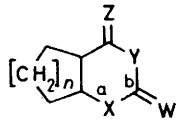
Stereochemical Studies. Part 30.[1,2] Synthesis and Conformational Analysis of Deca- and Dodeca-hydropyrido[2,1-*b*]quinazolin-11-ones

By **Gábor Bernáth,*† Gábor Tóth, Ferenc Fülöp, György Göndös,** and **Lajos Gera,** Institute of Organic Chemistry, József Attila University, H-6720 Szeged, Dóm tér 8, and † Institute of Organic Chemistry, Faculty of Pharmaceutical Sciences, Semmelweis Medical University, 1092 Budapest, Hungary

cis- and *trans*-Decahydro- and dodecahydro-pyrido[2,1-*b*]quinazolin-11-ones have been synthesized and their preferred conformations established by ^{1}H n.m.r. spectroscopy. At room temperature the A and B rings of the *cis*-decahydro derivatives are conformationally mobile, while the t-butyl derivatives have fixed conformations. The predominant conformation of the *cis*-dodecahydro-derivatives is that in which the C=O group is equatorial, the N atom is axial, and the configuration of the nitrogen bridgehead B/C fusion is *trans*.

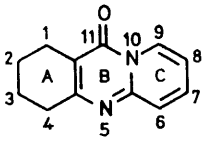
In connection with the reactions of 1,3-difunctional alicyclic systems, we have already reported the stereospecific synthesis and conformational study of various bicyclic saturated heterocyclic systems of the type (1)



(1)

n = 1, 2, or 3

cis or *trans*



(2)

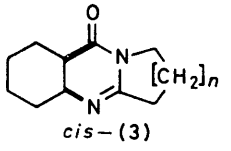
	X	Y	W	Z
a;	O	NH	Ar, H	H_2
b;	NH	O	Ar, H	H_2
c;	O	N	Ar	H_2
d;	N	O	Ar	H_2
e;	O	NH	O	H_2
f;	NH	O	O	H_2
g;	O	NH	Ar, H	O
h;	N	NH	Ar	O

containing two heteroatoms. For the *cis*-isomers of the trimethylene-, tetramethylene-, and pentamethylene-tetrahydro-oxazines [3,4] (1a, b), the analogous dihydro-oxazines [5,6] (1c, d), tetrahydro-oxazin-2-ones [7,8] (1e, f), tetrahydro-oxazin-4-ones [9,10] (1g), and dihydropyrimidin-4-ones [9] (1h), of the two most probable chair conformers the conformer that predominated was the one in which the heteroatom O, N, or NH adjacent to the ring junction was axial, while the methylene or carbonyl group was equatorial. We have also studied tricyclic analogues of the aforementioned diaza-bicyclic systems and various 1,2,3,4-tetrahydropyrido[2,1-*b*]quinazolin-11-ones (2) substituted in rings A and C and homologues of these with 5, 7, and 8 atoms in ring A have been synthesized for pharmacological purposes,[11] and some of their reactions have been studied.[12]

We now report the synthesis and stereochemical study of partially and fully saturated derivatives of tricycles of type (2), the decahydro- and dodecahydro-pyrido[2,1-*b*]quinazolin-11-ones (3) and (4; $n = 2$), and homologues of these in which ring A or C is a five- or seven-membered. There is widespread interest currently in the conformational analysis of saturated and partially saturated heterocycles; [13-17] the skeletal system under study is also present in some alkaloids.[18,19]

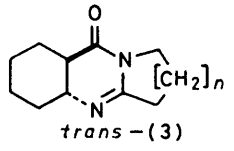
Synthesis.—Compounds (3a—g) were synthesized by three methods.

(a) Reactions between amino-acids and lactim ethers have been employed for the preparation of pyrimidinone derivatives.[20,21] The reaction of 2-aminocyclohexanecarboxylic acid, of unspecified configuration, with *O*-methyl-ε-caprolactim was reported to give a product of m.p. 100 °C.[22] We have found that the reaction of the stereohomogeneous *cis*- and *trans*-2-aminocyclohexanecarboxylic acids with lactim ethers containing 5—7 ring atoms gave the desired products (3a—f) in good yields. On the basis of the m.p.s of the stereohomogeneous products obtained with *O*-methyl-ε-caprolactim [(3c) *cis*: 81—82 °C; (3e) *trans*: 128—129 °C], it appears that



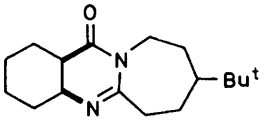
cis—(3)

(3a) n = 1
(3b) n = 2
(3c) n = 3

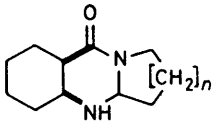


trans—(3)

