# 73. Structure and Reactivity of Five- and Six-Ring N,N-, N,O-, and O,O-Acetals: A Lesson in Allylic 1,3-Strain ($A^{1,3}$ Strain)

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The X-ray structures of fifteen 1,3-imidazolidine, 1,3-oxazolidine, 1,3-dioxan-4-one, and hydropyrimidine-4(1*H*)-one derivatives are described (*Table 2*) and compared with known structures of similar compounds (*Figs. 1–20*). The differences between structures containing exocyclic *N*-acyl groups and those lacking this structural element arise from the $A^{1,3}$ effect of the amide moieties. Even *t*-Bu groups are forced into axial positions of six-ring half-chair or into flag-pole positions of six-ring twist-boat conformers by this effect (*Figs. 16–20*). In the *N*-acylated five-membered heterocycles, a combination of ring strain and $A^{1,3}$ strain leads to strong pyramidalizations of the amide N-atoms (*Table 1*) such that the acyl groups wind up on one side and the other substituents on the opposite side of the rings (*Figs. 4–9* and *Scheme 3*). Thus, the acyl (protecting!) groups strongly contribute to the steric bias between the two faces of the rings. Observed, at first glance surprizing stereoselectivities of reactions of these heterocycles (*Schemes 1* and *2*) are interpreted (*Scheme 3*) as an indirect consequence of the amide $A^{1,3}$ strain effect. The conclusions drawn are considered relevant for a better understanding of the ever increasing role which amide groups play in stereoselective syntheses.

**1. Introduction.** – *Some Surprizing Stereochemical Courses of Reactions.* In our work on syntheses of entantiomerically pure α- and β-amino- and α- and β-hydroxy-

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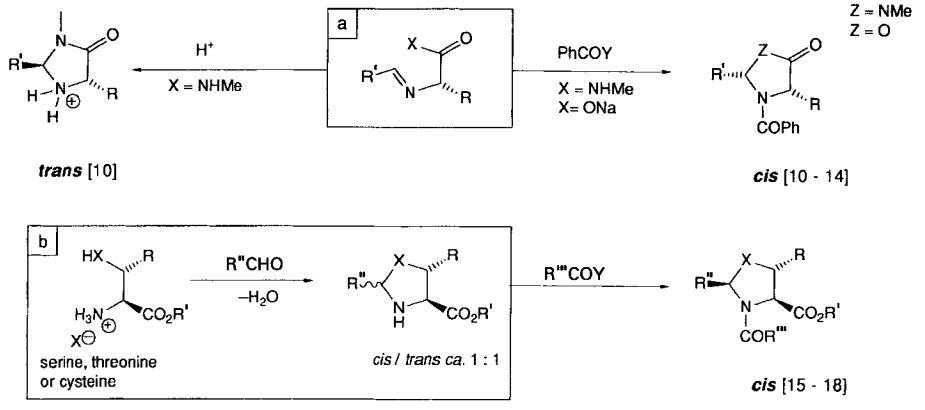
carboxylic acids through heterocyclic five- and six-ring acetal derivatives[6]), we repeatedly experienced dramatic effects of *N*-acyl substituents on the stereoselectivities of reactions. Some examples, together with leading references are collected in *Schemes 1* and *2* (reactions *a–i*). *a*) When the *Schiff* bases of amino acid *N*-methylamides are cyclized under acid catalysis, *trans*-imidazolidinone derivatives result, while the acylating cyclization of the same precursors and of the corresponding sodium salts produces products of *cis*-configuration. *b*) Acid-catalyzed acetalization of serine, threonine, and cysteine esters gives rise to *ca.* 1:1 mixtures of *cis*- and *trans*-substituted heterocycles; when these are acylated, pure *cis*-diastereoisomers result. *c*)*d*) The five-ring N,N-, N,O-, and O,O-acetal enolates with endocyclic double bonds react with electrophiles highly selectively from the face *trans* to the substituent on the acetal center[7]). In contrast, the bicyclic enolates from cyclic amino acids – bearing no acyl group on the N-atom – react exclusively from the face *cis* to the *t*-Bu group. *e*)*f*) Enolates derived from α,β-diamino acids, or from serine, threonine, or cysteine, and pivalaldehyde, having an *N*-acyl group next to the exocyclic double bond, combine with electrophiles in the expected way (*trans* to the *t*-Bu group). The

*Scheme 1*




analogs prepared from α,β-dihydroxy-acids, with a dioxolane structure, react preferentially from the face *cis* to the substituent on the neighboring stereogenic center. *g*)*h*) On going from *N*-acyl-2-(*tert*-butyl)tetrahydropyrimidin-4(1*H*)-one to 2-(*tert*-butyl)-1,3-dioxolan-4-one enolates, the directing effect of the *t*-Bu group reverses and becomes much weaker. *i*) Reactions which must involve *N*-acyliminium ions derived from imid-

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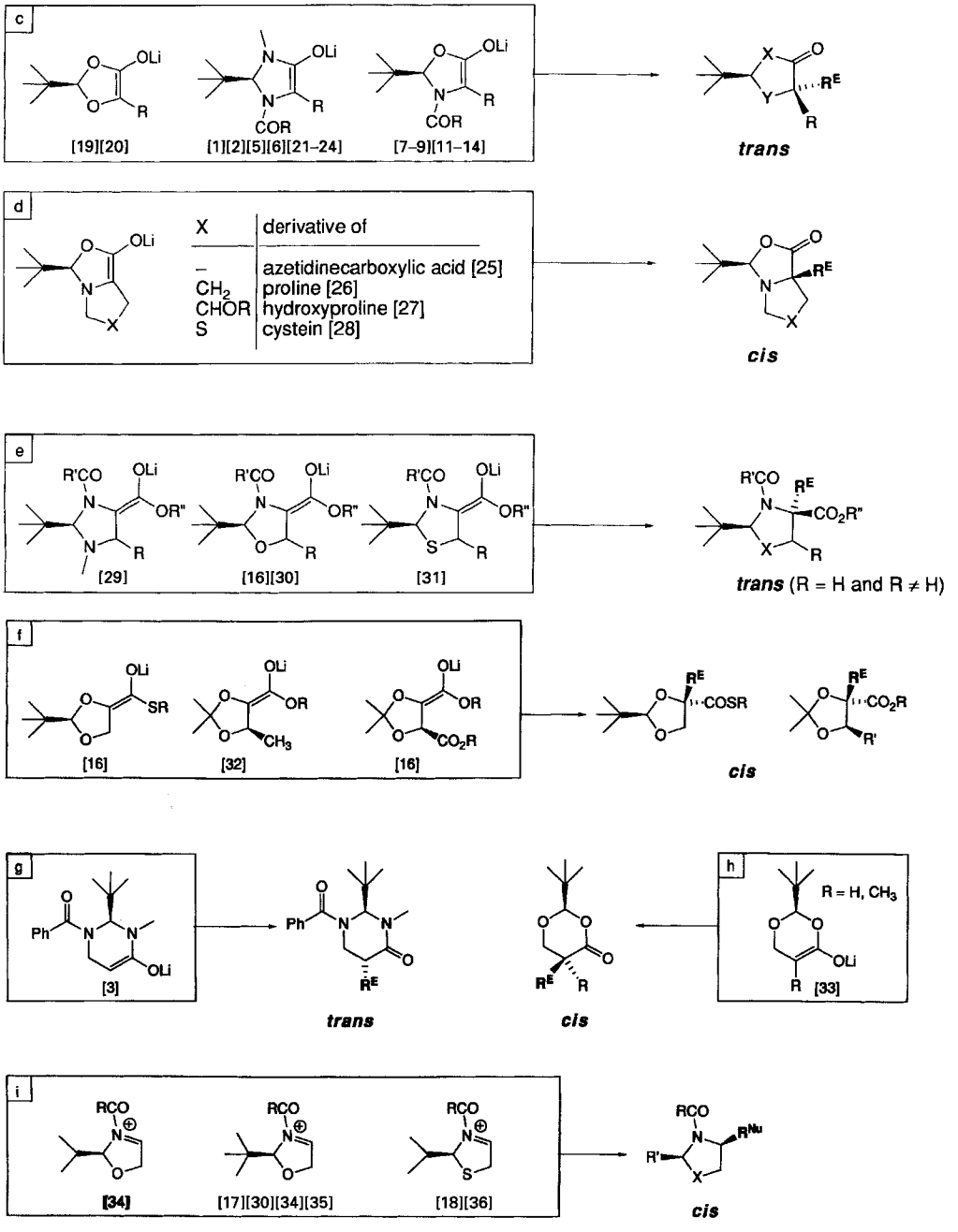
[6]) For an early review article, see [1]; for the most recent full papers, see [2–9], and ref. cit. therein.

[7]) In many cases, reactions with substituents on the acetal center other than *t*-Bu have been carried out and found to be of comparable selectivity. References to such cases are included in *Scheme 2*. For benzaldehyde and isobutyraldehyde derivatives (Ph and CHMe instead of *t*-Bu), see for instance [4] [9] [13] [14] [22]. Following the protocol published for the preparation of 1-[(*tert*-butoxy)carbonyl]-2-(*tert*-butyl)-3-methylimidazolidin-4-one (Boc-BMI) [23], we have recently resolved 3-methyl-2-isopropylimidazolidin-4-one by crystallizing its (+)-di-*O*,*O*′-(4-toluoyl)tartrate salt from EtOH (71% of the theoretical yield); treatment with $(Boc)_2O$/4-(dimethylamino)pyridine gave *tert*-butyl 3-methyl-2-isopropyl-4-oxoimidazolidine-1-carboxylate as an oil ($[\alpha]_D^{t.} = +1.26$ ($c = 0.91$, $CHCl_3$)), the Li enolate of which reacted with the benzylic bromide diethyl 3-(bromomethyl)-5-phenylbenzylphosphonate with > 98% ds [37].

*Scheme 2*[a])



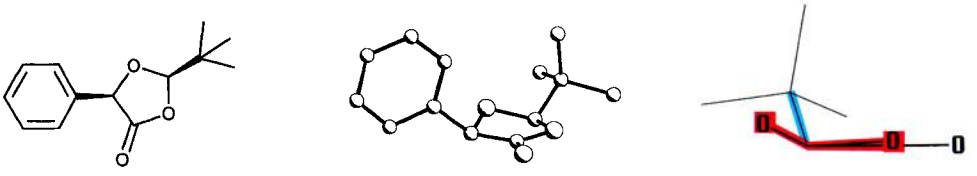

[a]) Only one enantiomer is shown for reactions performed with racemic materials; for the sake of uniformity of presentation, some formulae show the mirror image of the compound which was actually used in the experiment. The configurations of the enolates shown under *e*) and *f*) are drawn arbitrarily; they are unknown.

azolidine and thiazolidine show a preference for the formation of *cis*-products with a variety of nucleophiles; in addition, a peculiar difference between the i-Pr- and the *t*-Bu-substituted analogs was observed: in attempted *Lewis*-acid-mediated conversions, only the former ones would react, while the latter ones decompose.

