overlap than enamines derived from piperidine, morpholine, or aliphatic dialkyl amines [2][11]). This view is corroborated by the X-ray results presented here, which show that the pyramidality of the enamine nitrogen atom is indeed less pronounced in pyrrolidine derivatives than in those where the enamine N-atom is part of a six-membered ring (see *Table 1* and *Fig. 2*); furthermore, *Table 2* indicates that the decrease in pyramidality at N is accompanied by a slight shortening of the enamine N–C distance (more N–C 'double bond character'). These structural differences seem to be reflected in well-known differences in chemical reactivity: pyrrolidine enamines are more prone to alkylation at the β-carbon atom than corresponding piperidine or open-chain enamines, which tend to be alkylated at the nitrogen atom [2]. These differences remind us of a general property of cyclopentanoid systems compared with their six-membered counterparts, namely, their greater propensity to accommodate an exocyclic double bond.

An important result of the enamine structure analyses is the finding that one of the N–C(sp^3) bonds tends to be syn-periplanar to the enamine C=C bond. This tendency is particularly striking in the strongly pyramidal six-membered ring enamines (see *Fig. 2*), and it may come as no surprise, considering that the observed conformation is the exact analogue of the preferred conformation in vinyl ethers, olefines, and carbonyl compounds. The enamines thus provide a further class of examples of an important conformational regularity [26] that was foreseen two decades ago by *Pauling* [27] as a corollary of his adherence to the anti-*Hückel* (bent-bond) model of the double bond[12]). As far as pyramidal enamines are concerned,

[11]) For recent spectroscopic studies of enamines see [25].

[12]) Early support for *Pauling*'s viewpoint can be found in [23] [28].

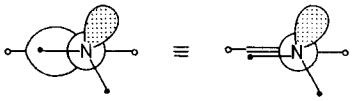


Fig. 15. Newman *projections of a pyramidal enamine group viewed along the N–C(sp²) bond*, showing the relationship between the virtual lone-pair orbital and 'bent-bonds'

the N–C bond that is anticlinal to the C=C bond axis is antiperiplanar to one of the virtual bent bonds, and the lone-pair direction is antiperiplanar to the other (see *Fig. 15*).

Certain facets of enamine formation and equilibria have been convincingly interpreted in terms of steric factors contingent on an assumed planar structure for the enamine group (see [2a], p. 2–11). Such interpretations are not necessarily invalidated by the new structural findings. For example, enamines of α-substituted cyclohexanones are formed more slowly than their unsubstituted counterparts and show a tendency for the double bond to avoid the position where it would be tetrasubstituted [29]. The steric congestion ascribed to the tetrasubstituted isomer in a supposedly planar enamine is not relieved by passing to a non-planar structure as long as the syn-periplanarity of one N–C bond and the double bond is preserved. As we have seen, this syn-periplanarity is in fact a characteristic feature of pyramidal enamines. Another example is provided by the observation that the *cis*-stilbenoid isomer of the enamines derived from morpholine and desoxybenzoin is thermodynamically more stable than the *trans*-stilbenoid isomer [30].

At this stage we return to the questions that were raised in the introduction. Now that the pyramidal nature of enamine N has to be taken into account, a specific question concerning enamine reactivity automatically arises: in attacking the enamine β-carbon atom does an electrophile prefer the syn or anti side of the double bond, relative to the lone pair? To the extent that the electrophilic attack occurs without assistance of an external nucleophile, *i.e.* is exclusively lone-pair assisted, the reaction is isoelectronic with an S_E2' process[13]). Necessary as an answer to this problem of stereoelectronic control is, it is obviously far from sufficient for interpreting the stereochemical course of enamine reactions. The actual stereochemical outcome will depend also on configurational (N-inversion) and conformational degrees of freedom (rotation by π-χ_N around the N–C(sp²) bond; see *Fig. 1*). Each of these processes can invert the outcome of a given type of stereoelectronic control, and since both processes can be presumed to be faster in general than reaction at the β-carbon atom the connection between stereochemical ground-state equilibria and the stereochemical course of enamine reactivity is likely to be far from simple.

Particular care is clearly called for in the interpretation of chiral induction paths brought about by optically active amines as chiral catalysts. In this connection, the behaviour of (*S*)-proline and (*S*)-homoproline derivatives as aldolization catalyst provides a cautionary tale.

Hajos & Parrish [3] have reported chemical and optical yields of over 90% for the transformation **1** → **2**, in which catalytic amounts of (*S*)-proline induce the 'natural' (*S*)-sense of chirality of product **2**. In conspicuous contrast, (*S*)-homo-

[13]) Experiments designed to answer this question are under way. For experimental information on the steric course of S_E-processes see [31].

proline induces opposite chirality of the same product in the same reaction (optical yield 58%, chemical yield 99%) [7]. This finding *per se* seems to indicate the inadequacy of any simple model in which the crucial chiral induction is ascribed to straightforward intramolecular participation of the carboxylate group in an intermediate enamine hydroxyalkylation step. It was in fact this unexpected difference in behaviour of the two homochiral catalysts that prompted us to seek information on the structure of crystalline enamine derivatives of the two amino acids.

A search for such compounds led ultimately to the two *N*-methylanilides **7** and **8** as crystalline racemates [10], whose structures are described in previous sections of this paper. In the crystalline state, these molecules have the same configurational relationship between the two chirality centres, namely the asymmetric carbon atom and the pyramidal nitrogen atom; however, they have 'opposite' conformational relationship, *i.e.* in the proline derivative **7** the sidechain in the pyrrolidine moiety is syn to the enamine double bond, whereas in the homoproline derivative **8** it is anti (compare *Fig. 13*). A corresponding difference in the structures of the reacting species is just what would be needed to account for the opposite sense of chiral induction by the two homologous, homochiral amino acid catalysts. As a check the corresponding optically active anilides (as ammonium salts of benzoic acid) were then prepared [10] and examined[14]) as catalysts of transformation **1** → **2** to see whether their sense of induction actually parallels that of the aminoacids. Their senses of induction were found to be indeed mutually opposite (optical yields 15–25%!). However, we have to mention the sobering fact that the sense of chirality induced by each anilide is also opposite to the sense induced by the corresponding amino-acid[15]).

It seems to us that the structural information on enamines provided in this paper is relevant to some of the problems concerning the mechanism of (non-catalytic) stereoselection as posed by several recent investigations in the field of enamine chemistry and asymmetric synthesis [32].

This work was supported by the *Swiss National Science Foundation*, the *Swiss Federal Institute of Technology* (Kredit Unterricht und Forschung) and the *Ciba-Geigy AG*, Basel. The low-temperature measurements would not have been possible without the help of Mr. *Paul Seiler*. We thank Dr. *J.M. Cassal* and Dr. *A. Fürst, Hoffmann-La Roche AG*, Basel, for samples of optical active (*S*)-Homoprolin.

Experimental Part[16])

Preparation of crystalline enamines. – *Enamine* **4**. A solution of 204 mg (1 mmol) 1,4-cyclohexanedione-catechol-monoacetal [33] (m.p. 183–184°[17])) and 830 µl (*ca.* 10 mmol) pyrrolidine[18]) in 10 ml benzene (degassed by purging with Ar) was heated under reflux for 6 h, using a *Dean-Stark* trap charged

[14]) We are indebted to *Dr. P. Buchschacher* and *Christiane Saroka* at *Hoffmann-La Roche AG*, Basel, for carrying out these examinations (*cf.* [7]).

[15]) (*S*)-Proline → **2**; (*S*)-proline-*N*-methylanilide → (enantio)-**2**; (*S*)-homoproline → (enantio)-**2**; (*S*)-homoproline-*N*-methylanilide → **2**.

[16]) The general remarks made in footnote 13) of [37] are valid; exceptions are mentioned. MS.: direct inlet. Molecular sieve: *Bender & Hobein* (Zürich) type 4 A, 1/16. Dry-box: N_2-Atmosphere, continuous circulation through molecular sieve 4 Å.

[17]) Spectral data (IR., ^{1}H-NMR., MS.) of the material used are given in [9].

[18]) *Fluka, puriss. p.a.* dried over molecular sieve 4 Å.

with molecular sieves 4 Å. The slightly yellow oil (263 mg) obtained upon removal of solvent (aspirator, phosphorous pentoxide-tower) and drying (0.01 Torr) crystallized spontaneously. It was dissolved in the dry-box in 10 ml boiling hexane (freshly passed through basic alumina, activity I). Since no crystallization occurred on cooling to RT., the solution was concentrated in the dry-box under a stream of dry N_2, warmed up again to the boiling point and cooled slowly to RT. Enamine **4** now crystallized as fine, white needles, which turned into large, transparent blocks overnight; they were used for X-ray analysis; m.p. 103–104° (sealed capillary). – IR. ($CHCl_3$[19])): 3055*w*, 2965*m*, 2930*m*, 2875*m*, 2840*m*, 1635*m*, 1600*m*, 1485*s*, 1460*w*, 1450*w*, 1430*w*, 1400*m*, 1373*w*, 1360*m*, 1348*m*, 1310*m*, 1268*m*, 1182*m*, 1140*w*, 1105*m*, 1070*w*, 1025*m*, 1009*m*, 998*w*, 962*m*, 913*w*, 875*w*, 861*m*. A weakband at 1718 cm^{-1} indicated slight hydrolysis; the spectrum is recorded in [9], p. 82. – ^{1}H-NMR. ($CDCl_3$[19])): 1.60–2.00 (*m*/centered at 1.88 ppm/4 H); 2.13 (*t*/*J* = *ca.* 6 Hz/2 H); 2.40–2.80 (*m*/4 H); 2.95–3.25 (*m*/centered at 3.10 ppm/4 H); 4.12 (*t*/*J* = *ca.* 4 Hz/1 H); 6.74 (*s*/4 H); the spectrum is recorded in [9], p. 83. – MS. (85°): 258 (8), 257 (41, M^+), 149 (7), 124 (10), 123 (100), 108 (16), 95 (35), 94 (12), 70 (5).

