Conformational Studies on Tricyclic Quinazolones derived from Cyclodipeptides incorporating Sarcosine

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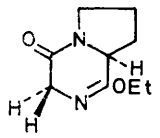
Ring C of the tricyclic quinazolone 2-methyl-1,2-dihydropyrazino[2,1-*b*]quinazoline-3(4*H*),6-dione (VII) has conformational flexibility. However, introduction of a 4-methyl group as in (IX) locks the molecule in the conformation in which the 4-methyl group is axial.

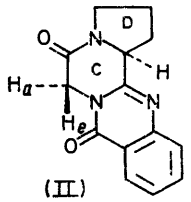
We have been studying the stereochemistry of quinazolones obtained by condensation of anthranilic acid with cyclodipeptide mono-imino-ethers. Such compounds can formally be regarded as anhydro-cyclic tripeptides in which one of the amino-acids is anthranilic acid. We have previously shown [1] that in the tetracyclic quinazolone (II), derived from *cyclo*(-Gly-L-Pro-) [*via* reaction of the imino-ether (I) with anthranilic acid] the chemical shifts of the two protons H_e and H_a differ

[1] S. Rajappa and B. G. Advani, *Tetrahedron*, 1973, **29**, 1299.

by more than 1·2 p.p.m. The lower field signal was assigned to H_e * since it was expected to be deshielded by the carbonyl group of the quinazolone. The molecule



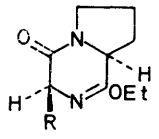
(I)



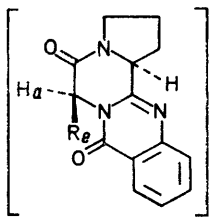
(II)

H_e δ 5·30
H_a δ 4·08

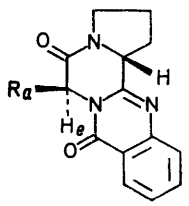
is rigid, since the 5-membered ring D does not permit conformational mobility in ring C. If glycine is replaced by another amino-acid belonging to the natural (L) series, the starting imino-ether is (III). However, instead of leading to the product (IV) with an equatorial alkyl substituent, reaction with anthranilic acid gives the diastereoisomer (V). Thus the situation with the substituent in



(III)



(IV)

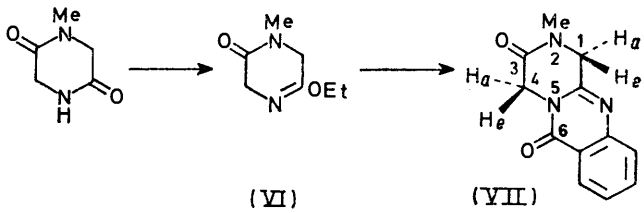


(V)

the equatorial position is so unfavourable that the proline centre epimerises: this is the only way in which ring C can change its conformation to permit R to occupy the axial position.

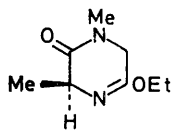
The question remains, however, whether the energy difference between the R_e and R_a forms would be so significant as to force the molecule exclusively to the R_a form. We have investigated this by removing ring D, thereby permitting flexibility to ring C. We now report the results of our studies on the conformation of such compounds.

The starting materials could be prepared from cyclodipeptides in which one of the amino-acid units is sarcosine. *cyclo*(-Sar-Gly-) gave the tricyclic quinazolone (VII) *via* the imino-ether (VI). Unfortunately, owing to the insolubility of the compound in $CDCl_3$, the n.m.r. spectrum was recorded in $(CD_3)_2SO$. However, the glycyl protons (4-H_a and 4-H_e) as well as the sarcosyl protons (1-H_a and 1-H_e) occur as two narrowly separated singlets at δ 4·62 and 4·57. For the glycyl protons, this value is obviously the time-averaged mean between the values δ 5·30 and 4·08 observed for (II), thus proving conformational mobility. The situation is essentially the same in C_5D_5N solution.

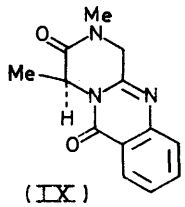


(VI) (VII)

We next determined the effect of introducing an alkyl group in ring C next to the carbonyl group. This was accomplished by taking the dioxopiperazine derived from L-alanine and sarcosine, converting it into the imino-ether (VIII), and treating this with anthranilic acid to give (IX). The product was optically active, $[\alpha]_D$ +149° (EtOH).

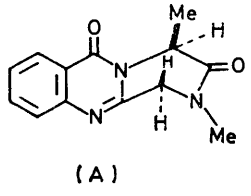


(VIII)

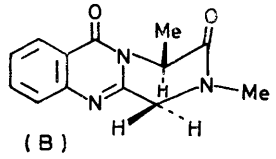


(IX)

Models indicate that this compound can exist in two conformers (A) and (B). In conformation (A), the methyl group derived from alanine is axial, whereas in (B) it is equatorial. If there were a rapid equilibration between (A) and (B) at room temperature, one would expect that the proton derived from alanine would resonate at δ *ca.* 4·60 as in (VII).