We have used X-ray crystal-structure determinations to elucidate the stereochemical outcome of the reactions studied. In most cases, we took these structures only to assign product configurations, without further interpretation. It now turns out that they also contain the clue for understanding most of the selectivities as being the consequence of a powerful $A^{1,3}$ effect[8]) from the *N*-acylamido groups in the starting materials used and in the intermediates involved.

For the discussions in the following sections, we use figures containing a formula, a PLUTO plot [41a] showing the structure, and a MacMoMo-generated [41b] view stressing structural features of interest. In the latter ones, the cyclic acetal (in *Fig. 22* the piperidine ring) is marked in red, the substituent on the acetal center in blue, and the exocyclic amidocarbonyl group in green, respectively. For the sake of uniformity the sense of chirality in all three presentations will be the same, but may be opposite to the one published for racemic compounds. For structures published by other groups and taken from the *Cambridge Structural Database* or for the ones deposited therein by us previously, the *CSD* codes will be given in the figure captions. There will be 16 structure determinations described in this paper (see *Table 2* in the *Exper. Part*).

**2. *N*-Acyl-Imidazolidinones and Oxazolidinones.** – *Envelope and Twist Conformations with Quasi-axial* t-*Bu Groups, Comparison with Non-acylated Analogs and with Dioxolanones.* In crystals, the structures of dioxolanones, the five-ring acetals from α-hydroxy-carboxylic acids and aldehydes or ketones, usually exhibit an envelope conformation[9]), with the ether-type O-atom out of plane with respect to the other four atoms of the ring. As can be seen from the two examples **1** and **2** shown in *Fig. 1* and *2*, respectively, the



**1**

Fig. 1. cis-*Dioxolanone* **1** (from pivalaldehyde and mandelic acid; *CSD:* GAZCUF) [43]. The envelope-type form with the RCH–O–CHR′ O-atom out of plane is quite common in this series of compounds, see also the corresponding malic-acid derivative (CBCXMD) [44] and a spiro-tricyclic *Diels-Alder* adduct (KAKXAV) [45]. Compounds of this type are used for enantiomerically pure compound (EPC) syntheses [46] with self-regeneration of stereogenic centers [1] [19] [20].

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[8]) The term $A^{1,3}$ strain (allylic 1,3-strain) was first introduced by *Johnson* and *Malhotra* [38], the former being the author of an early review article [39]. For an excellent recent discussion of the literature on the importance of the $A^{1,3}$ effect in the stereochemical course of synthetically useful reactions, see [40a], for a computational approach, see [40b].

[9]) A rigorous mathematical definition of five-ring envelope and twist and of six-ring chair, boat, twist-boat, half-boat ('sofa'), and half-chair forms is given in papers by *Pitzer*, *Pople*, and coworkers [42a]; a concise discussion can be found in *Dunitz*'s textbook on crystal structures [42b]. We have used phase angles and puckering amplitudes for an unambiguous analysis of the ring structures, which proved the conformations sometimes to be different from the first impression on the computer screen. Though none of the structures presented here is a 'pure' form, we use the terms of the conformers whose phase angles are next to the values of our structures.

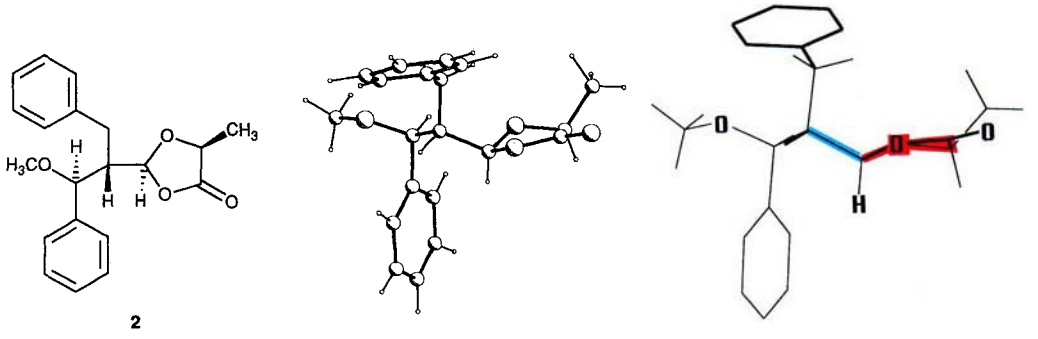


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Fig. 2. *Acetal* **2** (from an aldehyde RCHO with a bulky R group and lactic acid; *CSD:* KANKEP) [47]. The largest substituent occupies a quasi-equatorial position on the acetal-type C-atom, which is not, as it may seem from the MacMoMo representation, the apex of the envelope. As in *Fig. 1*, the ether-type O-atom is the out-of-plane atom.

large substituents occupy quasi-equatorial positions on these rings, just like in cyclopentanes and in simple pyrrolidine and tetrahydrofuran (DNA, RNA [48]) heterocycles.

The ring conformation of the imidazolidinone **3** shown in *Fig. 3* is slightly different:

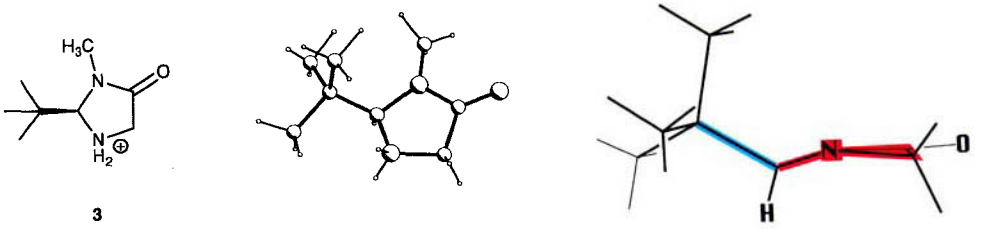


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Fig. 3. *Imidazolidinium ion* **3** *in the crystal structure of one of the diastereoisomeric mandelate salts.* The structures of both, the (*R,S*)- and the (*R,R*)-salt have been determined [49], with the heterocyclic moieties in the two structures being almost superimposable. The *t*-Bu group occupies an equatorial position on an almost twist conformer.

the NCCN array is essentially planar, and the acetal-type C-atom is out of plane, but still bears a *t*-Bu group in a quasi-equatorial position. This is not the case in the series of analogous *N*-acylated imidazolidines **4**–**7** and 2,3-dihydro-1*H*-imidazoles **8a** and **8b** (see *Figs. 4–8*): due to the incorporation of an amide N-atom, the ring is much flatter, and in all cases the *t*-Bu-substitued C-atom is slightly out of the plane formed by the other four ring atoms, with the bulky group in a quasi-axial position. The neighboring amide N-atom bearing an exocyclic acyl group is more or less strongly pyramidalized such that the acyl group occupies a position quasi-*trans* to the *t*-Bu group on the five-membered rings, while the endocyclic lactam-type N-atom is close to be planar (see the pyramidalizations $\Delta$ [56] in *Table 1*).

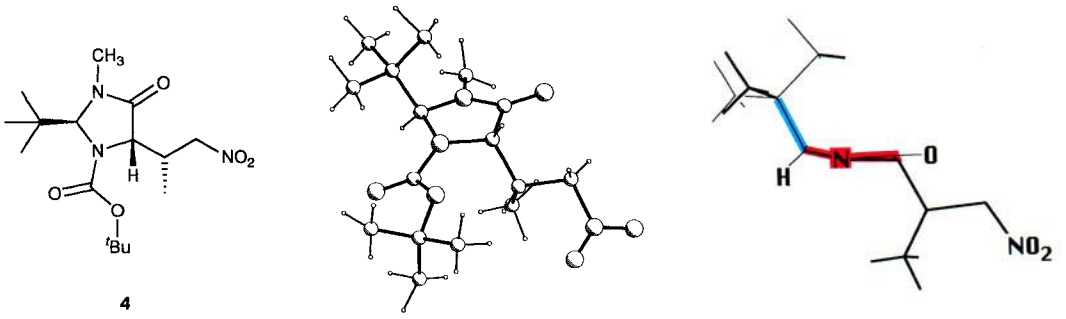



Fig. 4. Michael *adduct* **4** of the *1-Boc-2-(* tert-*butyl)-3-methylimidazolidinone enolate to nitropropene* [23] *with a* t-*Bu group quasi-axial on a twist conformer*. The trigonal centers of the precursors have combined with each other on the face of the ring *trans* to the *t*-Bu group, with relative topicity *lk* [50]. The structure of **4** had been assigned previously by chemical correlation and by NOE measurements [23]. For other examples of 1,4-additions of chiral heterocyclic enolates to nitroolefins and for a general discussion of the stereochmical course of such reactions, see [51] and [52], respectively.

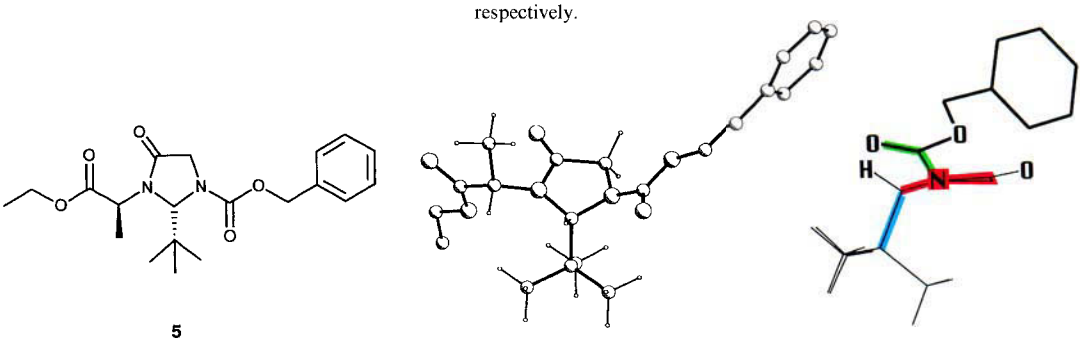



Fig. 5. *Imidazolidinone* **5** *derived from a dipeptide* (Gly-Ala-OH) *and pivalaldehyde* (*CSD:* SEYHIN) [53]. Note the strong pyramidalization ($\Delta = 0.20$ Å) of the carbamate N-atom, with the Z group above and the quasi-axial *t*-Bu group below the five-ring plane. Enolates of such dipeptide derivatives have been used for C-alkylations [54] [55].