$C_{16}H_{19}NO_2$ (257.33) Calc. C 74.68 H 7.44 N 5.44% Found C 74.63 H 7.50 N 5.39%

Enamine **5**. A solution of 102 mg (0.5 mmol) 1,4-cyclohexanedione-catechol-monoacetal [33] (m.p. 183–184°[17]), 475 µl (*ca.* 5 mmol) piperidine and a catalytic amount of *p*-toluenesulfonic acid (monohydrate, *Fluka, puriss.*) in 5 ml benzene (degassed by purging with Ar) was heated under reflux for 14 h, using a *Dean-Stark* trap charged with molecular sieves 4 Å. The colourless oil (130 mg) obtained upon removal of solvent (aspirator, P_2O_5-tower) and drying (0.01 Torr) crystallized slowly. It was dissolved in the dry-box in 10 ml boiling hexane (freshly passed through basic alumina activity I) and the solution concentrated to *ca.* 2 ml. On scratching with a glass rod white needles formed which turned into a single, transparent crystal during storage in the mother liquor (*ca.* 6 months, dry-box, darkness). This crystal (m.p. 72–74°, sealed capillary) was used for X-ray analysis and characterization. When exposed to the laboratory atmosphere, **5** in crystalline form was stable for at least 3 h (IR.), whereas in solution it decomposed rapidly. – IR. ($CHCl_3$[19])): 3060*w*, 2940*m*, 2955*w*, 2810*w*, 2745*w*, 1642*w*, 1488*s*, 1469*w*, 1455*w*, 1445*w*, 1438*w*, 1430*w*, 1392*w*, 1372*w*, 1361*w*, 1345*w*, 1315*w*, 1270*m*, 1155*w*, 1130*w*, 1118*w*, 1102*m*, 1072*w*, 1062*w*, 1027*m*, 1005*w*, 990*w*, 957*w*, 910*w*, 890*w*, 870*w*, 860*w*, 840*w*; spectrum recorded in [9], p. 88. – ^{1}H-NMR. ($CDCl_3$[19])): 1.3–1.8 (*m*/6 H); 2.12 (*t*, *m*/*J* = *ca.* 6 Hz/2 H); 2.26–2.56 (*m*/2 H); 2.56–2.76 (*m*/2 H); 2.76–2.96 (*m*/4 H); 4.55 (*t*/*J* = *ca.* 4 Hz/1H); 6.74 (*s*/4 H); spectrum recorded in [9], p. 88. Decoupling: Irradiation at 4.55 ppm turned the signal at 2.56–2.76 ppm into a singlet and irradiation at 2.68 ppm turned the signal at 4.55 ppm into a singlet. – MS. (200°): 272 (11), 271 (53, M^+), 163 (9), 147 (6), 138 (10), 137 (100), 136 (67), 135 (4).

$C_{17}H_{21}NO_2$ (271.36) Calc. C 75.24 H 7.80 N 5.16% Found C 75.07 H 7.77 N 4.99%

Enamine **6**. 218 mg (1 mmol) 4-benzoyloxy-cyclohexanone [34] (m.p. 62–63°[17]) was dissolved in the dry-box in 1 ml acetonitrile (*Fluka, puriss.*, distilled over P_2O_5) and treated with 100 µl (*ca.* 1.2 mmol) pyrrolidine[18]). After 3 min white needles separated spontaneously. The crystals were isolated, washed three times with little acetonitrile and dried at RT./0.01 Torr for 2 h: 217 mg (80%) enamine **6** as white needles, m.p. 133–135° (sealed capillary). When exposed to the laboratory atmosphere, **6** in crystalline form was stable for at least 3 h (IR.), whereas in solution it decomposed rapidly. – IR. ($CHCl_3$[19])): 2970*m*, 2880*w*, 2845*m*, 1710*s*, 1640*m*, 1605*w*, 1586*w*, 1490*w*, 1465*w*, 1453*m*, 1438*w*, 1398*m*, 1377*m*, 1357*m*, 1337*w*, 1318*m*, 1280*s*, 1177*m*, 1123*s*, 1103*w*, 1077*m*, 1050*w*, 1032*m*, 1012*w*, 1006*w*, 950*w*, 862*w*; spectrum recorded in [9], p. 79. – ^{1}H-NMR. ($CDCl_3$[19])): 1.7–2.2 and 2.2–2.8 (2 *m*/10 H); 2.8–3.2 (*m*/4 H); 4.04–4.26 (*m*/1H); 5.07–5.40 (*m*/1H); 7.2–7.6 (*m*/3 H); 7.8–8.15 (*m*/2 H); spectrum recorded in [9], p. 80. – MS. (85°): 272 (1), 271 (5, M^+), 150 (18), 149 (100), 148 (17).

$C_{17}H_{21}NO_2$ (271.36) Calc. C 75.24 H 7.80 N 5.16% Found C 75.16 H 7.81 N 5.09%

Enamine **7**. A degassed benzene solution of 587 mg (2.87 mmol) rac.-proline-*N*-methylanilide (preparation see below) and 380 mg (3.86 mmol) cyclohexanone was heated under reflux for 3 h, using a *Dean-Stark* trap charged with molecular sieves 4 Å to remove water. After evaporation of solvent (oil pump) the residue (solid, after seeding in the dry-box) was dried (RT., 10^{-3} Torr) and recrystallized by isothermal distillation from benzene/hexane in the dry-box: The flask containing crude **7** in 1 ml benzene[20]) was placed into a second, stoppered flask containing hexane[20]). After one day in the dark at

[19]) IR.-cell and NMR.-tube were charged in the dry-box and solvents for spectroscopy were freshly passed through basic alumina (activity I).

[20]) Freshly passed through basic alumina (activity I) in the dry-box.

RT. crystals had appeared, which were isolated one day later: colourless, thin, brittle plates, m.p. 113–115° (sealed capillary), electrostatically charged and extremely air-sensitive, turning into an oil within 2 min on exposure to the laboratory atmosphere. A sample of **7** for characterization (but not material for X-ray analysis) was dried (RT., 10^{-3} Torr); all manipulations (charging capillary, IR.-cell and NMR.-tubes) were performed in the dry-box and spectra run immediately. – IR. ($CHCl_3$[19])): 3040*w*, 3000*s*, 2970*s*, 2930*s*, 2870*m*, 2860*m*, 2835*m*, 1950*w*, 1880*w*, 1800*w*, 1652*s*, 1595*s*, 1494*s*, 1445*m*, 1430*m*, 1418*m*, 1388*s*, 1345*m*, 1334*m*, 1320*m*, 1296*m*, 1156*m*, 1138*w*, 1117*m*, 1071*m*, 1037*m*, 1021*w*, 1000*w*, 990*w*, 966*w*, 928*w*, 694*m*, 656*m*. On exposure of the IR.-solution to air (*ca.* 1 min) a new band at 1700 cm^{-1} appeared (cyclohexanone). – ^{1}H-NMR. ($CDCl_3$[19])): 1.3–2.2 (12 H); 3.26 (*s*/3 H); 2.9–3.58 (*m*/2 H); 3.8–4.0 (*m*/1H); 4.19

