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IMINOETHERS—III

TETRACYCLIC QUINAZOLONES DERIVED FROM CYCLODIPEPTIDE MONO IMINOETHERS[a,b]

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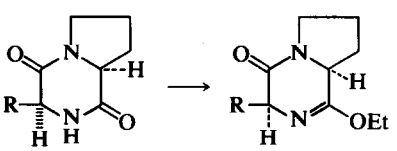
Abstract—Iminoethers derived from a series of prolyl diketopiperazines have been reacted with anthranilic acid to produce tetracyclic quinazolones. It has been shown that the two diastereomeric iminoethers derived from cyclo (L-Pro-L-Val) and cyclo (L-Pro-D-Val) lead to enantiomeric products with the two hydrogens at the asymmetric C atoms oriented *trans* to each other.

Although imine-enamine tautomerism is well-authenticated,[1,2] definite evidence regarding the existence of the corresponding two forms of iminoethers is available in just one case.[3,†] Indirect evidence has recently been adduced for the existence of the enamine form of iminoethers.[4] This is mainly based on UV and NMR data, and is valid only for the solvents used, namely, water or alcohol.

We have now prepared iminoethers with an asymmetric β-carbon in optically active forms (**2a** to **c**), where one nitrogen is tertiary (derived from proline) and the other secondary.



1 **2**

a **b** **c**

R = H, $CH{:}Me_2$, $CH_2{-}CH{=}Me_2$

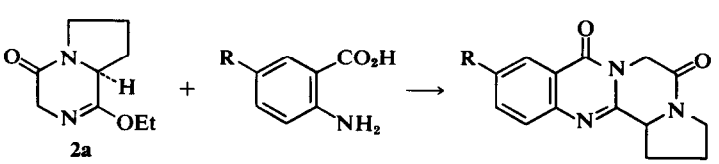
All amino acids used are from the natural series.

Since the iminoether (**2a**) possesses only one asymmetric centre, situated adjacent to the imino-ether carbon, it was an ideal substrate for carrying out racemization experiments. The compound has been shown not to lose its optical integrity on thermolysis (120°/2 hr); however, as expected, it racemised rapidly on acid-catalysis.[1] The significance of these results in terms of the mechanism of tautomerisation has already been discussed.[1]

The present study concerns the reaction of these iminoethers with various anthranilic acids to produce tetracyclic quinazolones. Initially the iminoether (**2a**) was reacted with the two anthranilic acids (**3** and **4**). The chloro anthranilic acid (**4**) reacted in refluxing methanol to give the quinazolone (**6**). However, under these conditions the unsubstituted anthranilic acid did not react; reaction could be achieved by heating the reactants together, without solvent, at 120° for 2 hr.

However, the product (**5**) in the latter instance was totally racemic. Two explanations suggest themselves: racemization of the iminoether could have been brought about by catalysis by anthranilic acid prior to reaction, or racemization could have taken place after quinazolone formation. That the latter was also a valid route to the loss of optical activity was demonstrated as follows: Compound **6**, as soon as it was prepared, had a specific rotation of +156° in DMF; but when the DMF solution was left at room temperature for 24 hr, the rotation was zero.

This facile racemization suggests that the reaction of iminoethers having two asymmetric



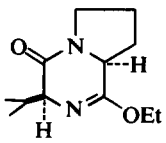
2a

3: R = H
4: R = Cl

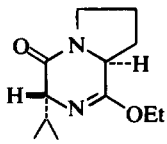
5: R = H
6: R = Cl

[a]Contribution No. 287 from CIBA Research Centre.
[b]For Part II, see ref. 1.
†For a possible explanation of the facile tautomerisation in this case, see Ref 1.

centres (as in 2b or 2c) with anthranilic acid might produce diastereomeric mixtures of quinazolones. In order to shed light on this problem, we have prepared the diastereomeric pair of iminoethers (7 = 2b and 8), and investigated their reaction with anthranilic acid.



7 (= 2b)



8

Compound 7 was prepared from the diketo piperazine derived from L-valine and L-proline. It had $[\alpha]_D = -97{\cdot}2°$ (EtOH); (8) was similarly obtained from the diketopiperazine derived from D-valine and L-proline. It had $[\alpha]_D = -61{\cdot}1°$ (EtOH). The NMR spectra of the two show significant differences attributable to the difference in their stereochemistry.