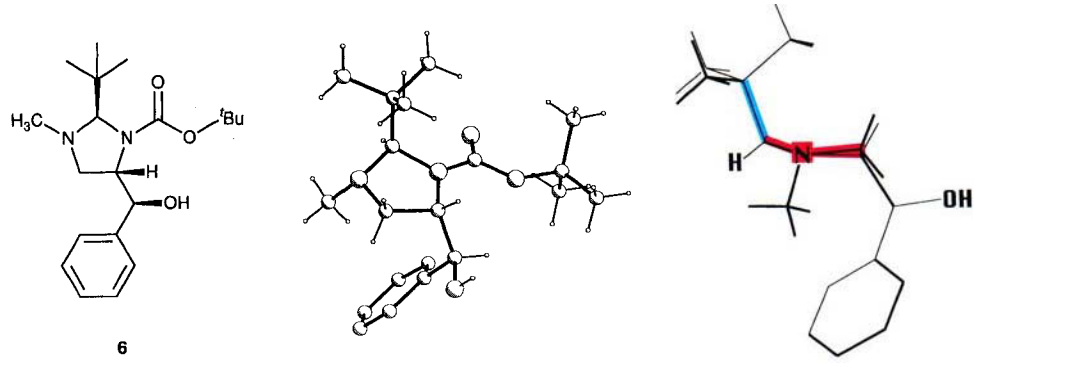
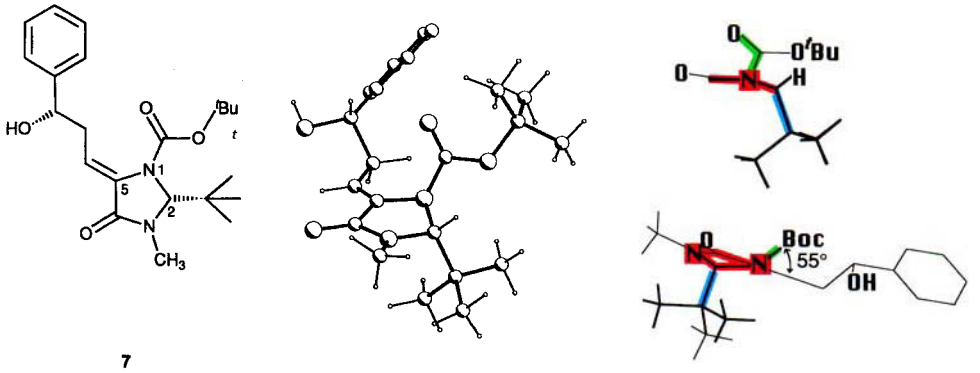



Fig. 6. N-*Boc*-N′-*methylimidazolidine* **6**. The structure has been used for assignment of the relative configuration on the two stereogenic centers [29]. Such derivatives of α,β-diamino acids are available from *tert*-butyl 2-(*tert*-butyl)-5-lithio-3-methylimidazolidine-1-carboxylate and electrophiles (here PhCHO) [29]. There is almost perfect eclipsing on the ethylene part of the ring. The *N*-Me group resides in a *trans*-position with respect to the *t*-Bu group which in turn is an axial substituent on the twisted envelope.




7

Fig. 7. *Alkylidene derivative* **7** *of 1-Boc-2-(* tert*-butyl)-3-methylimidazolidinone* (formed on addition of a Li dienolate to PhCHO; mentioned in [6]). The pyramidalization *Δ* on the carbamate N-atom is 0.28 Å. Due to the (*Z*)-configuration, the C=C bond and the amide moiety can not possibly be coplanar; even with a twisting of 55° between them, the carbonyl O-atom bumps into the $CH_2$ group (O···H non-bonding distance 2.4 Å). There are some very unusual angles around the trigonal centers. The carbamate moiety is not only pyramidalized on N, but also strongly twisted: dihedral angle C(2)–N(1)–C–O(*t*-Bu) 32.5°. Unlike all other structures shown in this paper, the carbamate RO O-atom and not the C=O O-atom of **7** is s-*cis* to the *t*-Bu substituted acetal-type C-atom (C(2)). Otherwise, this is only observed in geminally disubstituted heterocycles of this type [14]. For synthetic applications of 5-alkylidene-1-Boc-2-(*tert*-butyl)-3-methylimidazolidinone derivatives, see [6].

Table 1. *Sums of Bond Angles and Pyramidalizations Δ on Amide N-Atoms in the Five-Ring* (**3**–**13**) *and Six-Ring Acetals* (**16**–**20**) *and in Amide* **21**

| | *Σα endo* | *Δ endo* [Å] | *Σα exo* | *Δ exo* [Å] | $\tau_1$[a]) | $\tau_2$[a]) |
|---|---|---|---|---|---|---|
| Five-membered rings | | | | | | |
| (*R*)-Mandelate of **3** | 354.7 | 0.19 | – | – | – | – |
| (*S*)-Mandelate of **3** | 354.9 | 0.19 | – | – | – | – |
| **4** | 360.0 | | 358.4 | | 10.6 | 28.6 |
| **5**, molecule 1 | 359.5 | 0.06 | 354.3 | 0.20 | 16.6 | 12.5 |
| **5**, molecule 2 | 357.7 | 0.13 | 352.7 | 0.23 | 17.4 | 16.2 |
| **6** | – | – | 360.0 | | 16.7 | 16.9 |
| **7** | 359.8 | 0.04 | 348.6 | 0.28 | 9.5 | 32.6 |
| **8a** | – | – | 348.1 | 0.29 | 17.1 | 27.3 |
| **8b** | – | – | 353.5 | 0.21 | 23.1 | 10.7 |
| **9** | – | – | 349.5 | 0.27 | 12.4 | 29.1 |
| **10** | – | – | 351.8 | 0.24 | 9.7 | 27.2 |
| **11** | – | – | 356.9 | 0.15 | 1.5 | 21.5 |
| **13a** | – | – | 338.7 | 0.38 | 36.8 | 16.6 |
| **13b** | – | – | 334.9 | 0.43 | 42.3 | 13.5 |
| Six-membered rings | | | | | | |
| **16** | 359.9 | | 360.0 | | 7.0 | 7.1 |
| **17** | 360.0 | | 359.9 | | 7.6 | 13.5 |
| **18** | 358.2 | 0.11 | 358.8 | 0.09 | 9.9 | 3.5 |
| **19** | 359.9 | 0.02 | 359.6 | 0.05 | 8.1 | 1.1 |
| **20** | 360.0 | | 358.3 | 0.11 | 29.7 | 17.4 |
| **21** | – | – | 359.7 | 0.04 | 16.2 | 28.4 |

[a]) $\tau_1$ = torsion angle C–N–(carbonyl-C)–(carbonyl-O); $\tau_2$ = torsion angle C–N–(carbonyl-C)–X, with X = C in amides and X = ester-O in carbamates.

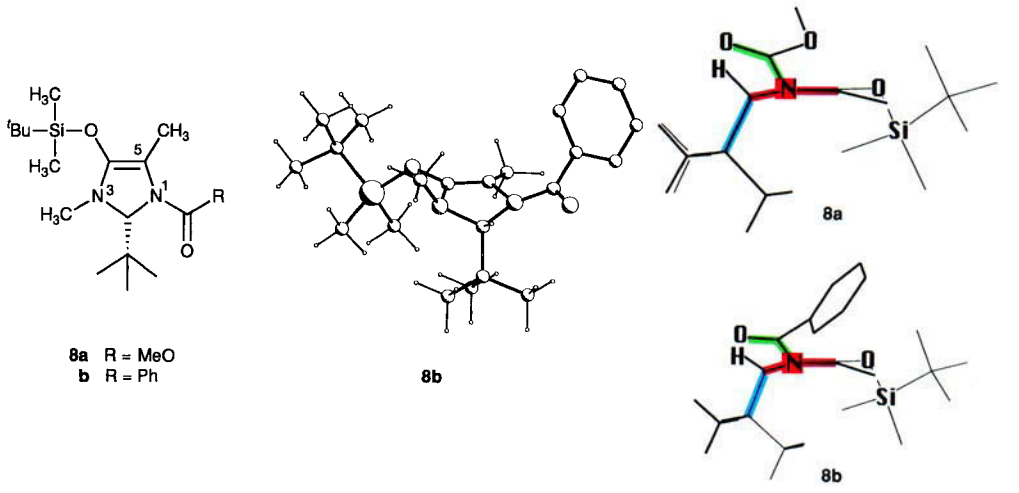



Fig. 8. *Silyl enol-ethers* **8a** *and* **8b** *of a methoxycarbonyl- and a benzoyl-substituted imidazolidinone.* The structures were thoroughly discussed, especially with respect to the pyramidalization on C(5) [2]. The *t*-Bu group occupies a quasi-axial position. Note the *ca.* 70° twist between the planes of the amide group and of the benzene ring, as well as the pyramidalization of the PhCON amide N-atom ($\Delta = 0.21$ Å) in **8b** (0.29 Å in **8a**).

The heterocyclic rings in the *N*-benzoyl- and *N*-(methoxycarbonyl)oxazolidines **9** and **10**, and in the *N*-(benzyloxycarbonyl)-dihydrothiazole *S*-oxide **11** (*Figs. 9–11*) are very close to planarity, but again the *t*-Bu and the acyl groups occupy opposite sides of the ring planes which is effected by pyramidalization of the amide N-atoms. In all but one case (the highly congested **7**)[10]), the *N*-acyl carbonyl O-atom occupies an s-*cis*-position with the *t*-Bu-substituted acetal C-atom[11]).

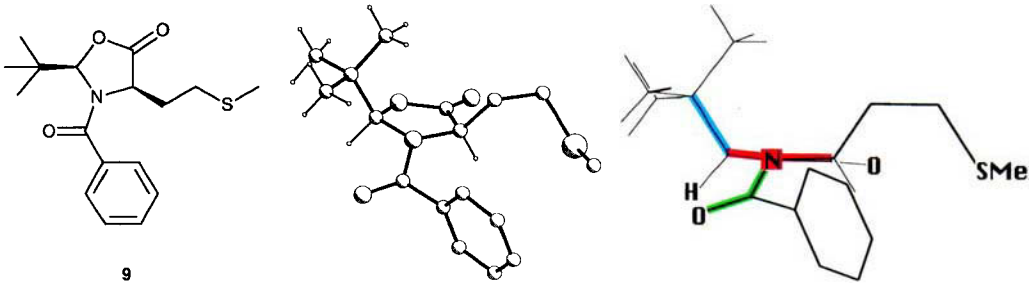



Fig. 9. cis-*Disubstituted oxazolidinone* **9** (from methionine and pivalaldehyde; *CSD:* FENJEN) [57]. Note the unusual conformation of the (methylthio)ethyl side chain and the essentially planar five-membered ring. The enolate of **9** was used to prepare α-branched methionines in enantiomerically pure form [1] [12] [57].