Table 4. *Compound 4; Positional and vibrational parameters ($\times 10^4$) with e.s.d.'s in parentheses.* The temperature factors have the form: (a) for isotropic vibrations, $T = \exp[-(8\pi^2 U_{iso} \sin^2/\lambda^2)]$ (b) for anisotropic vibrations, $T = \exp[-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2hka^*b^*U_{12} + \ldots)]$

	x/a	y/b	z/c	U_{11} or U	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N	915(1)	6363(1)	5409(3)	244(10)	401(12)	244(11)	-65(9)	-8(10)	91(10)
O(1)*	-1394(1)	6781(1)	921(2)	320(9)	287(8)	379(10)	57(8)	-113(9)	-4(9)
O(2)*	-589(1)	5791(1)	1190(2)	386(9)	299(8)	331(10)	78(8)	-163(10)	-70(8)
C(1)	357(1)	6484(1)	4296(3)	236(11)	248(11)	266(13)	-5(10)	-23(11)	-38(11)
C(2)	456(1)	6885(1)	2862(3)	295(12)	326(12)	281(14)	-57(11)	-16(12)	87(12)
C(3)	-153(1)	7046(1)	1682(3)	334(13)	341(13)	322(15)	-13(11)	-36(14)	72(12)
C(4)	-772(1)	6519(1)	1884(3)	287(11)	269(11)	286(13)	43(10)	-49(12)	-15(12)
C(5)	-979(1)	6418(1)	3693(3)	251(11)	296(12)	351(15)	-24(11)	-4(12)	2(12)
C(6)	-344(1)	6136(1)	4710(3)	266(11)	280(11)	296(14)	-38(10)	-5(12)	27(12)
C(7)	859(1)	5987(1)	7009(3)	331(12)	337(13)	265(14)	-46(11)	-42(13)	77(12)
C(81)56%	1655(3)	5808(3)	7388(7)	258(12)					
C(82)44%	1619(4)	6020(3)	7726(8)	412(15)					
C(91)80%	2035(2)	6537(2)	6771(4)	286(7)					
C(92)20%	2100(6)	6207(7)	6386(16)	350(23)					
C(10)	1614(1)	6725(1)	5202(3)	251(11)	464(15)	325(15)	-58(12)	-5(13)	43(13)
C(11)	-1480(1)	6289(1)	-382(3)	218(10)	281(11)	287(14)	-11(10)	17(11)	42(11)
C(12)	-1008(1)	5704(1)	-213(3)	211(10)	315(12)	270(13)	-12(10)	-55(11)	58(11)
C(13)	-997(1)	5115(1)	-1323(3)	263(12)	346(13)	250(13)	-1(11)	2(12)	14(11)
C(14)	-1498(1)	5140(1)	-2623(3)	304(12)	416(15)	261(14)	-53(12)	-18(13)	0(12)
C(15)	-1974(1)	5735(1)	-2804(3)	251(11)	474(15)	315(15)	-52(12)	-40(13)	47(13)
C(16)	-1969(1)	6333(1)	-1680(3)	228(10)	352(13)	335(15)	-16(11)	-57(12)	124(12)
H (C2)	916(31)	7146(29)	2681(74)	366(167)					
H1(C3)	-359(30)	7537(37)	1958(76)	454(173)					
H2(C3)	9(33)	7027(32)	547(78)	521(190)					
H1(C5)	-1144(29)	6939(29)	4164(71)	316(155)					
H2(C5)	-1378(34)	6078(35)	3770(82)	597(201)					
H1(C6)	-445(33)	6143(34)	5839(80)	537(192)					
H2(C6)	-295(36)	5510(36)	4430(87)	724(224)					
H1(C7)	600(34)	6301(34)	7725(81)	570(198)					
H2(C7)	586(31)	5474(31)	6911(74)	473(175)					
H1(C8)	1706(35)	5815(37)	8777(89)	725(217)					
H2(C8)	1867(34)	5459(35)	6859(82)	569(205)					
H1(C9)	1996(36)	6996(36)	7724(88)	759(221)					
H2(C9)	2534(36)	6320(31)	6414(78)	590(177)					
H1(C10)	1548(32)	7270(33)	5038(82)	561(195)					
H2(C10)	1878(33)	6529(33)	4142(79)	533(188)					
H (C13)	-676(31)	4720(33)	-1190(77)	495(180)					
H (C14)	-1526(26)	4751(27)	-3463(62)	188(132)					
H (C15)	-2364(32)	5696(31)	-3766(78)	410(179)					
H (C16)	-2311(28)	6811(28)	-1760(68)	339(153)					

* O(1) .... equatorial substituent
O(2) .... axial substituent

(*t*/*J* = 3 Hz/1H); 7.2–7.6 (*m*/5 H). – ^{13}C-NMR. ($CDCl_3$[19])): 22.7 (*t*/CH_2); 23.2 (*t*/2 CH_2); 24.4/27.1/31.1 (3 *t*/3 CH_2); 37.5 (*qa*/CH_3); 48.2 (*t*/CH_2); 57.9/93.3 (2 *d*/2 CH); 127.1 (2 *d*/2 CH); 127.7 (*d*/CH); 129.6 (2 *d*/2 CH); 141.0 (*s*); 143.3 (*s*); 174.2 (*s*) plus signals indicating the presence of *ca.* 5% proline-*N*-methylanilide. – MS. (< 95°): 285 (1) (= 23% of M^+), 284 (4, M^+), 150 (42), 107 (18), 106 (14), 77 (16), 71 (10), 70 (100).

$C_{18}H_{24}N_2O$ (284.40) Calc. C 76.02 H 8.51 N 9.85% Found C 72.01 H 8.01 N 10.02%

Enamine **8**. A degassed benzene solution of 280 mg (1.28 mmol) rac.-homoproline-*N*-methylanilide **14** (see below) and 200 mg (1.28 mmol) 1,4-cyclohexanedione monoethyleneacetal [35] was heated under reflux for 90 min, using a *Dean-Stark* trap charged with molecular sieves 4 Å to remove water. After evaporation of solvent (oil pump) the colourless oily residue was crystallized in the dry-box by isothermal distillation of hexane[20]) into a solution of **8** in 1.5 ml diisopropyl ether[20]). Spontaneous crystallization occurred to form small, colourless cubes (m.p. 75–76°, sealed capillary), which were sensitive to air (but less so than **7**). Capillary, IR.-cell and NMR.-tubes were charged in the dry-box and spectra run immediately. – IR. ($CHCl_3$[19])): 3040*w*, 3005*s*, 2955*s*, 2880*m*, 2840*m*, 1945*w*, 1880*w*, 1800*w*, 1635*s*, 1594*s*, 1494*s*, 1448*m*, 1426*m*, 1384*s*, 1344*m*, 1296*m*, 1282*m*, 1167*w*, 1115*s*, 1056*m*, 1034*w*, 1019*m*, 948*w*, 914*w*, 850*w*. On exposure of the IR.-solution to air (*ca.* 1 min) a new band at 1712 cm^{-1} appeared. – ^{1}H-NMR. ($CDCl_3$[19])): 1.5–1.95 (*m*/6 H); 1.95–2.6 (*m*/6 H); 2.75–3.05 (*m*/2 H); 3.21 (*s*/3 H); 3.90 (*s*/4 H); 3.7–4.1 (*m*/2 H); 7.05–7.52 (*m*/5 H). – ^{13}C-NMR. ($CDCl_3$[19])): 22.6/26.0/30.5/31.2/34.7 (5 *t*/5 CH_2); 37.2 (*qa*/CH_3); 37.7/47.5 (2 *t*/2 CH_2); 55.3 (*d*/CH); 64.3 (*t*/2 CH_2); 89.8 (*d*/CH); 108.0 (*s*); 127.5 (*d*/2 CH); 127.6 (*d*/CH); 129.7 (*d*/2 CH); 140.4 (*s*); 144.0 (*s*); 171.4 (*s*). – MS. (< 110°): 357 (5), 356 (20, M^+), 210 (20), 208 (28), 164 (41), 149 (12), 136 (28), 134 (11), 124 (52), 122 (43), 107 (25), 106 (18), 77 (17), 71 (7), 70 (100).

$C_{21}H_{28}N_2O_3$ (356.47) Calc. C 70.76 H 7.92 N 7.86% Found C 70.61 H 7.98 N 7.86%

*rac.-Proline-*N*-methylanilide*[21]). To a suspension of 6.45 g (30.95 mmol) PCl_5 in 30 ml dry CH_2Cl_2 was added at 0° 3.24 g (28.14 mmol) DL-proline *(Fluka, puriss.)*. The resulting clear (supersaturated) solution was treated with 22.6 g (211 mmol) *N*-methylaniline *(Fluka, puriss.)*, quenched after 5 min with 50 ml phosphate buffer (pH 7, 1M) and extracted with CH_2Cl_2 to remove excess *N*-methylaniline. The aqueous phase, after basification with ammonium hydroxide (white emulsion) and after extraction into CH_2Cl_2 gave 9.6 g of an oil which was chromatographed on 200 g basic alumina (activity II, ether, ether/methanol 10:1, then 1:1, fractions monitored by pH indicator and TLC.) to yield 3.0 g of crude product. Crystallization from ether/pentane by isothermal distillation (the flask containing the product in 4 ml ether was placed into a second, stoppered flask containing pentane) in the refrigerator (*ca.* 0°) gave 1.615 g colourless crystals. A sample was recrystallized twice in the same way, m.p. 70–71°. – UV. (EtOH): shoulders at 261 (2.63) and 223 (3.73). – IR. ($CHCl_3$): 3300*w*, 3005*s*, 2970*s*, 2940*s*, 2875*m*, 1650*s*, 1596*s*, 1496*s*, 1451*m*, 1415*m*, 1384*s*, 1330*w*, 1124*m*, 1095*m*, 1071*w*, 1042*w*, 1021*w*, 1000*w*, 937*w*, 913*w*, 855*w*, 698*s*, 660*m*. – ^{1}H-NMR. ($CDCl_3$): 1.4–1.8 (*m*/4 H); 2.38 (br. *s*/NH/exchangeable with D_2O); 2.5–2.82 (*m*/1 H); 3.0–3.3 (*m*/1 H); 3.28 (*s*/3 H); 3.4–3.66 (*m*/1 H); 7.2–7.62 (*m*/5 H). – ^{13}C-NMR. ($CDCl_3$): 26.7/31.5 (2 *t*/2 CH_2); 37.6 (*qa*/CH_3); 47.8 (*t*/CH_2); 58.5 (*d*/CH); 127.5 (*d*/2 CH); 127.8 (*d*/CH); 129.5 (*d*/2 CH); 143.0 (*s*); 174.2 (*s*). – MS. (< 100°): 204 (0.5, M^+), 187 (0.1), 176 (0.1), 162 (0.6), 147 (0.2), 134 (1), 107 (7), 106 (5), 77 (6), 71 (4), 70 (100).