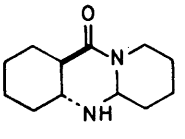
(3d) n = 2
(3e) n = 3



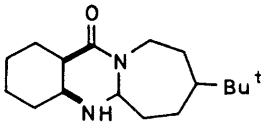
(3f)



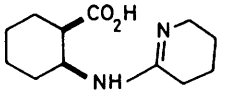
(4a) n = 2
(4b) n = 3



(4c)



(4d)

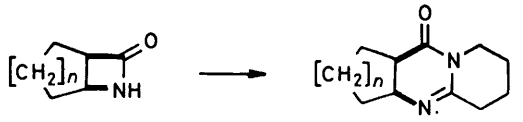


(5)

Petersen and Tietze probably used a *cis–trans* mixture of the amino-acid, and their product must have been a *cis–trans* isomeric mixture (3c) and (3e).

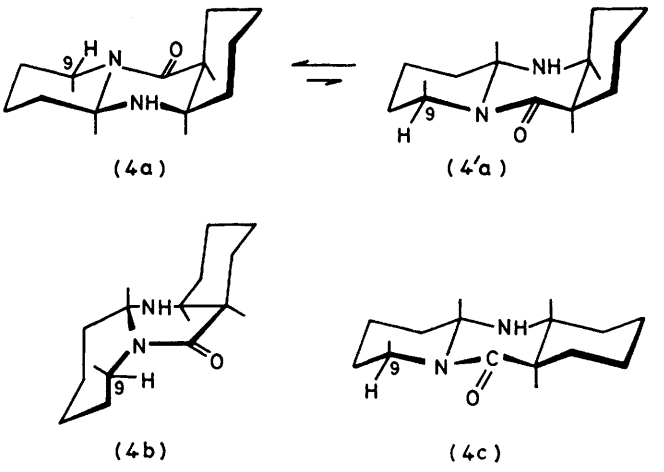
When *cis*-2-aminocyclohexanecarboxylic acid was allowed to react with *O*-methyl-δ-valerolactim in anhydrous ethanol for 15 min, the intermediate amidine (5) could be isolated in good yield, and when this was further refluxed in ethanol it was converted almost quantitatively into the pyridoquinazoline (3b).

(b) The tricyclic derivatives (3) were obtained in similarly good yields by ring expansion of the azetidinones (6a and b) [23,24] with methyl δ-valerolactim;



(6a) $n = 1$ (3g) $n = 1$
(6b) $n = 2$ (3b) $n = 2$

boiling for 5 h in chlorobenzene always resulted in the stereohomogeneous *cis* products (3g and b). In the reaction of *O*-methyl-ε-caprolactim with the *cis*-azabicyclo-octanone (6b), Bormann [25] obtained a product with m.p. 80—81 °C, the configuration of which was not given. On the basis of our experiments, this compound has the *cis*-configuration.



(4a) (4'a)
(4b) (4c)

show that the decahydro-derivatives (3a—g) prepared *via* procedures (a)—(c) are stereohomogeneous, and the C=N double bond is in the 5—5a position (for numbering see footnote to Table 3). Ring C in the *cis*-compounds (3a—c) is flexible, and the rapid interconversion of the conformers at room temperature results in an approximate averaging of the chemical shifts of the axial and equatorial methylene protons. However, the presence of the t-butyl group in compound (3f) leads to a preferred

TABLE 1

Physical and analytical data for compounds (3a)—(3g)

Compound	Cryst. solvent	M.p. (*t*/°C)	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H	Yield (%) Method (a)	Yield (%) Method (b)
(3a)		B.p. 142 °C at 6 mm Hg	68.6	8.5	$C_{11}H_{16}N_2O$	68.7	8.34	86	
(3b) [a]	Ether	68—71	69.4	8.7	$C_{12}H_{18}N_2O$	69.9	8.8	88	78
(3c) [b]	Ether	81—82	71.4	8.6	$C_{13}H_{20}N_2O$	70.9	9.15	71	81 [c]
(3d)	Light petroleum	129—130	69.7	8.8	$C_{12}H_{18}N_2O$	69.9	8.8	79	
(3e)	Light petroleum	128—129	70.6	9.3	$C_{13}H_{20}N_2O$	70.9	9.15	66	
(3f)	n-Hexane	96—100	73.6	10.2	$C_{17}H_{28}N_2O$	73.9	10.2	74	
(3g) [d]	Ethanol–ether	238—240	57.6	7.1	$C_{11}H_{17}ClN_2O$	57.8	7.05		84

[a] The hydrochloride was crystallized from ethanol–ether; m.p. 238—245 °C; the analytical data corresponded to those calculated. [b] Lit.[25] m.p. 80—81 °C. [c] Value from ref. 25. [d] Hydrochloride.