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[10]) *Cf.* geminally disubstituted heterocycles derived from α-branched amino acids [14].

[11]) Generally, it is not clear from inspection of models why this is so: the R group of COOR would point away from the neighboring acetal-type center in the other conformer. Maybe, the difference in the *van der Waals* radii of the carbonyl (small) and the RO O-atom (large) is causing this preference?

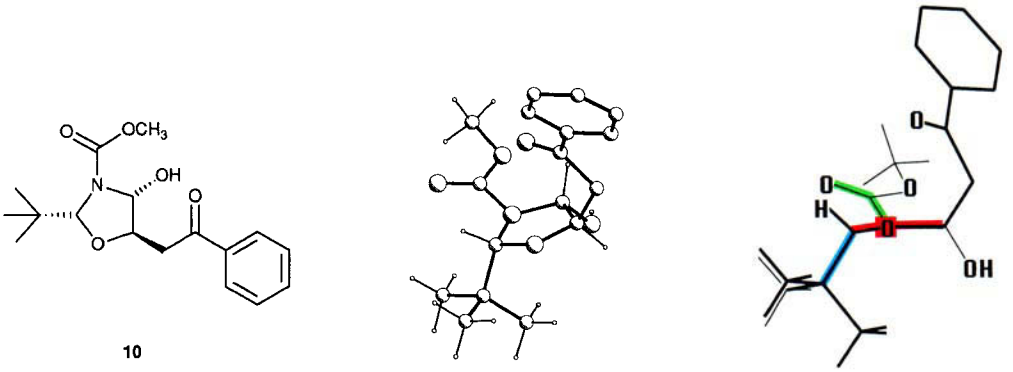


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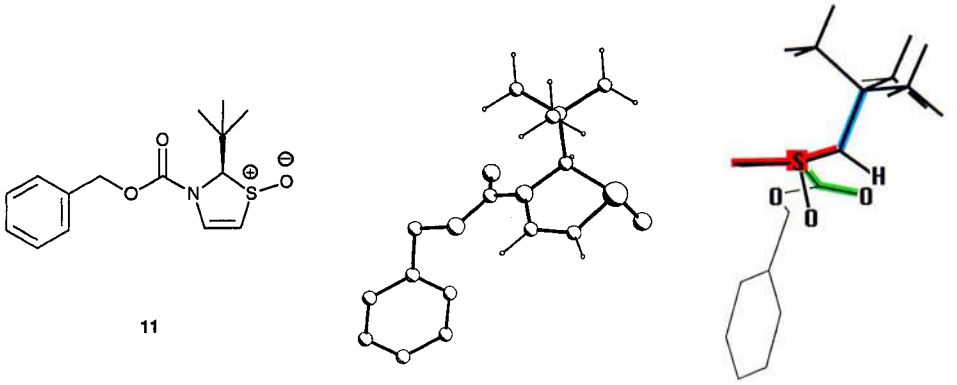
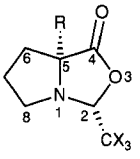
Fig. 10. *Oxazolidine* **10** *obtained in an unexpected acid-catalyzed rearrangement of a tricyclic oxaspiropentane* [35]. The OH group is introduced as the result of an attack on an acyliminium ion by $H_2O$ *cis* to the *t*-Bu group (see *i* in *Scheme 2*); the structure was mentioned in [35]. As in **9**, the heterocycle is practically planar.



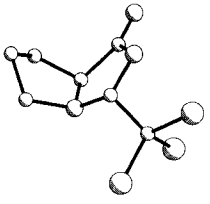

11

Fig. 11. *Dihydrothiazole* S-*oxide* **11** *prepared from cystein*. The structure determination has been described in [18]. In the preparation of **11**, the sulfoxidation has occurred from the face *trans* to the *t*-Bu group of the corresponding precursor [18] [31]. The COOR group and the sulfoxide O-atom are on one side, the *t*-Bu group in an axial position on the other side of the ring.

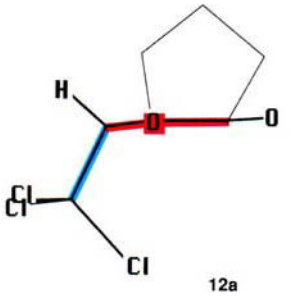
The 1,3-oxazolidin-2-one and -5-one moieties in the bicyclic structures **12** and **13** (*Figs. 12* and *13*) are of special interest, because they may be relevant with respect to the reactivity of proline-derived enolates (*Scheme 2, d*): even the bridgehead N-atoms of the carbamate units in **13a** and **13b** are pyramidalized like those of *tertiary* amines, as a consequence of ring strain (*cf.* the structures of pyrrolizidinones (*Fig. 13*), of penicillins, and other $\beta$-lactam derivatives [59a], and of lactams with the bridgehead N-atoms [59b]).



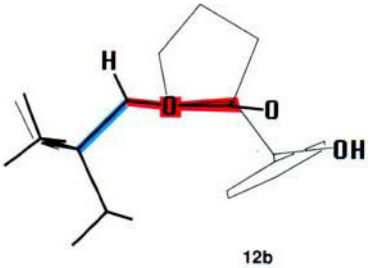

**12a** R = H, X = Cl
**b** R = CH(OH)Ph, X = $CH_3$



**12a**

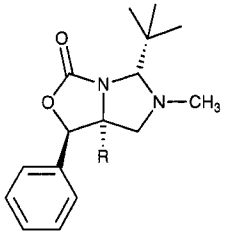



**12a**

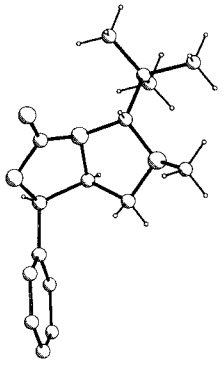



**12b**

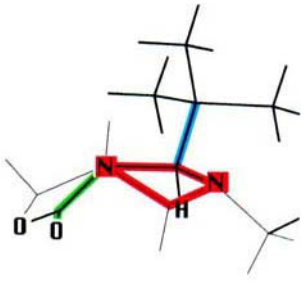
Fig. 12. *Acetals* **12** *derived from proline and aldehydes.* The structure of the chloral derivative **12a** has been thoroughly discussed (*CSD:* KATMUN); the one of the aldol adduct **12b** was used for configurational assignment (*CSD:* CALJOO). The bicyclic systems are bent; the two mean planes containing C(6), C(5), N, C(8) and C(4), C(5), N, C(2) form an angle of *ca.* 120°. Apart from the bridgehead substitution, the two structures are quite similar, in **12b** the pyrrolidine ring being more twisted. The oxazolidinone rings are essentially planar in both molecules. The '*endo*'-face of the diheterocyclic ring is blocked by the second ring, the '*exo*'-face by a $CCl_3$ (**12a**) or a *t*-Bu group (**12b**). The enolate of **12a** can be generated and added to benzaldehyde [58] with formation of a product analogous to **12b** [26].




**13a** R = H
**b** R = $CO_2Me$



**13a**




**13a**

Fig. 13. *Bicyclic carbamates* **13** *obtained by elimination of* t-*BuOH from the corresponding benzaldehyde aldol adducts* (*cf.* **6**; [29]). The basic skeletons of **13a** and **13b** are very similar: the bridgehead amide N-atom is pyramidalized like the N-atom of a *tertiary* amine ('$sp^3$ hybridization'). In contrast to the almost planar oxazolidinone ring in the structure **12**, both five-membered rings of **13a** and **13b** are strongly folded. Similar structures have been found in pyrrolizidinones and bicyclic hydantoins (there are 13 structures in the *CSD* as of August 1991 with bridgehead N-atom pyramidalization $\Delta$ of up to 0.39 Å).

**3. Dioxanones and Dioxinones *vs.* *N*-Acyl-hydro-pyrimidinones: a Classical Structural $A^{1,3}$-Strain Effect.** – When comparing different 1,3-dioxan-4-ones **14** (*Fig. 14*) and the corresponding dioxinones **15** (*Fig. 15*), it becomes evident that substituents occupy equatorial positions. In the known crystal structures, the *cis*-2,6-disubstituted dioxanones are 'sofa'-type conformers[9]) with O(1) out of plane of the other ring atoms. The *trans*-disubstituted dioxanone **14e** was found not to be in this conformation which would have the $CF_3$ group in an axial position. Rather, **14e** is a twist-boat-type conformer, with $CF_3$ in quasi-equatorial and *t*-Bu in a kind of bowsprit position. The corresponding dioxinone structures shown or alluded to in *Fig. 15* are also 'sofa'-type conformers, but now with the acetal C-atom out of plane (as the 'head rest of the sofa'); the large substituents on the only tetrahedral atoms of these rings are equatorial.

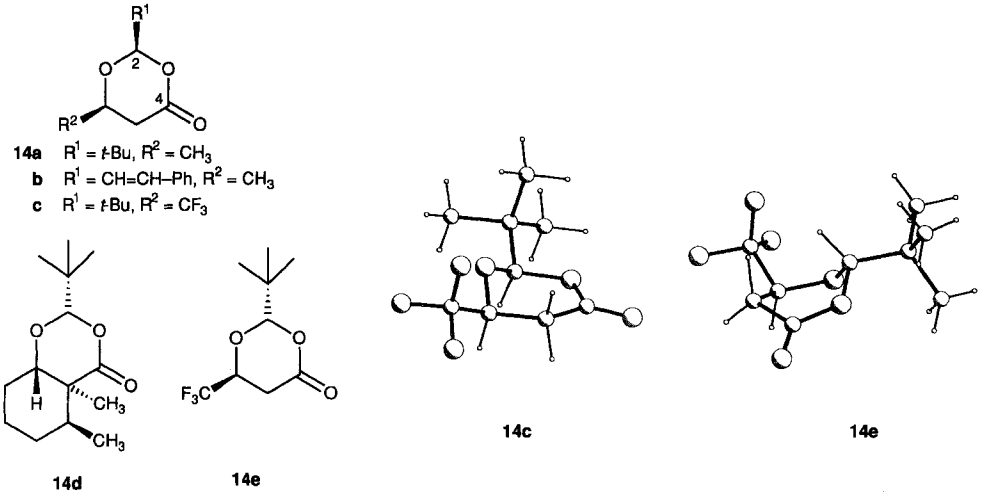



Fig. 14. *Conformations with the substituents in quasi-equatorial positions in 1,3-dioxan-4-ones* **14**, (*cf.* also *(tert-butyl)-methyl-dioxanone* **14a** (*CSD:* GEXLOK) [60]). Three new examples are the styryl derivative **14b**, the *cis*-$CF_3$ derivative **14c**, and the bicyclic compound **14d** (the latter ones have been mentioned in previous papers [61]; see also the structure of 2-cyclohexyl-6-methyl-5-neopentyl-1,3-dioxan-4-one [62]). The *trans*-isomer of **14c**, *i.e.* **14e**, is found to exist as a boat conformer in the crystalline state. Classical structural anomeric effects [63] are evident from the C–O bond lengths in these structures.