$C_{12}H_{16}N_2O$ (204.27) Calc. C 70.56 H 7.90 N 13.72% Found C 70.64 H 7.80 N 13.80%

*rac.-Homoproline-*N*-methylanilide* **14**[21]). 4.79 g (33.9 mmol) (Z)-2-aza-cyclopentylidene-acetic acid methylester (**11**)[22]) in 135 ml 0.4N methanolic HCl was catalytically hydrogenated (400 mg 10% Pt/C) at ambient pressure for 4 h. After removal of the catalyst *(Celite)* and of solvent crude **12** was obtained as an oil (6.6 g), which turned into a deliquescent, hygroscopic solid. This material was dissolved in 100 ml of CH_2Cl_2 and treated at 0° under N_2 with 7.55 g (74.6 mmol) triethylamine and 6.36 g (37.3 mmol) benzyl chloroformate *(Fluka, pract.)* while stirring for 80 min. Aqueous work-up (80 ml phosphate buffer, pH 7, 1M, extraction into CH_2Cl_2 and removal of solvent) gave crude **13a** (9.5 g; IR. in $CHCl_3$: 1735,

---

[21]) The preparation of the optically active material starting from (*S*)-proline (from (*S*)-homoproline in the case of **14**) will be described in [10].

[22]) The starting material **11** was available in our laboratory. It is best made by condensation of the *O*-methyl (or ethyl)-iminoether of *a*-pyrrolidone with *t*-butyl-*a*-cyanoacetate followed by decarboxylative methanolysis in 7.5N methanolic HCl [36].

Table 5. *Compound 5; Positional and vibrational parameters* (as in Table 4)

Atom	x/a	y/b	z/c	U_{11} or U	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O101	2646 (2)	5434 (2)	5700 (1)	785(13)	443(10)	568(11)	12(8)	265(9)	159(8)
O102	2112 (2)	3541 (2)	6166 (1)	888(14)	511(11)	678(12)	67(9)	354(11)	253(9)
N100	2705 (2)	4005 (2)	2511 (2)	492(12)	573(13)	508(13)	153(10)	138(10)	147(10)
C101	2661 (2)	3987 (2)	3466 (2)	412(14)	381(13)	530(15)	16(10)	106(12)	68(11)
C102	1330 (2)	4236 (3)	3653 (2)	401(14)	589(16)	602(16)	77(11)	118(12)	127(13)
C103	1111 (3)	3676 (2)	4485 (2)	437(14)	539(15)	671(18)	57(12)	203(13)	128(13)
C104	2351 (3)	4030 (2)	5360 (2)	610(17)	467(16)	581(16)	95(12)	223(13)	213(12)
C105	3573 (3)	3508 (3)	5131 (2)	535(15)	564(16)	584(17)	100(12)	112(13)	214(13)
C106	3670 (2)	3693 (2)	4158 (2)	378(14)	530(15)	608(17)	51(11)	150(12)	125(13)
C107	3934 (3)	3699 (3)	2283 (2)	590(17)	754(19)	597(17)	210(14)	236(14)	180(14)
C108	3718 (4)	3374 (4)	1191 (2)	929(25)	945(27)	690(22)	376(21)	322(19)	160(19)
C109	3160 (4)	4440 (4)	726 (3)	1266(31)	1131(29)	644(21)	478(24)	436(21)	294(20)
C110	1914 (4)	4789 (4)	999 (3)	1200(30)	1205(31)	683(22)	654(25)	349(21)	403(21)
C111	2180 (4)	5063 (3)	2095 (2)	857(22)	628(21)	577(18)	289(18)	253(16)	205(16)
C112	2438 (2)	5724 (2)	6597 (2)	447(13)	560(15)	440(13)	81(11)	107(11)	191(11)
C113	2134 (3)	4603 (3)	6875 (2)	489(15)	623(17)	538(16)	98(12)	166(12)	236(13)
C114	1920 (3)	4614 (3)	7761 (2)	673(19)	835(22)	638(19)	183(16)	244(15)	361(17)
C115	1998 (3)	5837 (4)	8358 (2)	723(20)	1072(28)	512(17)	193(18)	207(15)	261(18)
C116	2306 (3)	6970 (3)	8081 (2)	698(18)	831(22)	497(17)	173(16)	87(14)	116(15)
C117	2547 (3)	6936 (3)	7180 (2)	480(15)	639(17)	576(16)	54(12)	78(12)	153(13)
O202	1380 (2)	-2265 (2)	3234 (1)	825(13)	418(10)	707(12)	10(9)	59(10)	68(9)
O201	2159 (2)	-87 (2)	3907 (1)	827(13)	421(10)	583(11)	-6(9)	43(9)	86(8)
O202	1380 (2)	-2265 (2)	3234 (1)	825(13)	418(10)	707(12)	10(9)	59(10)	68(9)
N200	4014 (2)	170 (2)	7211 (2)	626(14)	589(14)	564(14)	193(11)	202(11)	143(11)
C201	3435 (2)	-376 (2)	6200 (2)	506(14)	450(14)	586(17)	97(11)	195(12)	183(12)
C202	1942 (3)	-312 (3)	5794 (2)	501(15)	763(19)	702(18)	208(13)	236(14)	196(15)
C203	1268 (3)	-1345 (3)	4866 (2)	424(14)	666(18)	839(20)	55(13)	145(14)	183(16)
C204	2072 (3)	-1350 (2)	4154 (2)	600(16)	379(13)	598(16)	35(11)	119(13)	95(12)
C205	3472 (3)	-1664 (3)	4577 (2)	608(17)	560(16)	647(17)	102(13)	251(14)	139(13)
C206	4113 (2)	-968 (2)	5622 (2)	439(14)	537(15)	660(17)	83(11)	176(13)	167(13)
C207	5445 (3)	53 (3)	7649 (2)	640(18)	806(21)	667(20)	161(15)	80(15)	146(16)
C208	5827 (4)	326 (4)	8750 (3)	972(27)	993(30)	712(24)	246(22)	92(20)	316(22)
C209	5508 (5)	1641 (4)	9167 (3)	1255(34)	1138(32)	608(21)	239(25)	137(22)	-16(20)
C210	4051 (5)	1764 (5)	8683 (3)	1341(37)	1350(36)	721(24)	562(28)	202(25)	-56(23)
C211	3717 (4)	1455 (3)	7576 (3)	964(25)	744(22)	713(22)	344(19)	128(19)	33(17)
C212	1366 (3)	-259 (3)	2957 (2)	578(15)	522(16)	505(15)	70(12)	159(13)	96(13)
C213	915 (3)	-1554 (3)	2560 (2)	527(15)	529(17)	564(17)	0(12)	155(13)	60(13)
C214	132 (3)	-2007 (3)	1604 (2)	788(21)	673(19)	679(21)	-93(16)	191(17)	41(17)
C215	-197 (4)	-1081 (4)	1057 (2)	937(26)	1069(30)	590(20)	-128(21)	92(18)	156(20)