The iminoether (7) was first reacted with anthranilic acid. Two products were obtained which were separated by fractional crystallisation. The higher-melting product A was the minor component, while the lower-melting product B was the major one. Reaction of the diastereomeric iminoether (8) with anthranilic acid under the same conditions produced only one product C. The physical data for these compounds is presented in Table 1.

Table 1.

	A	B	C
m.p.	175–180°	127–130°	127–129°
$[\alpha]_D$ (DMF)	0	+178·5°	−178°

The IR spectra of B and C were identical, as were their NMR spectra. They had identical mobility on TLC. In the NMR, especially, one notes that the signals due to the protons attached to the two asymmetric centres can be easily discerned and identified (discussion of the chemical shift is deferred to a later section); the lack of any difference in the signal shape or chemical shift proves that the relative stereochemistry is the same in both B and C. Further, a mixture of equal quantities of B and C, on recrystallisation, gave a product, melting at 179–181°, which appeared to be identical with A.

The data presented above suggests strongly that, although the starting iminoethers (7 and 8) are diastereomeric, *the products* B and C are enantiomeric; further, the minor, high-melting product A appears to be the corresponding racemic form. As a further check on this, the C.D. curves of B and C were recorded through the kind courtesy of Prof. W. Klyne. The curves were nearly enantiomeric in shape but not precisely in magnitude (the differences are, most probably, not significant, and might be attributable to the presence of small quantities of A in this sample of B). (Table 2).

Table 2.

	Δε	(nm)
B	+1·73 sh	318
	+1·88 m	305
	−1·26 m	265
	+14·6 m	232
	−7·08 m	212
C	−1·64 sh	317
	−1·92 m	306
	+1·64 m	268
	−17·5 m	229
	+9·85 m	212

Assuming then, that B and C are truly enantiomeric, the relative configuration of the hydrogens at the two asymmetric centres can be either *cis* or *trans* in both. In the following discussion, the symbol V is used to denote the asymmetric centre in the valine part of the molecule and P to denote that associated with proline. It is obvious that in the formation of either B or C, there has to take place epimerization at just *one* centre to make the products enantiomeric; such a centre is indicated by an asterisk.

Table 3. Starting materials for B: L-V amd L-P. Starting materials for C: D-V and L-P.

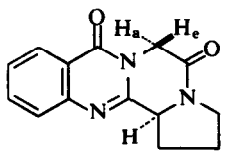
Relative configuration	*Product configuration* B	C
cis	L-V, L-P*	D-V, D-P*
trans	L-V, D-P*	D-V, L-P*

Inspection of Table 3 shows that whichever possibility is correct, *it has to involve epimerisation at the proline centre*. This, of course, is entirely in line with our experience on the racemization of (5) and (6).

We believe that the products have the *trans* relative configuration for the following reasons: Formation of the racemic product A along with B would involve simultaneous inversion of both centres if it had to have a *cis* configuration; but a *trans* configuration would demand only epimerization at one centre at a time (L-V, D-P* + D-V, L-P*). A weightier reason emerges from an inspection of models. In the product with a *cis* configuration of the two hydrogens at the asymmetric centres, one

notices a pronounced steric interaction between the methyl groups of the valine moiety and the carbonyl group of the quinazolone. Such an interaction does not exist in the *trans* configuration.

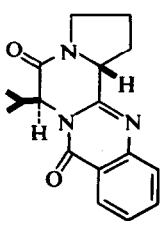
An even more convincing argument for the assignment of a *trans* configuration arises from a comparison of the NMR chemical shifts of the glycyl methylene protons of compound **5** with the chemical shift of the proton belonging to the valine moiety in B or C. In **5**, ring C is in a rigid boat-like conformation; one of the two geminal protons of the glycine unit is almost in the plane of the quinazolone ("equatorial", H_e) whereas the other is perpendicular to the plane ("axial", H_a). In the NMR spectrum, the two occur as doublets due to geminal coupling (J = 16·5 c/s), but there is a large chemical shift difference between them—the two are centred at 5·30 and 4·08 ppm. The lower field signal should undoubtedly be ascribed to H_e since this would be strongly deshielded by the adjacent, parallel, carbonyl of the quinazolone.