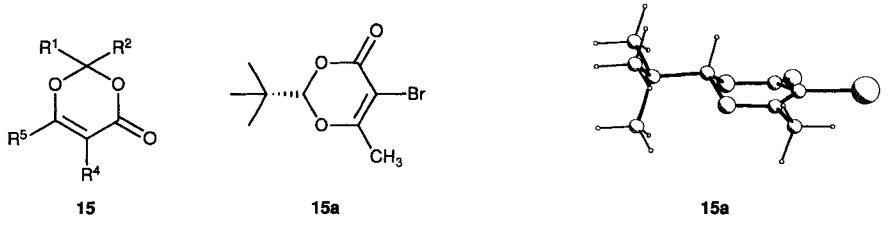



Fig. 15. *Sofa conformations for dioxinones* **15**, *like for dioxanones* **14**, *but with the acetal-type C-atom, rather than the ether-type O-atom out of plane* (see **15a** (CSD: GEXLUQ), some further examples (*CSD:* GANLOW, FARBEF, FENHEL, VENKEE), and the extensive discussion in [60]). In the known crystal structures, the more bulky substituent on the 2-position of the dioxinone ring occupies the equatorial position.

The analogous N-containing heterocycles, *N*-benzoyl-2-(*tert*-butyl)tetrahydropyrimidin-4(1*H*)-ones and -dihydropyrimidinones, look similar in the ring conformation, but quite different in the substitution on the acetal C-atom, see **16–20** in *Figs. 16–20.*

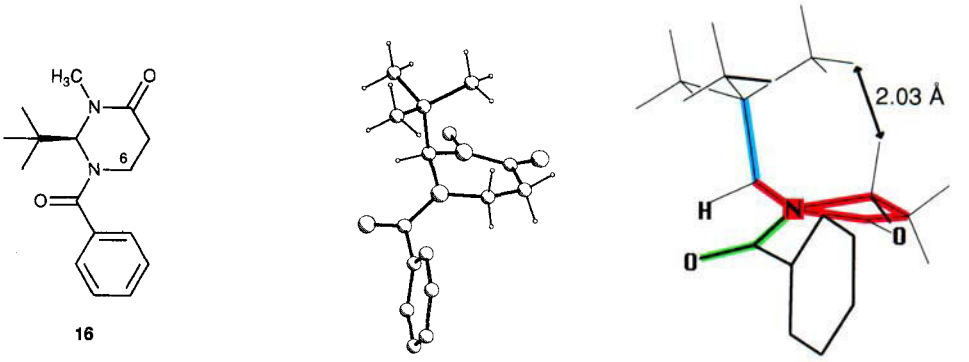



Fig. 16. *Crystal structure of 1-benzoyl-2-(* tert-*butyl)tetrahydro-3-methylpyrimidin-4(1*H*)-one* (**16**; preparation from *β*-aminopropionic acid *N*-methylamide and pivalaldehyde, see [3]). The close proximity of one of the Me groups of the axial *t*-Bu and of the $CH_2$ group in the 6-position is indicated in the MacMoMo presentation (*van der Waals* radius of Me and $CH_2$ 2.0 Å, of an H-atom 1.2 Å [64]).

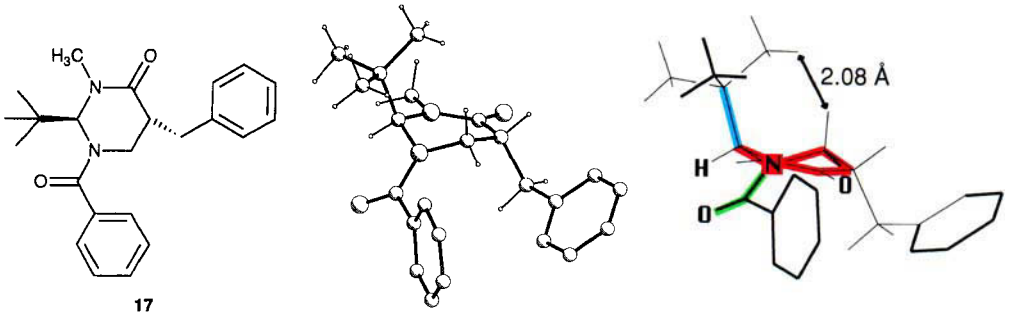



Fig. 17. trans-*1-benzoyl-5-benzyl-2-(* tert-*butyl)tetrahydro-3-methylpyrimidin-4(1*H*)-one* (**17**; obtained by benzylation of the enolate from **16** as the sole product [3]). The 6-$CH_2$ and one of the *t*-Bu Me groups are on *van der Waals* contact (1,3-diaxial-type interaction).

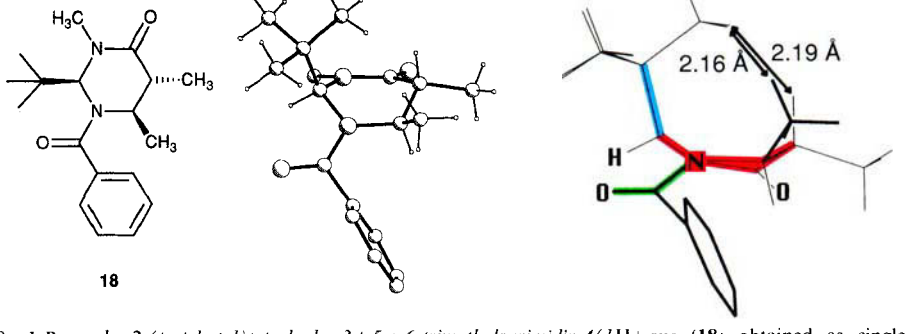



Fig. 18. *1-Benzoyl-*r-*2-(* tert-*butyl)tetrahydro-3,*t-*5,*c-*6-trimethylpyrimidin-4(1*H*)-one* (**18**; obtained as single product on methylation of the Li enolate from the corresponding *cis*-(*tert*-butyl)-6-methyltetrahydropyrimidinone [65]). The six-membered ring is a boat conformer with the *t*-Bu group on a flagpole position.

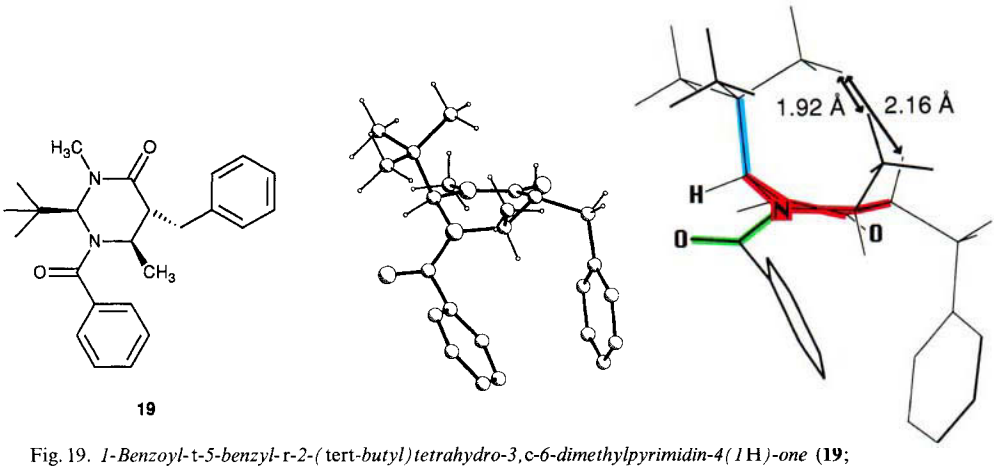



Fig. 19. *1-Benzoyl-*t*-5-benzyl-*r*-2-(*tert*-butyl)tetrahydro-3,*c*-6-dimethylpyrimidin-4(1*H*)-one* (**19**; obtained on benzylation of the corresponding tetrahydropyrimidinone Li enolate [65]). As in **18**, the 6-ring heterocycle is in a boat-like conformation. See the short distances between the *t*-Bu and a Me group (1,3 interaction) as well as a methine H-atom (1,4 interaction).

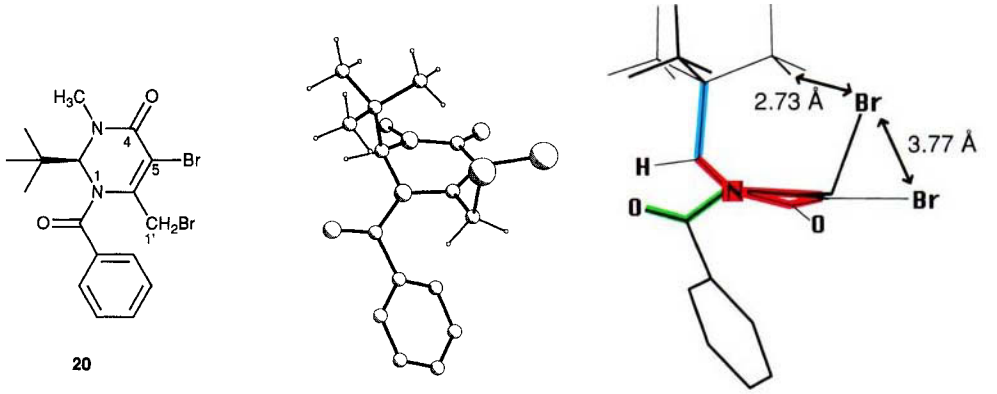


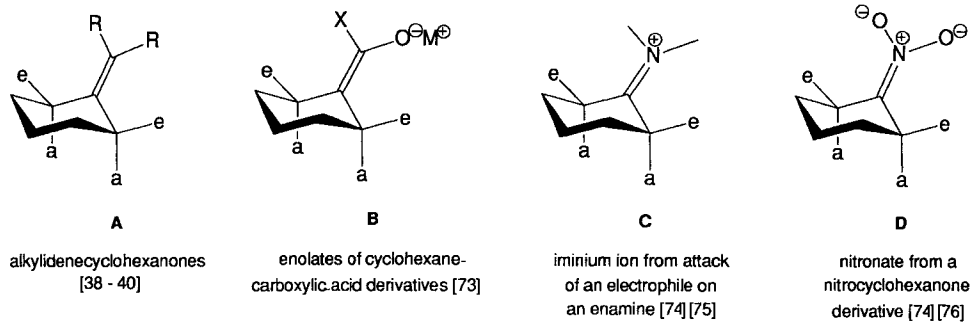

Fig. 20. *Dibromide* **20** *obtained from the corresponding saturated 6-methyl derivative by treatment with* N-*bromosuccinimide* [66] (*cf.* [67–69]). Compound **20** can be used for the preparation opf the Br-free dihydropyrimidinone (by catalytic hydrogenation). The short distances given in the MacMoMo presentation must be compared with the *van der Waals* radius of Br of 1.95 Å (for Me and $CH_2$ see *Fig. 16*). The atoms C(6), C(1′), and Br on C(1′) form a plane which is almost ($\tau$(C=C–C–Br) 81°, $\tau$(N–C–C–Br) 96°) perpendicular to the plane of the double-bond system; the C(5)–Br distance is 1.88 Å, the C(1′)–Br distance 2.02 Å. For a discussion of the structure of $\alpha$-halo-ketones (**20** is a vinylogous $\alpha$-bromo-lactam), see [70].