C216	245 (4)	227 (4)	1456 (3)	1029(27)	933(27)	691(23)	43(21)	165(20)	337(20)	
C217	1068 (3)	670 (3)	2428 (2)	844(22)	608(18)	661(20)	77(15)	217(17)	174(15)	
H1021	1368 (34)	5210 (32)	3828 (24)	583(94)						
H1022	578 (33)	3862 (31)	3026 (24)	788(96)						
H1031	357 (34)	4084 (32)	4707 (25)	564(95)						
H1032	924 (34)	2711 (32)	4312 (24)	697(94)						
H1051	4383 (33)	3952 (32)	5649 (24)	748(94)						
H1052	3459 (34)	2533 (32)	5098 (24)	563(94)						
H1061	4497 (34)	3516 (33)	4037 (24)	594(94)						
H1071	4713 (33)	4494 (31)	2624 (24)	721(96)						
H1072	4229 (33)	2958 (32)	2540 (24)	646(96)						
H1081	4641 (33)	3223 (32)	1051 (24)	825(95)						
H1082	3005 (33)	2492 (32)	900 (24)	975(95)						
H1091	3891 (33)	5233 (32)	1011 (24)	991(95)						
H1092	2932 (34)	4173 (32)	6 (24)	875(94)						
H1101	1604 (34)	5614 (32)	727 (24)	934(95)						
H1102	1133 (33)	4083 (31)	718 (24)	1146(95)						
H1111	2904 (34)	5875 (32)	2397 (24)	828(94)						
H1112	1323 (34)	5276 (33)	2296 (24)	829(95)						
H1141	1707 (33)	3749 (32)	7959 (24)	583(94)						
H1151	1765 (34)	5852 (32)	8957 (24)	868(94)						
H1161	2315 (33)	7838 (32)	8520 (24)	813(94)						
H1171	2709 (33)	7666 (31)	6936 (23)	686(94)						
H2021	1476 (33)	-424 (32)	6270 (23)	788(94)						
H2022	1818 (33)	583 (32)	5631 (24)	601(94)						
H2031	1197 (33)	-2261 (31)	5012 (24)	707(94)						
H2032	365 (33)	-1168 (32)	4533 (24)	756(94)						
H2051	3308 (33)	-2656 (31)	4482 (24)	664(94)						
H2052	4002 (33)	-1474 (31)	4141 (24)	631(94)						
H2061	5091 (34)	-966 (32)	5893 (24)	678(93)						
H2071	5659 (33)	-433 (31)	7418 (24)	811(93)						
H2072	6088 (32)	695 (32)	7478 (24)	926(95)						
H2081	5339 (32)	-358 (31)	8949 (24)	960(95)						
H2082	6878 (33)	338 (31)	9091 (23)	885(94)						
H2091	5665 (33)	1300 (31)	9894 (24)	988(94)						
H2092	6120 (33)	2277 (31)	9028 (24)	1126(94)						
H2101	3439 (33)	1101 (31)	8871 (24)	1096(95)						
H2102	3893 (34)	2702 (32)	8886 (24)	1279(94)						
H2111	2715 (33)	1480 (32)	7248 (24)	840(93)						
H2112	4316 (33)	2149 (31)	7371 (23)	998(95)						
H2141	-76 (33)	-2921 (31)	1342 (24)	792(94)						
H2151	-814 (33)	-1402 (31)	340 (24)	838(94)						
H2161	-62 (32)	843 (31)	1039 (24)	903(95)						
H2171	1399 (34)	1604 (32)	2741 (24)	807(93)						

Table 6. *Compound 6; Positional and vibrational parameters* (as in Table 4)

ATOM	X/a	Y/b	Z/c	U11 or U	U22	U33	U12	U13	U23
O1	5044 (5)	7707 (4)	5113 (4)	417(25)	792(32)	495(28)	215(22)	131(21)	-101(23)
O2	6065 (6)	6937 (6)	7462 (5)	628(32)	1209(46)	585(34)	268(31)	290(28)	66(31)
N1	-883 (6)	7432 (5)	2077 (6)	448(33)	480(34)	839(42)	134(27)	165(29)	-26(30)
C1	821 (7)	7466 (6)	2697 (6)	411(37)	539(41)	449(41)	142(31)	176(30)	-63(32)
C2	1268 (7)	6127 (7)	3410 (7)	468(38)	505(43)	869(51)	135(33)	208(35)	-131(38)
C3	3132 (7)	6168 (7)	4028 (7)	481(36)	516(44)	717(52)	134(34)	166(34)	-83(39)
C4	4223 (7)	7632 (7)	4556 (7)	387(34)	644(42)	507(46)	193(31)	150(31)	-76(36)
C5	3924 (7)	8842 (7)	3270 (7)	475(39)	521(44)	656(48)	83(33)	146(34)	-63(38)
C6	2073 (7)	8825 (7)	2643 (7)	425(38)	591(45)	650(48)	181(34)	169(35)	68(37)
C7	-1472 (8)	9723 (7)	1418 (9)	507(42)	646(45)	747(54)	237(35)	153(37)	46(40)
C8	-3349 (8)	8209 (9)	953 (10)	508(46)	913(58)	1612(82)	315(41)	175(48)	-107(57)
C9	-3839 (8)	6656 (8)	1379 (10)	446(46)	766(57)	1683(82)	164(41)	344(51)	50(54)
C10	-2273 (8)	6124 (7)	2052 (9)	499(38)	616(46)	966(63)	143(35)	264(40)	-5(44)
C11	6797 (8)	7343 (7)	6600 (8)	501(42)	487(42)	504(49)	133(32)	139(38)	-57(37)
C12	8648 (8)	7499 (6)	7027 (7)	490(39)	459(39)	490(47)	154(31)	117(34)	-134(34)
C13	9447 (8)	8007 (7)	5991 (8)	519(42)	735(47)	528(48)	248(35)	112(38)	-107(37)
C14	11151 (8)	8143 (8)	6449 (9)	502(45)	872(55)	732(58)	193(39)	208(41)	-141(45)
C15	12081 (9)	7756 (8)	7930 (9)	461(45)	882(57)	865(61)	264(41)	23(45)	-288(47)
C16	11305 (9)	7268 (8)	8961 (8)	698(54)	893(58)	571(51)	379(43)	-51(41)	-165(43)
C17	9593 (9)	7129 (7)	9535 (7)	631(49)	702(47)	507(48)	213(33)	118(37)	-119(37)
H21	831 (53)	5782 (46)	4273 (52)	1303(149)					
H22	559 (51)	5323 (44)	2938 (49)	957(156)					
H31	3333 (45)	5354 (40)	4846 (42)	921(122)					
H32	3514 (45)	6061 (39)	3246 (44)	847(126)					
H41	3956 (44)	7743 (37)	5440 (40)	952(127)					
H51	4603 (42)	9739 (38)	3598 (38)	614(115)					
H52	4205 (46)	8703 (40)	2432 (42)	965(129)					
H71	-935 (47)	9449 (40)	2080 (45)	1021(134)					
H72	-1063 (55)	9253 (46)	629 (52)	1148(151)					
H81	-3735 (53)	8584 (48)	1422 (54)	1238(160)					
H82	-3996 (59)	8535 (51)	-16 (56)	1725(183)					
H91	-4446 (52)	6310 (54)	1975 (60)	1534(179)					
H92	-4590 (56)	6083 (49)	682 (57)	1380(165)					
H101	-2135 (49)	5632 (43)	2089 (46)	1002(139)					
H102	-2282 (51)	5455 (44)	1471 (48)	1315(155)					
H131	9766 (42)	8230 (36)	4980 (39)	833(118)					
H141	11702 (46)	8502 (40)	5772 (44)	961(134)					
H151	13339 (42)	7874 (37)	8216 (40)	742(118)					
H161	11947 (50)	6944 (42)	10005 (44)	1025(144)					
H171	8935 (45)	6725 (38)	9245 (42)	889(123)					

Table 7. *Compound 7; Positional and vibrational parameters* (as in Table 4)