(A)



(B)

However, in $CDCl_3$, the compound is seen to exist almost 100% in the form (A). The H_e of alanine occurs as a quartet centred at δ 5·39; further, the CH_2 protons of sarcosine now form an AB quartet (J 17 Hz) at δ 4·85 and 4·36. The corresponding figures in $(CD_3)_2SO$ solution at room temperature are H_e (δ 5·14) and CH_2ABq (δ 5·07 and 4·44). In an attempt to estimate the energy barrier to the conformation change from (A) to (B), the spectrum was recorded in $(CD_3)_2SO$ at 150°. We expected the following changes as conformational equilibrium was established: (i) an upfield shift of the alanine quartet to δ *ca.* 4·60 and (ii) coalescence of the AB quartet of sarcosine. However, the spectrum was essentially unchanged even at 150°. We therefore conclude that the introduction of a single methyl group in (VII) [to give (IX)]

* In this paper, equatorial (*e*) represents a substituent (or hydrogen) in the plane of the aromatic rings; axial (*a*) represents a substituent (or hydrogen) in the plane perpendicular to the aromatic rings.

forces the molecule into that conformation in which the methyl group can occupy the axial position. Both in (IV) and in (IXB), the quinazolone carbonyl–equatorial alkyl interaction is apparently extremely severe. As a consequence, (IXB) flips to (IXA), whereas (IV) is forced to epimerise to give (V).

EXPERIMENTAL

N.m.r. chemical shifts are expressed in p.p.m. downfield from internal Me_4Si.

Dioxopiperazines.—These were prepared by the general procedure outlined by Grahl-Nielsen.[2]

cyclo(-L-*Ala*-*Sar*-). *N*-Benzyloxycarbonyl-L-alanine was coupled with sarcosine methyl ester (dicyclohexylcarbodiimide method). The oily dipeptide was deprotected by hydrogenolysis in methanol solution. Evaporation of the solvent gave 1,3-*dimethylpiperazine*-2,5-*dione* which was crystallised from acetone–ether, m.p. 124—126°, $[\alpha]_D$ −10·85° (*c* 2 in water) (Found: C, 50·7; H, 7·4; N, 20·05. $C_6H_{10}N_2O_2$ requires C, 50·7; H, 7·1; N, 19·7%).

Imino-ethers.—The general method of preparation of these peptide imino-ethers has been given in ref. 1.

5-*Ethoxy*-1-*methyl*-3,6-*dihydropyrazin*-2(1H)-*one* (VI). *cyclo*(-Gly-Sar-) [3] (26 g) gave the imino-ether (VI) (10 g), b.p. 135—138° at 4—5 mmHg.

(3S)-5-*Ethoxy*-1,3-*dimethyl*-3,6-*dihydropyrazin*-2(1H)-*one*. *cyclo*(-L-Ala-Sar-) (20 g) gave the imino-ether (VIII) (12 g), b.p. 100° at 2 mmHg. The solid distillate was crystallised from hexane to give *needles*, m.p. 65—68°, $[\alpha]_D$ +9·65 (*c* 2 in EtOH) (Found: C, 56·45; H, 8·5; N, 16·7. $C_8H_{14}N_2O_2$ requires C, 56·45; H, 8·3; N, 16·45%).

2-*Methyl*-1,2-*dihydropyrazino*[2,1-b]-*quinazoline*-3(4H),6-*dione* (VII).—A mixture of the imino-ether (VI) (4·0 g) and anthranilic acid (3·5 g) was heated on an oil-bath at 150° under nitrogen for 0·5 h. After cooling, the mixture was basified with ammonia and extracted with chloroform. The chloroform layer was washed with water, dried, and evaporated at reduced pressure. The residual solid was crystallised from chloroform–hexane to give the *quinazolone* (VII) (1·9 g), m.p. 219—223° (Found: C, 62·75; H, 4·75; N, 18·55. $C_{12}H_{11}N_3O_2$ requires C, 62·85; H, 4·85; N, 18·35%).

(4S)-2,4-*Dimethyl*-1,2-*dihydropyrazino*[2,1-b]*quinazoline*-3(4H),6-*dione* (IX).—A mixture of the imino-ether (VIII) (10·0 g) and anthranilic acid (7·5 g) was heated at 120° under nitrogen for 1 h. After cooling, the melt was dissolved in water, basified with ammonia, and extracted with ethyl acetate. The organic layer was washed with water, dried and evaporated. The residue was crystallised from ethyl acetate–hexane to give the *quinazolone* (IX) (5·1 g), m.p. 153—156° $[\alpha]_D$ +149·25° (*c* 2 in EtOH) (Found: C, 64·0; H, 5·25; N, 17·15. $C_{13}H_{13}N_3O_2$ requires C, 64·2; H, 5·4; N, 17·3%).

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[2] O. Grahl-Nielsen, *Tetrahedron Letters*, 1969, 2827.

[3] L. Birkofer, A. Ritter, and P. Neuhausen, *Annalen*, 1962, **659**, 190.