These cyclic acetals of $\beta$-amino-amides have sofa- (**16**, **17**, **20**) or twist-boat-like (**18**, **19**) conformations, where in **16** and **17** the N-atom bearing the exocyclic C=O group is the out-of-plane atom and in **20** the acetal C-atom, like in the O,O-cycles. But here, we have the astonishing feature of the *t*-Bu group in quasi-axial[12]) or quasi-flagpole position! In contrast to the five-membered ring analogs, the endo- and exocyclic amide moieties of the perhydropyrimidinones **16**–**19** are only slightly pyramidalized and twisted (compare

[12]) In their independent work on 2-(*tert*-butyl)-dihydropyrimidinones and -tetrahydropyrimidinones, *Konopelski* and coworkers presented evidence from NMR spectra for the presence of axial *t*-Bu groups [71] [72].

the $\Delta$ values for pyramidalization and $\tau$ for dihedral angles of twist in *Table 1*). The dibromo-dihydropyrimidin-4(1*H*)-one **20** is the most congested one in this series, with the $CH_2$-bonded Br-atom pushed right into the axial *t*-Bu group on one side of the ring. The torsional angles O–C–N–C(*t*-Bu) and (aryl)C–C–N–C($CH_2Br$) are 30° and 17°, respectively.

**4. Discussion and Conclusions.** – The origin of the difference between the heterocycles with and without *N*-acyl substituent described in the previous sections is the well known

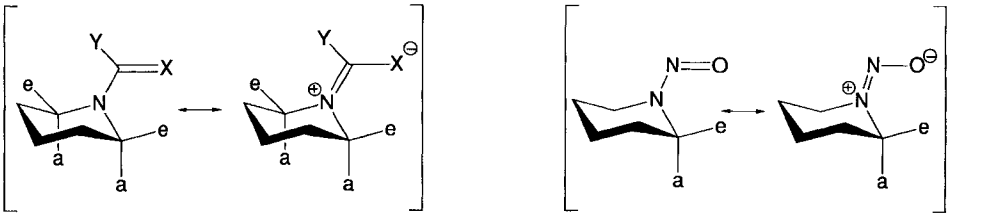


**A** alkylidenecyclohexanones [38 - 40]

**B** enolates of cyclohexane-carboxylic acid derivatives [73]

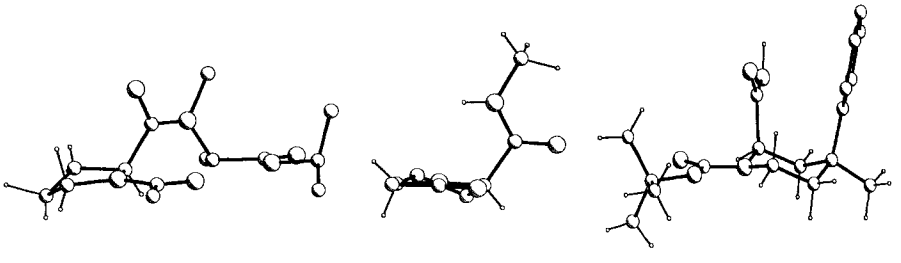
**C** iminium ion from attack of an electrophile on an enamine [74] [75]

**D** nitronate from a nitrocyclohexanone derivative [74] [76]



**E** *N*-acyl, *N*-thioacyl, *N*-amidino, *N*-carbamoyl, and *N*-alkoxycarbonyl derivatives of piperidine (amide, thioamide, amidine, urea and carbamate from piperidine) [77]

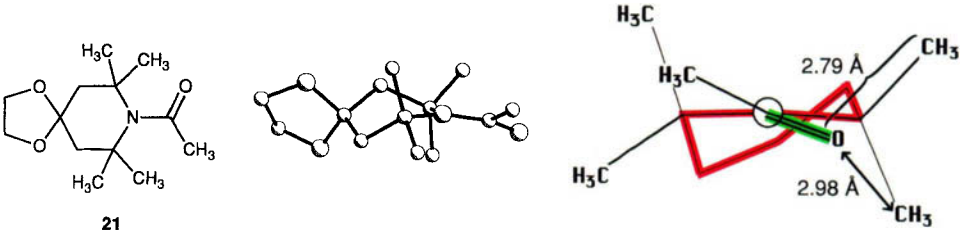
**F** nitrosopiperidine [78] (*cf.* triazines, hydrazones *etc.*)



**G** **H** **I**

Fig. 21. *Cyclohexane, piperidine, and pyrrolidine derivatives* **A**–**I**. In **A**–**F** and in **I**, $A^{1,3}$ strain places large substituents into axial positions of the six-membered rings. **G** and **H** are two typical conformations found in *N*-acylproline amides, the latter being just the simple *N*-acetylproline *N'*-methylamide (*CSD:* APROLM), the former a fraction of the dipeptide derivative Boc-Pro-MeAlaNH($CHMe_2$) (*CSD:* BABYAE). For *N*-acylproline esters, see *CSD ALPDLM and AMOLPR*. **I** shows the crystal structure of *N*-Boc-protected 4-methyl-4-phenyl-piperidine-2-carboxylic acid (*CSD:* DETBIN) with the typical axial disposition of the carboxylic group [77b] (for examples of other piperidine-2-carboxylic-acid derivatives, see also *CSD* DETBOT, CUPVEO, and JEBNUZ).

$A^{1,3}$ effect exerted by an amide group. This effect [38–40] has been studied in most detail with derivatives of six-membered rings (see the examples **A**–**F** and some leading ref. in the upper part of *Fig. 21*). The energy required to rotate an amide bond is 15–20 kcal·mol$^{-1}$, much larger than the conformational strain resulting, *e.g.*, by putting substituents in the axial position of a cyclohexane chair[13])[14]) or by converting a chair into a twist boat conformer[15]) (*cf.* the structure of the *N*-acetylpiperidine **21** with seven substituents on the piperidine ring in *Fig. 22*). The consequence of the $A^{1,3}$ strain caused by amide bonds is, of course, most important in determining the structure of peptides and proteins, see *e.g.*, the proline[16]) and piperidine-2-carboxylic-acid derivatives **G**–**I** (*Fig. 21*, bottom), and in the rotation around the amide C–N bond[17]) (*trans*/*cis* peptide-bond isomerization[18])) catalyzed by rotamase enzymes, which is the subject of intensive current research [88] [89].




**21**

Fig. 22. *Crystal structure of acetamide* **21** *obtained from the ethylene acetal of tetramethylpiperidin-4-one.* For derivatives of this amide with a sterically protected but electronically effective carbonyl group in synthesis, see [82]. The piperidinone ring of **21** is in a twist-boat-type conformation, thus avoiding $A^{1,3}$ strain more effectively than would be possible in a chair conformation. The twisting angle of the amide group is C–N–C–O 16° and C–N–C–$CH_3$ 28°; the pyramidalization $\Delta$ at the N-atom and the one on the carbonyl C-atom are both 0.04 Å. A similar structure of an *N*-acyltetramethylpiperidine has been published in this journal [83]. The structural features are very similar (*CSD:* DIWPUU).

The effect of *N*-acyl groups on the stereoselective reactions of our five- and six-ring acetals (*Schemes 1* and *2*), can be discussed with the help of the drawings **J**–**Q** in *Scheme 3*. The acyl group can be viewed as simply pushing the neighboring substituent(s) from the normally preferred equatorial (**J**, **M**, **O**) into an axial position of the ring, it causes an effective steric blocking of one of the ring faces (→ **K**, **N**). Especially in the five-membered

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[13]) See the so-called *A*-values for the preference of substituents in equatorial *vs.* axial position of cyclohexane and other six-membered rings [79].

[14]) For an excellent review article on hindered rotation, with > 300 references and a discussion of all known types of molecules studied, see [80].