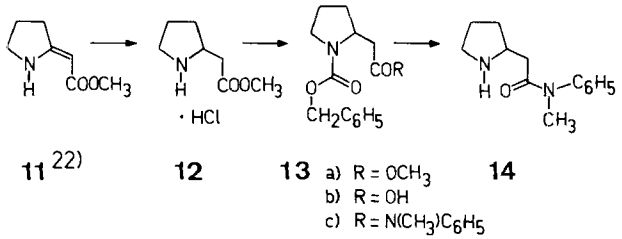
Atom	x/a	y/b	z/c	U_{11} or U	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O1	2249 (2)	7576 (2)	3558 (1)	528(11)	213(9)	402(10)	29(8)	-39(9)	51(8)
N1	4497 (2)	6757 (2)	4373 (1)	342(10)	281(11)	327(12)	-55(9)	20(9)	-50(10)
N2	1577 (2)	5238 (2)	3665 (1)	329(10)	249(10)	276(10)	2(9)	-72(9)	28(9)
C1	5077 (2)	6357 (3)	3621 (2)	249(11)	283(13)	320(13)	14(10)	-9(10)	10(11)
C2	6145 (2)	7286 (3)	3384 (2)	379(14)	498(16)	415(15)	-99(12)	-7(12)	-32(13)
C31(80)	6938 (4)	6552 (6)	2716 (3)	361(21)	598(29)	559(26)	-176(20)	137(20)	-27(24)
C32(20)	6446 (13)	7157 (14)	2413 (10)	326(74)	171(63)	452(80)	70(54)	31(63)	74(58)
C41(80)	6172 (4)	5880 (5)	1993 (3)	397(23)	521(27)	433(23)	-47(20)	126(19)	-45(21)
C42(20)	6709 (15)	5502 (18)	2297 (12)	277(76)	300(82)	465(96)	-34(63)	168(70)	-43(74)
C5	5395 (2)	4669 (3)	2363 (2)	370(12)	356(14)	367(14)	47(11)	49(11)	-59(12)
C6	4735 (2)	5179 (3)	3142 (2)	280(11)	262(13)	372(13)	-23(10)	69(10)	-4(11)
C7	4637 (3)	8165 (3)	4787 (2)	452(15)	357(15)	452(16)	-99(13)	29(13)	-136(14)
C8	3972 (3)	8304 (4)	5611 (2)	623(18)	442(17)	403(16)	-28(15)	35(15)	-153(14)
C9	2999 (3)	6332 (3)	5436 (2)	444(14)	352(15)	303(13)	-4(12)	15(12)	-14(12)
C10	3344 (2)	6173 (3)	4590 (2)	317(12)	211(12)	273(12)	-12(9)	38(10)	-2(10)
C11	2351 (2)	6354 (3)	3887 (2)	362(12)	211(12)	232(12)	15(10)	51(10)	-10(10)
C12	651 (3)	5483 (4)	2975 (2)	472(15)	519(19)	450(16)	-31(14)	-127(14)	81(15)
C13	1615 (2)	3795 (3)	4035 (2)	271(11)	239(12)	278(12)	-25(9)	-28(10)	-5(10)
C14	1182 (2)	3540 (3)	4848 (2)	399(13)	317(14)	357(14)	3(11)	4(12)	10(11)
C15	1136 (3)	2121 (3)	5167 (2)	498(16)	460(18)	433(16)	-96(14)	-24(14)	144(15)
C16	1551 (3)	963 (3)	4686 (2)	515(16)	326(15)	609(20)	-116(13)	-182(15)	144(15)
C17	1993 (3)	1217 (3)	3883 (2)	418(14)	243(13)	590(19)	-15(11)	-71(14)	-86(13)
C18	2028 (2)	2629 (3)	3545 (2)	353(13)	314(14)	379(14)	-55(11)	10(11)	-38(12)
H21	5805 (27)	3276 (37)	3248 (22)	453(34)					
H22	5657 (31)	7371 (39)	3902 (25)	589(97)					
H31	7447 (40)	7395 (49)	2445 (31)	561(122)					
H32	7399 (33)	5636 (43)	2979 (27)	424(102)					
H41	5657 (35)	6768 (46)	1721 (27)	491(105)					
H42	5779 (30)	5415 (39)	1635 (24)	273(88)					
H51	4859 (24)	4425 (33)	1928 (19)	328(71)					
H52	5814 (29)	3780 (36)	2493 (23)	482(98)					
H61	4103 (23)	4593 (30)	3317 (18)	306(68)					
H71	5439 (26)	8457 (34)	4855 (21)	412(79)					
H72	4128 (31)	8970 (39)	4441 (24)	618(97)					
H81	4541 (35)	7509 (43)	6021 (27)	688(114)					
H82	3721 (32)	8817 (41)	5859 (26)	632(99)					
H91	2971 (29)	6089 (36)	5893 (22)	503(87)					
H92	2248 (32)	7239 (39)	5374 (25)	600(97)					
H101	3452 (24)	5010 (31)	4651 (18)	275(68)					
H121	827 (29)	4933 (38)	2532 (24)	551(90)					
H122	-42 (31)	5292 (37)	3147 (24)	513(93)					
H123	817 (28)	6420 (36)	2626 (23)	515(86)					
H141	923 (26)	4308 (34)	5186 (20)	429(79)					
H151	786 (32)	1987 (42)	5782 (26)	641(99)					
H161	1553 (36)	-20 (47)	4923 (29)	761(119)					
H171	2231 (30)	481 (39)	3552 (24)	556(95)					
H181	2331 (31)	2899 (39)	2983 (25)	583(95)					

Table 8. *Compound* ***8****; Positional and vibrational parameters* (as in Table 4)

ATOM	X/a	Y/b	Z/c	U11 or U	U22	U33	U12	U13	U23
O101	12219 (4)	7640 (4)	6385 (2)	539(26)	1122(38)	562(28)	50(25)	-92(21)	-146(26)
O102	14418 (4)	6682 (4)	5845 (3)	415(24)	935(34)	769(31)	17(23)	-190(21)	14(26)
O103	8328 (5)	9145 (5)	7123 (3)	1107(42)	1338(47)	1206(45)	-506(36)	-738(36)	515(37)
N100	9273 (4)	7656 (4)	4592 (3)	391(27)	670(34)	604(32)	-214(24)	-142(23)	100(26)
N101	10238 (5)	9789 (4)	2299 (3)	687(34)	699(36)	643(36)	-193(29)	-169(27)	212(29)
C101	10600 (6)	7358 (5)	4835 (3)	424(34)	503(39)	452(37)	-128(29)	-45(27)	-19(31)
C102	11428 (6)	8252 (5)	4776 (4)	474(37)	766(46)	570(40)	-238(33)	-191(30)	260(34)
C103	12943 (6)	7808 (5)	4943 (4)	500(38)	796(47)	591(42)	-273(34)	-170(31)	141(36)
C104	12999 (5)	7041 (5)	5674 (4)	341(33)	617(41)	580(40)	-22(29)	-115(28)	16(33)
C105	12430 (7)	6037 (5)	5518 (4)	655(45)	613(46)	1013(57)	-144(36)	-313(40)	167(41)
C106	11058 (6)	6362 (5)	5171 (4)	539(41)	574(43)	933(52)	-188(34)	-276(37)	117(39)
C107	8916 (6)	8540 (6)	3960 (4)	349(33)	371(52)	485(39)	-156(33)	-111(28)	52(35)
C108	7305 (7)	8538 (7)	4931 (4)	574(41)	1297(70)	808(53)	11(43)	-188(36)	126(48)
C109	7128 (7)	7423 (7)	4202 (5)	714(49)	1376(74)	1047(61)	-516(49)	-340(43)	310(54)
C110	8398 (6)	6844 (6)	4597 (4)	570(41)	799(49)	826(51)	-336(36)	-151(36)	85(40)
C111	13137 (8)	7858 (9)	6912 (5)	802(74)	1907(131)	1058(90)	168(78)	-498(67)	-549(86)
C112	14580 (7)	7348 (7)	6496 (5)	657(63)	1186(87)	1128(85)	94(58)	-440(59)	-377(68)
C113	9697 (6)	8159 (5)	3103 (4)	504(38)	643(43)	686(45)	-116(32)	-152(33)	85(36)
C114	9377 (7)	9074 (6)	2461 (4)	727(45)	767(49)	619(44)	-67(37)	-201(35)	165(38)
C115	9933 (8)	10656 (6)	1674 (4)	949(54)	884(55)	649(48)	-115(43)	-190(40)	385(42)
C116	11402 (6)	9807 (5)	2722 (3)	514(36)	595(40)	458(36)	-169(31)	-60(28)	195(30)
C117	12664 (7)	9010 (5)	2543 (4)	640(43)	5[illegible](41)	516(40)	-57(33)	78(33)	79(32)
C118	13781 (6)	9076 (6)	2939 (4)	437(39)	[illegible]33(51)	754(50)	-23(35)	44(36)	190(42)
C119	13655 (7)	9916 (6)	3492 (4)	572(45)	[illegible](51)	754(52)	-273(41)	-147(37)	231(43)
C120	12404 (7)	10727 (5)	3665 (4)	712(48)	629(46)	622(44)	-198(39)	-97(37)	34(35)
C121	11275 (6)	10669 (5)	3077 (4)	511(38)	538(40)	639(43)	-18(31)	-44(32)	115(33)
O201	828 (4)	4990 (4)	7725 (3)	503(27)	939(35)	935(38)	-31(25)	308(25)	145(29)
O202	2915 (4)	3930 (3)	2088 (3)	616(27)	509(27)	1054(37)	-75(21)	229(25)	21(25)
O203	6861 (5)	8892 (5)	-412 (3)	904(36)	1425(48)	1019(40)	-784(35)	-163(30)	298(35)
N200	5925 (5)	6195 (4)	1418 (3)	490(32)	871(40)	639(34)	-273(29)	-289(26)	139(30)
N201	4840 (5)	8557 (4)	-713 (3)	559(31)	767(37)	602(35)	-300(28)	-84(26)	62(29)
C201	4644 (6)	5975 (5)	1774 (3)	472(36)	476(36)	516(38)	-56(28)	-158(30)	-34(29)
C202	3624 (6)	5913 (5)	1212 (4)	469(36)	784(46)	576(40)	-279(33)	-121(30)	270(34)
C203	2166 (6)	5826 (5)	1622 (4)	478(36)	563(39)	577(40)	-150(30)	-54(29)	66(32)
C204	2227 (6)	5056 (5)	2347 (4)	476(38)	545(41)	686(45)	-40(31)	120(33)	58(35)
C205	3015 (7)	5453 (6)	2962 (4)	781(49)	724(49)	487(42)	132(39)	40(37)	63(36)
C206	4368 (7)	5740 (6)	2575 (4)	670(44)	919(53)	516(41)	-150(39)	-113(34)	-64(37)
C207	6186 (6)	5719 (5)	588 (4)	327(34)	658(47)	1208(59)	-219(32)	-240(35)	165(42)
C208	7816 (7)	6445 (6)	397 (5)	651(45)	979(57)	1058(61)	-228(40)	-106(42)	30(46)
C209	8232 (8)	6521 (8)	1281 (6)	696(51)	1420(81)	1611(86)	-478(52)	-544(54)	295(66)
C210	7048 (7)	6240 (6)	1895 (4)	679(45)	921(55)	878(53)	-150(39)	-393(40)	-151(42)
C211	570 (8)	3946 (6)	2536 (6)	834(75)	720(68)	2009(125)	-339(59)	224(76)	120(73)
C212	1958 (8)	3224 (7)	2182 (6)	695(64)	906(76)	1779(122)	-368(58)	286(70)	9(77)
C213	5555 (7)	7975 (6)	629 (4)	657(45)	838(54)	740(50)	-268(40)	-47(36)	-84(41)
C214	5780 (7)	8521 (6)	-216 (4)	760(48)	765(49)	726(48)	-374(39)	32(37)	106(39)
C215	5014 (7)	9145 (6)	-1501 (4)	894(52)	796(51)	690(48)	-279(41)	36(38)	337(40)
C216	3630 (6)	8172 (5)	-548 (4)	537(39)	552(41)	462(37)	-198(32)	-114(30)	133(32)
C217	3656 (6)	7084 (5)	-933 (4)	615(42)	585(44)	571(42)	-163(35)	-80(32)	63(35)