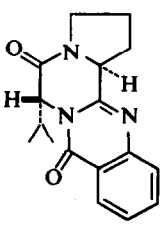
H_e: 5·30 ppm
H_a: 4·08 ppm
J_{H_e,H_a} = 16·5 cps

In the NMR spectra of both B and C, the hydrogen associated with the valine moiety occurs as a doublet due to vicinal coupling (J = 8·5) centred at 5·28 ppm. This undoubtedly means that this hydrogen occupies the "equatorial" position in both, and consequently, the isopropyl group has to be "axial". This situation represents the *trans* relative configuration of the hydrogen atoms attached to the two asymmetric centres.

Our conclusions then are that B and C can be represented by the formulae **9** and **10** respectively.



9: (= B)



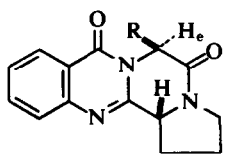
10: (= C)

The question now remains whether the products (**9**) and (**10**) represent the thermodynamically more stable configurations. An alternate, although remote, possibility is that this selective obtention of the *trans* products might have been achieved during crystallisation. If the latter were the case, then one might expect the compounds to exhibit mutarotation under conditions where the quinazolone (**6**) has been shown to racemise rapidly. In the event, the specific rotation of both the compounds showed no change over a period of 24 hr in DMF solution.

To summarise, the iminoether derived from cyclo (L-Val-L-Pro) produces a tetracyclic quinazolone in which the proline centre has epimerised, so that the product has the S configuration at the valine centre, but an R configuration at the proline unit. Such a *trans* configuration results directly from cyclo (D-Val-L-Pro) without any need for epimerisation. The two products are therefore enantiomeric.

It only remains to be pointed out that in every case where a bicyclic iminoether of type (**2b**) has been reacted with anthranilic acid, the product **11** appears to bear the *trans* stereochemistry as revealed by the NMR chemical shift of the relevant proton (Table 4). The absolute configuration of the products would be as shown in **11** if one starts with amino acids of the L-series.

Table 4.



11

	R	Chemical shift of H_e
a	—Me	5·52 (quartet)
b	—CH_2—CH=Me_2	5·58 (triplet)
c	—CH(Me)(Et)	5·33 (doublet)

EXPERIMENTAL

M.ps are uncorrected. NMR spectra were taken in an A-60 instrument; values given are in ppm downfield from TMS.

Preparation of diketopiperazines. These were prepared by the standard route;[5] condensation of the appropriate carbobenzoxy amino acid with proline methyl ester (DCCI) was followed by hydrogenolysis of the protecting group, resulting in cyclisation. Cyclo (D-Val-L-Pro) had $[\alpha]_D = -97·3°$ (*c*, 1·7 in water).

Preparation of the iminoethers. To a stirred soln of 0·1 mole of the diketopiperazine in dry CH_2Cl_2 (100 ml) was added in drops, a soln of 0·12 mole freshly prepared, anhydrous, Meerwein's reagent in dry CH_2Cl_2. Stirring was continued overnight, after which it was decomposed by careful addition of a soln of K_2CO_3 (13·8 g) in water (28 ml). The CH_2Cl_2 soln was decanted, and the slurry washed with more CH_2Cl_2. The combined CH_2Cl_2 soln was dried and evaporated *in vacuo*. The residue was digested with hexane and any insoluble material filtered

off. Evaporation of the filtrate gave the iminoether which was then distilled *in vacuo*.

Iminoether	B.p.	$[\alpha]_D$ (EtOH)
2a	138–140°/3–4 mm	−122°
2b	135–140°/1 mm	−97·2°
2c	150–154°/1 mm	−56·7°
8	145–148°/2 mm	−61·1°

Product quinazolones

(i) 10-*Chloro*-5,8-*dioxo*-1,2,3,5,6,13b-*hexahydro*-8H-*pyrrolo*[1.2-a]*pyrazino*[3.4-b]*quinazoline* (**6**). The iminoether **2a** (4·2 g) was refluxed with **4** (4·2 g) in MeOH (50 ml) for 15 hr. The solvent was evaporated *in vacuo*, the residue digested with aqueous ammonia, cooled and filtered. The solid (3·0 g) was recrystallised from MeOH to give the **6**, m.p. 219–223°. (Found: C, 57·86; H, 4·42; N, 14·46. $C_{14}H_{12}ClN_3O_2$ requires: C, 58·03; H, 4·18; N, 14·50%).