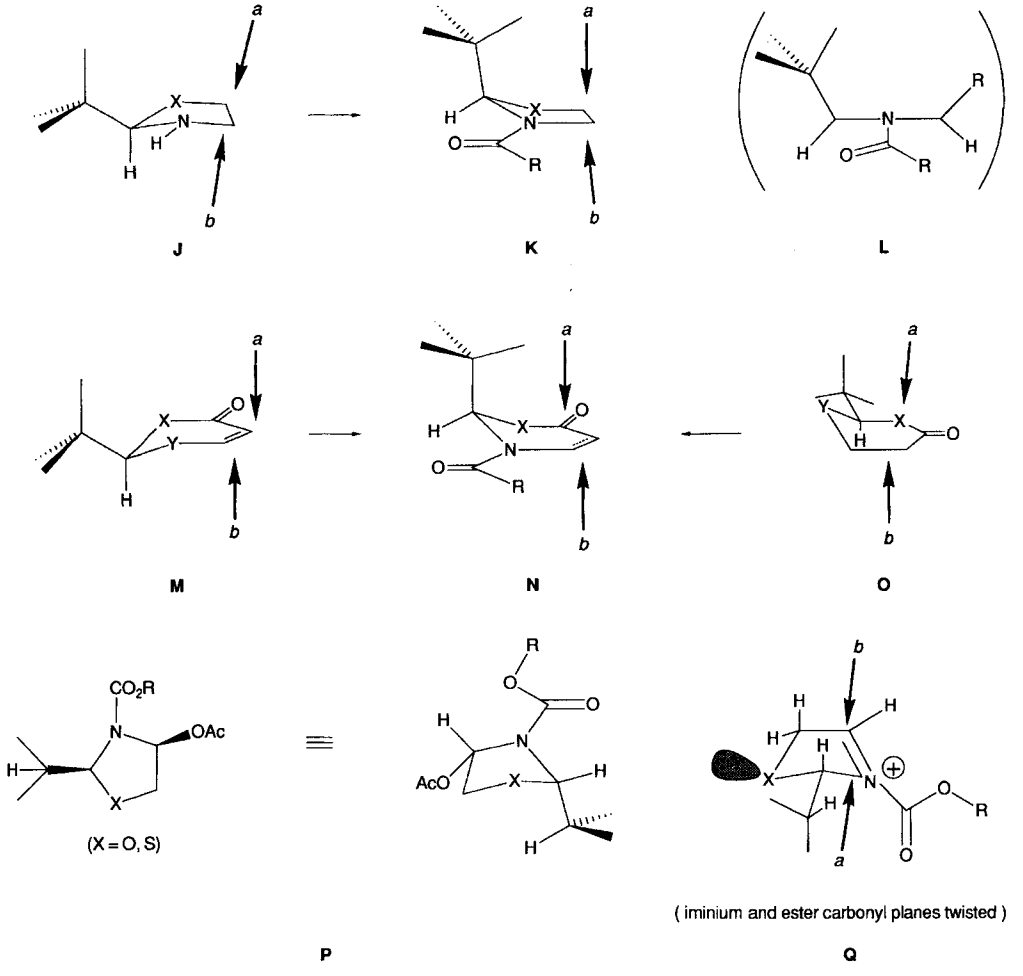
[15]) Difference of free enthalpy between chair and twist-boat of unsubstituted cyclohexane $\Delta\Delta G° = 5.5–8$ kcal·mol$^{-1}$ [81].

[16]) Analysis of pyrrolidine-ring conformations in prolyl peptides from $^{13}$C-NMR spin-lattice relaxation times [84].

[17]) A now classical investigation of the rotation around amide bonds is the structure determination of lactams with increasing ring size: with small rings, the amide bond is necessarily s-*cis*, and in large rings, it can adapt the more stable s-*trans*-conformation. In intermediate ring sizes, distortions are seen which probably resemble those occurring during rotation [85]. For a theoretical investigation about a correlation between amide distortion, charge distribution, and solvolysis rate, see [86].

[18]) See also the *trans*/*cis*-isomerization occurring in cyclosporine A upon incorporation of thioamide units [87a] and the *cis*/*trans*-isomerization upon complexation with LiCl [87b], or upon binding to cyclophilin [87c].

*Scheme 3*[a])




[a]) Acylated and non-acylated *t*-Bu-substituted five- and six-ring heterocycles with the face *cis* to the *t*-Bu group marked by *a* and the opposite face by *b*.

rings, pyramidalization of the amide N-atom (which becomes thereby a sterogenic center!) places the COR group on one face of the ring, with both the α- and the α′-substituent winding up on the other face (**L**).

The '*cis*-effect' [17] [18] [30] [34–36] [90–92] in reactions occurring through acyliminium ions (*i* in *Scheme 2*) may be due to the fact that the barrier to rotation around the N–CO bond is decreased in these ions (by *ca.* 65% according to *ab initio* calculations [93]), so that the substituent on the acetal center might be in an equatorial position, with the adjacent acyl group twisted out of plane (**P** and **Q** in *Scheme 3*)[19]).

[19]) For an alternative interpretation, see [35] [94].

The amide group as a structural element for controlling the stereochemical course of reactions is gaining more and more importance in organic synthesis involving pericyclic, nucleophilic, electrophilic, and radical reactions[20–27]). The structural investigation described here is a contribution towards a better understanding of these effects.

We thank Prof. *Jack D. Dunitz* for his critical and most valuable comments on the manuscript.

## Experimental Part

*General.* IR Spectra: *Perkin-Elmer-283* (KBr) and Perkin-Elmer-297 ($CHCl_3$). NMR Spectra: if not otherwise indicated, at r.t. in $CDCl_3$; *Varian EM-360*, *Varian EM-390*, and *Bruker WM 300* spectrometer; chemical shifts ($\delta$) in ppm rel. to internal TMS, coupling constants $J$ in Hz. MS: *Hitachi-Perkin-Elmer RMU-6M*.

*Syntheses.* The syntheses of *tert*-butyl (2*S*,5*S*,1′*S*)-2-(*tert*-butyl)-3-methyl-5-(nitroprop-2-yl)-4-oxoimidazolidine-1-carboxylate (**4**) [23], *tert*-butyl (2*R*,5*S*,1′*S*)-2-(*tert*-butyl)-5-(1′-hydroxybenzyl)-3-methylimidazolidine-1-carboxylate (**6**) [29], *tert*-butyl (2*R*,3′*S*,5*Z*)-2-(*tert*-butyl)-5-(3′-hydroxy-3′-phenylpropylidene)-3-methyl-4-oxoimidazolidine-1-carboxylate (**7**) [6], methyl (2*R*,4*R*,5*R*)-2-(*tert*-butyl)-4-hydroxy-5-(2-oxo-2-phenylethyl)-1,3-oxazolidine-3-carboxylate (**10**) [35], (4*R*,5*S*,8*R*)-8-(*tert*-butyl)-7-methyl-4-phenyl-3-oxa-1,7-diazabicylo[3.3.0]octan-2-one (**13a**) [29], methyl (4*R*,5*S*,8*R*)-8-(*tert*-butyl)-7-methyl-2-oxo-4-phenyl-3-oxa-1,7-diazabicylo[3.3.0]octane-5-carboxylate (**13b**) [29], *rac-cis*-2-(*tert*-butyl)-6-(trifluoromethyl)-1,3-dioxan-4-one (**14c**) [61], (2*S*,4a*S*,5*S*,8a*S*)-2-(*tert*-butyl)perhydro-4a,5-dimethyl-2*H*,4*H*-1,3-benzodioxin-4-one (**14d**) [62], *rac-trans*-2-(*tert*-butyl)-6-(trifluoromethyl)-1,3-dioxan-4-one (**14e**) [61], *rac*-1-benzoyl-2-(*tert*-butyl)tetrahydro-3-methylpyrimidin-4(1*H*)-one (**16**) [3], *rac-trans*-1-benzoyl-5-benzyl-2-(*tert*-butyl)tetrahydro-3-methylpyrimidin-4(1*H*)-one (**17**) [3], *rac*-1-benzoyl-*r*-2-(*tert*-butyl)tetrahydro-3,*t*-5,*c*-6-trimethylpyrimidin-4(1*H*)-one (**18**) [65], and *rac*-1-benzoyl-*t*-5-benzyl-*r*-2-(*tert*-butyl)-3,*c*-6-dimethylpyrimidin-4(1*H*)-one (**19**) [65] have been described in the lit. The synthesis of 8-acetyl-7,7,9,9-tetramethyl-1,4-dioxa-8-azaspiro[4.5]decane (**21**) was mentioned only in a short communication [83] and shall be described here in detail.

*(1R,6R)-6-Methyl-2-styryl-1,3-dioxan-4-one* (**14b**) was obtained following a published procedure for the preparation of dioxanones from unsaturated aldehydes [111]: a soln. of 943 mg (5.3 mmol) of cinnamic aldehyde dimethyl acetal and 530 mg (5.1 mmol) of (*R*)-3-hydroxybutyric acid in dry benzene (80 ml) was gently heated at reflux with stirring under Ar. The benzene/MeOH mixture was allowed to distill off slowly within 7 h. The remaining concentrated soln. of the dioxanone (*ca.* 3 ml) was cooled to −78° under Ar. The cooling bath was removed and the solvent evaporated. The solid residue was then immediately crystallized from $Et_2O$ under Ar. Most of the $Et_2O$ was removed by syringe, and the remaining traces of $Et_2O$ were removed by passing a fast stream of Ar. The crystals were dried under vacuum: 452 mg (41%) of **14b**. The dioxanone is stable when contact with moisture is prevented. $^1$H-NMR (300 MHz): 1.39 (*d*, $J$ = 6.1, Me); 2.46 (*dd*, $J$ = 17.7, 10.8, 1 H, $CH_2COO$); 2.72 (*dd*, $J$ = 17.7, 4.3, 1 H, $CH_2COO$); 4.15 (*m*, H–C(6)); 5.86 (*d*, $J$ = 5.3, H–C(2)); 6.20 (*dd*, $J$ = 16, 5.3, PhCH=C*H*); 6.86 (*d*, $J$ = 16, PhC*H*=CH); 7.25–7.42 (*m*, Ph).

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[20]) See 3-acyl-1,3-oxazolidin-2-ones as auxiliary groups for *Diels-Alder* [95] [96], aldol [97–99], *Claisen* [100], and acylation reactions [101].

[21]) See the chiral sultames used for overall enantioselective [3 + 2] cycloadditions [102], enolate reactions, and *Michael* additions [103].

[22]) For the use of 1-acyl-2-(methoxymethyl)- and 1-acyl-2,5-bis(methoxymethoxymethyl)pyrrolidines for enantioselective syntheses, see [104] [105].

[23]) For the different effects for formamidine and urethane groups in the alkylation of α-lithiopiperidines, see [106].

[24]) For the discovery of highly stereoselective radical reactions involving amide groups for fixing the conformations of reactands, see [107].

[25]) For the use of *Kemp* acid derivatives with amide structure for stereoselective [3 + 2] cycloadditions, see [108].

[26]) For the comparison of the *Eschenmoser-Meerwein*, *Irland*, and *Johnson* modifications of the *Claisen* rearrangement, see [109].

[27]) Many examples of such reactions are cited in recent review article [110] (see especially Scheme 26 therein).