C218	2476 (9)	6634 (6)	-812 (4)	940(57)	713(50)	653(49)	-340(46)	-251(43)	58(39)
C219	1296 (8)	7168 (7)	-311 (5)	643(49)	975(62)	771(55)	-418(46)	-209(42)	242(48)
C220	1254 (7)	8150 (7)	73 (4)	475(42)	976(59)	685(49)	-99(41)	-13(35)	239(44)
C221	2424 (7)	8631 (5)	-40 (4)	629(45)	649(44)	570(42)	-134(37)	-49(35)	13(34)
H1021	11451 (58)	8011 (47)	4232 (35)	698(225)					
H1022	10886 (63)	8308 (51)	5215 (39)	846(236)					
H1031	13569 (60)	7295 (48)	4435 (36)	762(236)					
H1032	13291 (59)	8479 (48)	5037 (35)	709(226)					
H1051	13134 (72)	5518 (57)	5106 (43)	1068(263)					
H1052	12285 (68)	5016 (54)	6049 (41)	949(250)					
H1061	11455 (64)	5053 (51)	5246 (38)	886(251)					
H1071	9091 (54)	9311 (43)	4059 (32)	564(195)					
H1081	6793 (84)	9301 (67)	4542 (52)	1459(279)					
H1082	7059 (73)	9118 (59)	3499 (45)	1145(247)					
H1091	6380 (91)	7259 (71)	4465 (55)	1504(293)					
H1092	7349 (83)	7123 (65)	3645 (51)	1286(283)					
H1101	8168 (48)	6621 (39)	5198 (29)	368(187)					
H1102	8954 (67)	6053 (54)	4268 (40)	954(246)					
H1131	10759 (61)	7881 (49)	3202 (36)	797(218)					
H1132	9138 (86)	7357 (69)	3095 (50)	1446(289)					
H1151	10835 (87)	10627 (67)	1298 (49)	1654(294)					
H1152	9221 (83)	10397 (65)	1358 (47)	1612(302)					
H1153	9588 (80)	11435 (65)	1973 (47)	1598(281)					
H1171	12746 (57)	8456 (46)	2112 (34)	658(229)					
H1181	14634 (69)	8493 (55)	2788 (40)	991(250)					
H1191	14447 (58)	10011 (46)	3837 (34)	652(227)					
H1201	12296 (59)	11324 (47)	4090 (34)	685(222)					
H1211	10413 (57)	11207 (46)	3405 (34)	671(238)					
H2021	3609 (51)	6522 (42)	844 (36)	483(207)					
H2022	4053 (68)	5178 (56)	815 (40)	975(240)					
H2031	1587 (54)	6594 (45)	1831 (32)	611(232)					
H2032	1706 (56)	5529 (46)	1231 (34)	635(215)					
H2051	2375 (59)	6139 (48)	3226 (34)	709(227)					
H2052	3145 (64)	4886 (52)	3422 (37)	856(227)					
H2061	5023 (58)	5815 (47)	2929 (34)	696(226)					
H2071	5816 (57)	6407 (46)	134 (33)	639(223)					
H2081	8158 (92)	5537 (75)	89 (53)	1803(301)					
H2082	7915 (93)	7275 (77)	-174 (54)	1867(304)					
H2091	8964 (68)	6057 (54)	1561 (41)	1066(281)					
H2092	8019 (**)	7472 (88)	1433 (63)	3163(290)					
H2101	7239 (60)	5523 (50)	2235 (35)	732(242)					
H2102	6679 (67)	6819 (56)	2297 (39)	945(258)					
H2131	4526 (76)	6034 (61)	936 (45)	1179(297)					
H2132	6434 (88)	8253 (71)	1207 (51)	2036(305)					
H2151	4095 (83)	9737 (65)	-1496 (46)	1593(295)					
H2152	5749 (85)	9047 (66)	-1404 (48)	1642(296)					
H2153	5324 (61)	8557 (66)	-1949 (47)	1681(297)					
H2171	4444 (55)	6037 (45)	-1288 (33)	613(240)					
H2181	2504 (58)	5911 (47)	-1119 (34)	714(220)					
H2191	503 (66)	6302 (55)	-213 (39)	894(262)					
H2201	490 (53)	8548 (43)	490 (31)	572(240)					
H2211	2365 (57)	9411 (46)	221 (34)	625(209)					

Schema 3



11 [22] **12** **13** a) R = OCH_3 **14**
b) R = OH
c) R = $N(CH_3)C_6H_5$

1690 cm^{-1}) as an oil. This crude ester was saponified at RT. for 2 h in a mixture of 50 ml 1N NaOH and 80 ml methanol. Acidification (70 ml 1N HCl) and extraction into CH_2Cl_2 gave after removal of the solvent 7.35 g crude acid **13b**. This was without purification transformed to the *N*-methylanilide **13c** by dissolving it in 100 ml dry CH_2Cl_2, cooling the solution to $-7°$ adding under stirring to it 3.39 g (33.5 mmol) triethylamine *(Fluka, puriss.)*, then 3.63 g (33.5 mmol) ethyl chloroformate *(Fluka, purum)* and after 15 min at $-7°$ 4.48 g (41.9 mmol) *N*-methylaniline *(Fluka, puriss.)*. The cooling-bath was removed and stirring continued for 1 h. Washing the organic layer with 1N HCl (three 50-ml-portions) and evaporation of solvent yielded 11.0 g crude **13c** as a yellow oil (IR. in $CHCl_3$: 1690, 1645 cm^{-1}) which was directly subjected to hydrogenolysis (300 mg 10% Pd/C, *Fluka, puriss.*, 100 ml methanol, RT., 4 h). The reaction product was chromatographed on 600 g basic alumina, activity III: Elution (with *ca.* 0.6 l ether/methanol 9:1 then with 1 l ether/methanol 1:1) yielded a TLC.-pure[23]) product which was distilled in several batches (kugelrohr oven temperature 140°, $5 \cdot 10^{-3}$ Torr) to give 3.256 g **14** (44% from **11**); the analytical and spectral data of such material are shown below. – UV. (EtOH): 226 (3.74). – IR. ($CHCl_3$): 3350*w*, 3010*s*, 2965*s*, 2875*m*, 2500*w*, 1950*w*, 1880*w*, 1800*w*, 1645*s*, 1597*s*, 1496*s*, 1425*m*, 1389*m*, 1362*w*, 1350*w*, 1170*w*, 1121*m*, 1071*w*, 1033*w*, 1000*w*, 965*w*, 916*w*, 699*s*, 660*m*. – ^{1}H-NMR. ($CDCl_3$): 1.0–1.4 (*m*/1H); 1.5–2.0 (*m*/3 H); 2.15–2.38 (superposition of *s* (NH) and *d* (CH_2CO)/3 H, after H→D exchange with D_2O: *d* at 2.24 ppm, $J = 6$ Hz→*s* after decoupling by irradiation at 3.4 ppm); 2.8–3.0 (*m*/2 H); 3.26 (*s*/3 H); *ca.* 3.2–3.6 (*m*/1H); 7.2–7.6 (*m*/5 H). – ^{13}C-NMR. ($CDCl_3$): 24.7 (*t*/CH_2); 31.0 (*t*/CH_2); 37.1 (*qa*/CH_3); 40.5 (*t*/CH_2); 46.0 (*t*/CH_2); 55.4 (*d*/CH); 127.4 (*d*/3 (or 2?) CH); 129.7 (*d*/2 (or 3?) CH); 144.1 (*s*); 171.6 (*s*). – MS. (<95°): 218 (5, M^+), 107 (36), 106 (19), 92 (12), 84 (11), 83 (12), 77 (15), 71 (6), 70 (100).