TABLE 2

Physical and analytical data for compounds (4a)—(4d)

Compound	Cryst. solvent	M.p. (*t*/°C)	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H	Yield (%)
(7a)	Ether	111—113	69.2	9.7	$C_{12}H_{20}N_2O$	69.2	9.7	76
(7b)	Light petroleum	126—128	70.2	9.9	$C_{13}H_{22}N_2O$	70.2	10.0	72
(7c)	Ether	175.5	69.1	9.5	$C_{12}H_{20}N_2O$	69.2	9.7	77
(7d)	Ether	154—156	73.2	10.7	$C_{17}H_{30}N_2O$	73.3	10.9	70

(c) Cyclization of β-amino-acids and lactams in phosphoryl chloride can likewise be employed for the synthesis of our target compounds,[26,27] but in the reaction of δ-valerolactam and *cis*-2-aminocyclohexanecarboxylic acid in benzene the yield of the pyridoquinazoline derivative (3b) was <10%.

In aqueous methanol the decahydropyridoquinazolines (3) are readily reduced by sodium borohydride to give the perhydro-derivative (4a—d).

Conformation.—The ^{1}H n.m.r. spectra of the products

conformation in which the 9*eq*-H is presumably coplanar with the C=O group, the anisotropic deshielding effect of which causes the comparatively high chemical shift (δ 4.78; [28,29] Table 3).

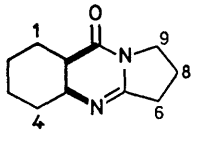
In agreement with earlier results for related derivatives,[3,7-9] in view of the *cis* A–B ring fusion in compounds (3a—c, f), of the two conformers the predominant one will be that in which the 4a-H proton is equatorial to ring A. This is proved by the high chemical shift (δ 3.60—3.75) for 4a-H and by the three $J_{gau\,he}$ coupling

TABLE 3

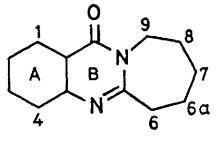
^{1}H n.m.r. chemical shifts (δ) and coupling constants (J/Hz) in $CDCl_3$ solution

Compound	9*eq*-H		9*ax*-H	8-H_2	6-H_2	5a-H	4a-H	11a*ax*-H	Overlapping bands of skeletal protons
(3a)		3.77 (2 H)		2.10 (2 H)	2.74 (2 H)		3.75 (1 H) J 4, 4, and 4	2.53 (1 H) J 9, 5, and 4	1.30—2.00 (8 H)
(3b)		3.72 (2 H)		1.85 *	2.59 (2 H)		3.60 (1 H) J 4, 4, and 4	2.59 (1 H)	1.30—2.00 (12 H)
(3c)		4.00 (2 H)		1.75 *	2.70 (2 H)		3.63 (1 H) J 4, 4, and 4	2.56 (1 H) J 9, 5, and 4	1.20—2.05 (14 H)
(3d)	4.14 (1 H) J 4 and 4	J_{gem} 13.0	3.39 (1 H) J 8 and 2	1.88 *	2.59 (2 H)		3.04 (1 H) J 11.0, 11.0, and 2		1.10—2.45 (13 H) 4*ax*-H 1.35 * 4*eq* 2.32 *
(3e)	4.18 (1 H) J 4 and 2.5	J_{gem} 15.0	3.49 (1 H) J 9 and 2	1.70 *	2.67 (2 H)		2.95 (1 H) J 13.0, 11.0, and 2.5	1.85 *	1.20—2.45 (15 H) 4*ax*-H 1.45 * 4*eq*-H 2.25 *
(3f)	4.78 (1 H) J 6.0 and 1.5	J_{gem} 14.5	3.06 (1 H) J 10.0 and 1	8*eq*-H 2.15 *			3.63 (1 H) J 4, 4, and 4		1.10—2.80 (16 H) Me_3C 0.92 (9 H)
(3g)		3.72 (2 H)			2.55 (2 H)		3.93 (1 H) J 4.5, 4.5, and 4.5	2.65 (1 H)	1.30—2.35 (8 H)
(4a)	2 (1 H) J 3.5 and 1.7	J_{gem} 13.2	2.40 *			4.13 (1 H) J 10.0 and 2.5	3.24 (1 H) J 3.5, 3.5, and 3.5	2.35 *	1.15—2.60 (16 H) 4-H_2 1.75 *
(4b)	^4J 1.7 4.20 (1 H) J 4 and 3	J_{gem} 14.0	2.75 (1 H) J 9.5 and 2	1.75 *	2.00 *	4.56 (1 H) J 4 and 3	3.28 (1 H) J 3.5, 3.5, and 3.5	2.35 (1 H) J 11.2 and 3.5	1.20—2.20 (16 H)
(4c)	4.71 (1 H) J 3.5 and 1.7 ^4J 1.7	J_{gem} 13.8	2.40 *		1.25 *	4.16 (1 H) J 9.6 and 2.5			0.90—2.20 (14 H) 2.30—2.75 (3 H)
(4d)	4.31 (1 H) J 4 and 3	J_{gem} 14.0	2.61 (1 H) J 11.0 and 1.5			4.58 (1 H) J 4 and 3	3.26 (1 H) J 3.5, 3.5, and 3.5	2.32 (1 H) J 11.5, 3.5, and 3.5	1.00—2.20 (15 H) Me_3C 0.90 (9 H)