Table 2. *Crystal Data of All New Structures*

| | **4** | **6** | **7** | **10** | **13a** | **13b** | **14b** | **14c** |
|---|---|---|---|---|---|---|---|---|
| Formula | $C_{16}H_{29}N_3O_5$ | $C_{20}H_{32}N_2O_3$ | $C_{22}H_{32}N_2O_4$ | $C_{17}H_{23}NO_5$ | $C_{16}H_{22}N_2O_2$ | $C_{18}H_{24}N_2O_4$ | $C_{13}H_{14}O_3$ | $C_9H_{13}F_3O_3$ |
| $M_r$ | 343.42 | 348.49 | 388.51 | 321.37 | 274.36 | 332.40 | 218.25 | 226.20 |
| $T$ | r.t. | r.t. | r.t. | r.t. | r.t. | r.t. | r.t. | 268 K |
| Crystal system | orthorhombic | monoclinic | monoclinic | monoclinic | orthorhombic | orthorhombic | monoclinic | orthorhombic |
| Space group | $P2_12_12_1$ | $P2_1$ | $C2$ | $P2_1$ | $P2_12_12_1$ | $P2_12_12_1$ | $P2_1$ | $Pna2_1$ |
| $a$ [Å] | 6.270(2) | 6.493(3) | 23.011(9) | 10.508 | 7.251(4) | 8.391(4) | 8.420(2) | 34.222(8) |
| $b$ [Å] | 10.528(5) | 11.621(7) | 9.775(3) | 6.024 | 10.218(5) | 9.696(5) | 16.066(5) | 5.944(2) |
| $c$ [Å] | 29.91(2) | 14.004(8) | 11.454(3) | 13.772 | 20.87(1) | 22.34(1) | 8.440(2) | 10.528(1) |
| $\alpha$ [°] | 90.00 | 90.00 | 90.00 | 90.00 | 90.00 | 90.00 | 90.00 | 90.00 |
| $\beta$ [°] | 90.00 | 92.84(4) | 117.56(3) | 101.98 | 90.00 | 90.00 | 95.63(2) | 90.00 |
| $\gamma$ [°] | 90.00 | 90.00 | 90.00 | 90.00 | 90.00 | 90.00 | 90.00 | 90.00 |
| $V$ [Å$^3$] | 1975. | 1055. | 2284. | 853. | 1546. | 1818. | 1136. | 2142. |
| $Z$ | 4 | 2 | 4 | 2 | 4 | 4 | 4 | 8 |
| $D_x$ [g cm$^{-3}$] | 1.16 | 1.10 | 1.13 | 1.25 | 1.18 | 1.21 | 1.28 | 1.40 |
| $F(000)$ | 744 | 380 | 840 | 344 | 592 | 712 | 464 | 944 |
| Unique reflect. | 1623 | 2708 | 2130 | 1787 | 2572 | 3086 | 3410 | 2765 |
| of which $I > 3\sigma$ | 771 | 2502 ( $> 2\sigma$) | 1431 | 1433 | 2060 ( $> 2\sigma$) | 2778 ( $> 2\sigma$) | 2586 | 1085 |
| Final $R$ value | 0.033 | 0.035 | 0.030 | 0.036 | 0.045 | 0.042 | 0.041 | 0.030 |

| | **14d** | **14e** | **16** | **17** | **18** | **19** | **20** | **21** |
|---|---|---|---|---|---|---|---|---|
| Formula | $C_{14}H_{24}O_3$ | $C_9H_{13}F_3O_3$ | $C_{16}H_{22}N_2O_2$ | $C_{23}H_{28}N_2O_2$ | $C_{18}H_{26}N_2O_2$ | $C_{24}H_{30}N_2O_2$ | $C_{17}H_{20}Br_2N_2O_2$ | $C_{13}H_{23}NO_3$ |
| $M_r$ | 240.34 | 226.20 | 274.36 | 364.49 | 302.42 | 378.51 | 444.17 | 241.33 |
| $T$ | r.t. | 193 K | r.t. | r.t. | r.t. | r.t. | r.t. | r.t. |
| Crystal system | monoclinic | orthorhombic | monoclinic | monoclinic | orthorhombic | monoclinic | monoclinic | triclinic |
| Space group | $P2_1$ | $Pbca$ | $P2_1/c$ | $P2_1/c$ | $Pbca$ | $P2_1/c$ | $P2_1/c$ | $P\bar{1}$ |
| $a$ [Å] | 6.572(1) | 8.677(3) | 8.448(2) | 11.590(2) | 20.712 | 8.311(2) | 9.911(6) | 6.190 |
| $b$ [Å] | 11.008(5) | 25.34(1) | 8.404(2) | 11.160(2) | 15.076 | 22.648(2) | 18.56(1) | 7.810 |
| $c$ [Å] | 10.377(4) | 20.234(6) | 21.390(3) | 15.891(3) | 10.807 | 11.782(3) | 9.711(6) | 14.423 |
| $\alpha$ [°] | 90.00 | 90.00 | 90.00 | 90.00 | 90.00 | 90.00 | 90.00 | 92.74 |
| $\beta$ [°] | 108.76(2) | 90.00 | 96.40(2) | 99.39(2) | 90.00 | 105.48(1) | 90.86(5) | 93.31 |
| $\gamma$ [°] | 90.00 | 90.00 | 90.00 | 90.00 | 90.00 | 90.00 | 90.00 | 109.52 |
| $V$ [Å$^3$] | 711. | 4449. | 1509. | 2028. | 3375. | 2137. | 1786. | 654. |
| $Z$ | 2 | 16 | 4 | 4 | 8 | 4 | 4 | 2 |
| $D_x$ [g cm$^{-3}$] | 1.12 | 1.35 | 1.21 | 1.19 | 1.19 | 1.18 | 1.65 | 1.22 |
| $F(000)$ | 264 | 1888 | 592 | 784 | 1312 | 816 | 888 | 264 |
| Unique reflect. | 1314 | 2858 | 2531 | 3552 | 4894 | 3146 | 4223 | 2304 |
| of which $I > 3\sigma$ | 734 | 1891 | 1294 | 1922 | 1814 | 1978 ( $> 4\sigma$) | 1771 | 743 |
| Final $R$ value | 0.030 | 0.038 | 0.042 | 0.041 | 0.049 | 0.052 | 0.058 | 0.12 |

rac-*1-Benzoyl-5-bromo-6-(bromomethyl)-2-(*tert*-butyl)-3-methyl-2,3-dihydropyrimidin-4(1*H*)-one* (**20**) was prepared according to the procedure for the bromination of **14a** [66]: in a 25-ml round-bottom flask provided with condenser and magnetic stirrer, 245 mg (0.8 mmol) of *rac-cis*-1-benzoyl-2-(*tert*-butyl)tetrahydro-3,6-dimethylpyrimidin-4(1*H*)-one [65], 0.39 g (2.2 mmol) of *N*-bromosuccinimide, one drop of *tert*-butyl hydroperoxide, and 10 ml of $CCl_4$ were placed. The mixture was heated at reflux for 10 h, and then filtered and evaporated: 270 mg of crude product. Partial purification was accomplished by gradient flash chromatography (hexane/AcOEt 99:1→80:20): 250 mg of 65:35 mixture of mono- and dibrominated products. Slow crystallization afforded 55 mg (16% yield) of **20**. Cubic crystals. M.p. 151.0–151.5°. X-Ray analysis confirmed the proposed structure. $^1$H-NMR (60 MHz) 1.15 (*s*, *t*-Bu); 3.27 (*s*, MeN); 3.60 (*d*, $J_{gem}$ = 12, 1 H, $CH_2Br$); 4.37 (*d*, $J_{gem}$ = 12, 1 H, $CH_2Br$); 5.58 (*s*, H–C(2)); 7.60 (*m*, Ar). $^{13}$C-NMR (22.49 MHz): 26.77; 29.88; 38.18; 39.35; 79.57; 112.68; 127.69; 129.16; 132.13; 134.81; 141.49; 158.70; 170.02.

*8-Acetyl-7,7,9,9-tetramethyl-1,4-dioxa-8-azaspiro[4.5]decane* (**21**). In a round-bottom flask, 3.7 ml (51.8 mmol) of AcCl were dissolved in 120 ml of benzene, and at 0°, 20.0 g (100.4 mmol) of 2,2,6,6-tetramethylpiperidin-4-one ethylene acetal [112] were slowly added. The resulting mixture was stirred at r.t. for 3 d, the solid residue filtered off and washed with pentane. The combined org. phases were washed three times with 0.1N HCl, two times with sat. $Na_2CO_3$ soln. and once with $H_2O$. Drying ($MgSO_4$) and evaporation yielded 10.0 g (80%) of a slowly crystallizing oil, which was purified by distillation. B.p. 90–100°/0.02 Torr. M.p. 49° (pentane). IR (KBr): 2975, 2935, 2880, 1630, 1465 (br), 1415, 1400, 1385, 1370, 1360, 1335, 1285, 1140, 1110, 1035, 1020, 980, 945, 930, 836, 800. IR ($CHCl_3$): 2975, 2940, 2885, 1630–1610, 1455, 1370, 1340, 1130, 1105, 1030, 1015. $^1$H-NMR (90 MHz): 1.47 (*s*, 2 Me–C(7), 2 Me–C(9)); 2.06 (*s*, 2 H–C(6), 2 H–C(10)); 2.16 (*s*, Ac); 3.89 (*s*, $OCH_2CH_2O$). $^{13}$C-NMR (r.t.): 28.27 (*q*, $CH_3CO$); 29.97 (*q*, 2 $CH_3$–C(7), 2 $CH_3$–C(9)); 49.29 (*t*, C(6), C(10)); 55.90 (*s*, C(7), C(9)); 63.71 (*t*, $OCH_2CH_2O$); 105.75 (*s*, C(5)); 173.57 (*s*, $CH_3CO$). $^{13}$C-NMR ($CD_2Cl_2/CF_2Br_2$ 1:3, $T = -120°$): 25.98 (br.); 27.14 (br.); 28.43, 31.09 (br.); 33.70 (br.); 47.91 (br.); 49.34 (br.); 54.86, 57.26, 63.78 (br.); 105.49; 173.82. MS: 241 (2, $M^+$, $C_{13}H_{23}NO_3$), 227 (10), 226 (65), 184 (53), 170 (9), 140 (6), 128 (12), 127 (73), 100 (12), 98 (100), 87 (21), 86 (13), 84 (11), 58 (13), 55 (13), 43 (32), 42 (21), 41 (12). Anal. calc. for $C_{13}H_{23}NO_3$ (241.33): C 64.70, H 9.61, N 5.80; found: C 64.59, H 9.59, N 5.77.

*X-Ray Analyses*. The data were collected on *Enraf-Nonius-CAD-4* (**4**, **7**, **10**, **14b–e**, **16–19**, and **21**), and *Picker-Stoe* (**6**, **13a, b**, and **20**) diffractometers (in all cases Mo$K_\alpha$ radiation, $\lambda$ = 0.71069 Å, graphite monochromator). The structures were solved by direct methods using the programs MULTAN 11/84 [113] (**19**), SHELX76 [114] (**21**), and SHELXS86 [114] (all other structures) and refined using the program SHELX76. Space groups, cell constants, number of reflections measured, and final *R* values are collected in *Table 2*. If not mentioned otherwise, refinement was achieved using reflections with intensity $I > 3 \cdot \sigma(I)$, where the non-H-atoms were refined anisotropically, H-atoms isotropically. Only for the structure determination of **20**, an empirical absorption correction was used.

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