$C_{13}H_{18}N_2O$ (218.30) Calc. C 71.52 H 8.31 N 12.83% Found C 71.55 H 8.39 N 12.75%

REFERENCES

[1] *G. Stork, R. Terrell & J. Szmuszkovicz*, J. Amer. chem. Soc. *76*, 2029 (1954).
[2] a) *A. G. Cook*, 'Enamines: Synthesis, Structure, and Reactions', Marcel Dekker New York, London 1969; b) *S. F. Dyke*, 'The Chemistry of Enamines', Cambridge University Press 1973.
[3] *Z. G. Hajos & D. R. Parrish*, J. org. Chemistry *39*, 1615 (1974).
[4] *U. Eder, G. Sauer & R. Wiechert*, Angew. Chem. *83*, 492 (1971); *J. Ruppert, U. Eder & R. Wiechert*, Chem. Ber. *106*, 3636 (1973).
[5] *G. Saucy & R. Borer*, Helv. *54*, 2121 (1971).
[6] *S. Danishefsky & P. Cain*, J. Amer. chem. Soc. *97*, 5282 (1975); *iidem.* ibid. *98*, 4975 (1976); *K. Nagasawa, H. Takahashi, K. Hiroi & S. Yamada*, J. pharm. Soc. Japan *95*, 33 (1975); *K. Nagasawa, K. Hiroi & S. Yamada*, ibid. *95*, 46 (1975).
[7] *P. Buchschacher, J.-M. Cassal, A. Fürst & W. Meier*, Helv. *60*, 2747 (1977); *T. Wakabayashi, K. Watanabe & J. Kato*, Synthetic Commun. *7*, 239 (1977).
[8] *N. Cohen*, Accounts chem. Res. *9*, 412 (1976).
[9] *R. Hobi*, «Zur Reaktivität und räumlichen Struktur von Enaminen», thesis ETH-Zürich Nr. 6030, aku-Fotodruck Zürich 1977.
[10] *L. Damm*, thesis ETH-Zürich (in preparation).

[23]) Silica gel, ether/ethanol/aqueous ammonia 10:2:1, Rf 0.45.

[11] *M.P. Sammes, R.L. Harlow & S.H. Simonsen*, J. chem. Soc. Perkin II *1976*, 1126.
[12] *M. Forchiassin, A. Risaliti, C. Russo, N.B. Pahor & M. Calligaris*, J. chem. Soc. Perkin I *1977*, 935.
[13] *C.S. Huber*, Acta crystallogr. *B28*, 2015 (1972).
[14] *R. Meyer*, Helv. *61*, 1418 (1978).
[15] *K. Müller & L.D. Brown*, Helv. *61*, 1407 (1978).
[16] *D.W.J. Cruickshank*, Acta crystallogr. *9*, 757 (1956); *W.R. Busing & H.A. Levy*, ibid. *17*, 142 (1964); *V. Schomaker & K.N. Trueblood*, ibid. *B24*, 63 (1968).
[17] *F.K. Winkler & J.D. Dunitz*, J. mol. Biol. *59*, 169 (1971); Acta crystallogr. *B31*, 251 (1975).
[18] *H.B. Bürgi*, Inorg. Chemistry *12*, 2321 (1973); *idem*, Angew. Chem. *87*, 461 (1975); *H.B. Bürgi, J.D. Dunitz & E. Shefter*, J. Amer. chem. Soc. *95*, 5065 (1973); *H.B. Bürgi, E. Shefter & J.D. Dunitz*, Tetrahedron *31*, 3089 (1975); *H.B. Bürgi, J.D. Dunitz, J.M. Lehn & G. Wipff*, ibid. *30*, 1563 (1974); *P. Murray-Rust, H.B. Bürgi & J.D. Dunitz*, J. Amer. chem. Soc. *97*, 921 (1975); *J.D. Dunitz*, Phil. Trans. Roy. Soc. London *B272*, 99 (1975).
[19] *G. Germain, P. Main & M.M. Woolfson*, Acta crystallogr. *B26*, 274 (1970).
[20] *P. Coppens*, Angew. Chem. *80*, 33 (1977); Angew. Chem. Internat. Ed. *16*, 32 (1977).
[21] *O. Ermer & J.D. Dunitz*, Acta crystallogr. *A26*, 163 (1970).
[22] *C. Altona, H.J. Geise & C. Romers*, Tetrahedron *24*, 13 (1968).
[23] *J.D. Dunitz & P. Strickler*, in 'Structural Chemistry and Molecular Biology', ed. A. Rich and N. Davidson, Freeman, San Francisco 1968, p. 595.
[24] *W.D. Gurowitz & M.A. Joseph*, Tetrahedron Letters *1965*, 4433; *iidem*, J. org. Chemistry *32*, 3289 (1967).
[25] *W. Schwotzer & W.v. Philipsborn*, Helv. *60*, 1501 (1977); *P.W. Westerman & J.D. Roberts*, J. org. Chemistry *42*, 2249 (1977); *H. Ahlbrecht & G. Papke*, Tetrahedron Letters *1972*, 4443; *Md.G. Ahmed, P.W. Hickmott & R.D. Soelistyowati*, J. chem. Soc. Perkin II *1978*, 372; *L.N. Domelsmith & K.N. Houk*, Tetrahedron Letters *1977*, 1981; *R.S. Brown*, Canad. J. Chemistry *54*, 1521 (1976).
[26] *G.J. Karabatsos & D.J. Fenoglio*, 'Rotational Isomerism about sp^2–sp^3 Carbon-Carbon Single Bonds', in E.L. Eliel & N.L. Allinger (Ed.) 'Topics in Stereochemistry' *5*, 167 (1970); *R.K. Bohn*, 'Electron Diffraction Studies of Molecular Conformation' in 'Molecular Structure by Diffraction Methods' *5*, 23 (1977), Specialist Periodical Report, The Chemical Society, London.
[27] *L. Pauling*, 'Kekulé and the Chemical Bond', IUPAC Symposium on Theoretical Chemistry, Butterworths Sc. Publ., London 1958, p.1; *L. Pauling*, 'The Nature of the Chemical Bond' 3. Ed., Cornell University Press 1960, p.136ff.
[28] *J.D. Dunitz & P. Strickler*, Helv. *49*, 2505 (1966); *K. Radcliffe & J.L. Wood*, Trans. Faraday Soc. *62*, 2038 (1966); see also *E.L. Eliel, N.L. Allinger, S.J. Angyal & G.A. Morrison*, 'Conformational Analysis', Interscience N.Y. 1965, p. 20.
[29] *G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz & R. Terrell*, J. Amer. chem. Soc. *85*, 207 (1963); *M.E. Kuehne*, ibid. *81*, 5400 (1959).
[30] *M.E. Munk & Y.K. Kim*, J. org. Chemistry *30*, 3705 (1965).
[31] *I.M. Cunningham & K.H. Overton*, J. chem. Soc. Perkin I *1975*, 2140; *H. Felkin, Y. Gault & G. Roussi*, Tetrahedron *26*, 3761 (1970); *G. Popják & J.W. Cornforth*, Biochem. J. *101*, 553 (1966).
[32] *K. Hiroi, K. Achiwa & S. Yamada*, Chem. pharm. Bull. (Tokyo) *20*, 246 (1972) and earlier as well as later papers; *S. Hashimoto, S. Yamada & K. Koga*, J. Amer. chem. Soc. *98*, 7450 (1976); *S. Hashimoto & K. Koga*, Tetrahedron Letters *1978*, 573. – *A.I. Meyers, G.S. Poindexter & Z. Brich*, J. org. Chemistry *43*, 892 (1978); *A.I. Meyers, G. Knaus, K. Kamata & M.E. Ford*, J. Amer. chem. Soc. *98*, 567 (1976) and related papers. – *J.F. Hansen & C.S. Cooper*, J. org. Chemistry *41*, 3219 (1976). – *J.K. Whitesell & M.A. Whitesell*, J. org. Chemistry *42*, 377 (1977); *J.K. Whitesell & S.W. Felman*, ibid. *42*, 1663 (1977). – *L. Duhamel & J.-Ch. Plaquevent*, Tetrahedron Letters *1977*, 2285; *H. Matsushita, Y. Tsujino, M. Noguchi, M. Saburi & S. Yoshikawa*, Bull. chem. Soc. Japan *51*, 862 (1978).
[33] *A.H. Rees*, J. chem. Soc. *1962*, 3097.
[34] *E.R.H. Jones & F. Sondheimer*, J. chem. Soc. *1949*, 615.
[35] *P. Mussini, F. Orsini & F. Pelizzoni*, Synthetic Commun. *5*, 283 (1975).
[36] *R. Scheffold, E. Bertele, P. Wehrli, W. Häusermann, W. Huber & A. Eschenmoser*, Helv. (to be published); *W. Häusermann*, Diss. ETH-Zürich Nr. 3754, Juris-Verlag Zürich 1966; see also *Y. Yamada, D. Miljković, P. Wehrli, B. Golding, P. Löliger, R. Keese, K. Müller & A. Eschenmoser*, Angew. Chem. *81*, 301 (1969); Angew. Chem. Internat. Ed. *8*, 343 (1969).
[37] *A. Rüttimann, A. Wick & A. Eschenmoser*, Helv. *58*, 1450 (1975).