(ii) 5,8-*Dioxo*-1,2,3,5,6,13b-*hexahydro*-8H-*pyrrolo*[1.2-a]*pyrazino*[3.4-b]*quinazoline* (**5**). A mixture of **2a** (3·0 g) and anthranilic acid (2·5 g) was heated in an oil-bath at 120° for 2 hr under N_2. The melt was cooled, digested with aqueous ammonia and extracted with chloroform. The organic layer was dried, evaporated, and the residue passed through a short column of alumina in chloroform. After evaporation of the eluate, the product was crystallised from EtOAc-hexane to give the **5** (0·8 g), m.p. 188–190°. (Found: C, 66·08; H, 5·32; N, 16·22. $C_{14}H_{13}N_3O_2$ requires: C, 65·87; H, 5·13; N, 16·46%).

6(S), 13b(R)-5,8-*Dioxo*-1,2,3,5,6,13b-*hexahydro*-6-*isopropyl*-8H-*pyrrolo*[1.2-a]*pyrazino*[3.4-b]*quinazoline* (**9**). A mixture of **2b** (6·0 g) and anthranilic acid (3·8 g) was heated on an oil-bath at 130° for 1 hr under N_2. The melt was cooled, basified with ammonia and extracted with chloroform. The organic layer was washed with water, dried and evaporated. The residue was passed through alumina in benzene-hexane (1:1). Evaporation of the eluate left an oil which was dissolved in ether and left for some time. The less soluble racemic form (A) separated out first and was filtered off (m.p. 175–180°). The filtrate was concentrated and again let stand to remove any more racemic material. The process was repeated until all the higher-melting form had been removed. Finally the ether solution was treated with hexane and allowed to crystallise, **9** was deposited as stout needles, m.p. 127–130° (1·5 g). (Found: C, 68·52; H, 6·48; N, 14·33. $C_{17}H_{19}N_3O_2$ requires: C, 68·66; H, 6·44; N, 14·13%).

6(R), 13b(S)-5,8-*Dioxo*-1,2,3,5,6,13b-*hexahydro*-6-*isopropyl*-8H-*pyrrolo*[1.2-a]*pyrazino*[3.4-b]*quinazoline* (10). A mixture of **8** (22·0 g) and anthranilic acid (13·7 g) was heated at 130° for 1 hr under N_2 and worked up as before. In this case no racemic (higher melting) product could be isolated. The quinazolone (**10**) crystallised from EtOAc-hexane (5·3 g), m.p. 127–129°. (Found: C, 68·46; H, 6·64; N, 14·08. $C_{17}H_{19}N_3O_2$ requires: C, 68·66; H, 6·44; N, 14·13%).

The racemic form (A). 100 mg each of **9** and **10** was dissolved in EtOAc and mixed together. The racemate crystallised from the EtOAc soln, m.p. 179–181°.

The quinazolone (**11a**). The iminoether in this case was not distilled; the crude liquid (10·5 g) was reacted with anthranilic acid (7·0 g) and worked up in the usual way, to give **11a** (1·5 g), m.p. 161–164° from EtOAc-hexane. (Found: C, 67·09; H, 5·72; N, 15·31. $C_{15}H_{15}N_3O_2$ requires: C, 66·90; H, 5·61; N, 15·61%).

The quinazolone (**11b**). The iminoether (**2c**) (7·0 g) was reacted as usual with anthranilic acid (4·0 g) to give **11b**, m.p. 180–183° (2·3 g), after crystallisation from EtOAc-hexane. (Found: C, 69·65; H, 6·95; N, 13·17. $C_{18}H_{21}N_3O_2$ requires: C, 69·43; H, 6·80; N, 13·50%).

The quinazolone (**11c**). The corresponding crude, undistilled iminoether (11·5 g), (derived from L-Proline and L-Isoleucine) was reacted as usual with anthranilic acid (6·8 g) to give, after crystallisation from ether-hexane, the quinazolone (**11c**) (2·2 g), m.p. 131–134°. (Found: C, 69·11; H, 6·86; N, 13·27. $C_{18}H_{21}N_3O_2$ requires: C, 69·43; H, 6·80; N, 13·50%).

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