* Value based on double resonance experiments. For ease of comparability of the spectroscopic data for compounds (3a, c, e, g) and the corresponding perhydro derivatives (4b, d), the following numbering has been used:

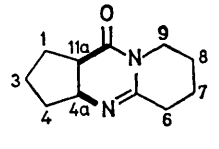


(3a)



(3c) A-B *cis*

(3e) A-B *trans*



(3g)

constants of 4 Hz observed in all cases. In contrast, in the *trans* compounds (3d) and (3e) 4a-H appears at δ 3.04 and 2.95, respectively (*i.e.* >0.5 p.p.m. smaller than for the *cis*-isomers), and one *gauche* and two *trans diaxial* coupling constants are observed. This is in accordance with a *trans* A–B ring fusion.

The *trans*-dodecahydro derivative (4c) has a fairly complex spectrum, in which the assignment of only two signals is distinct, at δ 4.16 and 4.71. The multiplicity of these signals and double resonance measurements show that, in contrast with expectations, 9*eq*-H and not 5a-H has the higher chemical shift. The very high δ value for 9*eq*-H indicates that the conformer which predominates is that in which the tetrahydropyrimidinone

ring has a semi-chair conformation, as in this case 9*eq*-H is coplanar with, and in a *peri* position to, the C=O group, the deshielding effect of the latter giving rise to the high chemical shift. Conversely, 9*ax*-H is above the plane of the C=O group, in the region causing a diamagnetic shift, and double resonance measurements show that it resonates at δ 2.40. The correct assignment of 9*eq*-H is confirmed by the fact that, besides the 13.8 Hz geminal coupling constant, there are three more such couplings (*J* 3.5, 1.7, and 1.7 Hz), which are due to $J_{ax,eq}$, $J_{eq,eq}$, and $^4J_{eq,eq}$ interactions. This latter long-range coupling between equatorial protons would be observed only if they are in a zigzag (W) arrangement. The multiplicity of the 5a-H signal (dd, *J* 9.6 and 2.5 Hz) clearly proves that it is axial.

In the spectrum of the *cis*-isomer (4a) the chemical shifts characteristic of the piperidine ring, and also the signal multiplicities, correspond closely with those for the *trans*-compound (4c), and so the conformations of rings B and C are the same in the two compounds. In (4a) 4a-H gives a separate signal, at δ 3.24; the three coupling constants of 3.5 Hz indicate that this proton is equatorial to ring A. Thus, of the two chair–chair conformers possible as a consequence of the *cis* A–B ring junction, the conformer that predominates is the one in which the N atom linked to the cyclohexane ring is axial, while the C=O group is equatorial. On irradiation at δ 2.35 (11a*ax*-H), the 4a*eq*-H signal simplifies to a triplet.

In the spectrum of (4b) the chemical shift and multiplicity of 4a*eq*-H agree with those for (4a), and so similar conclusions may be drawn about the configuration of the A–B ring junction. Characteristic differences are observed, however, for the 9- and 5a-H signals. The large chemical shift (δ 4.56) for 5a-H and its multiplicity (*J* 4 and 3 Hz) show that it is equatorial and *gauche* to both 6-methylene protons. This can arise only with a twisted-boat conformation of the tetrahydropyrimidinone ring. In this conformation, 9*eq*-H cannot be coplanar with the C=O group, while 9*ax*-H is well separated from this group. The decrease in the chemical shift of 9*eq*-H and the increase in the shift of 9*ax*-H agree with this. The difference between the positions of these signals is only 1.45 p.p.m., in contrast with the difference of 2.3 p.p.m. found for compounds (4a) and (4c).

In contrast with the differences observed in the n.m.r. spectra of the decahydro-compounds (3c) and (3f), the corresponding data for the dodecahydro-analogues (4b) and (4d) are similar (Table 3), and consequently the conformations of the completely saturated compounds (4b) and (4d) are the same, even though (4d) contains a t-butyl group in ring C and (4b) does not.

EXPERIMENTAL

M.p.s were determined with a Boetius M. hot-stage apparatus. ^{1}H N.m.r. spectra were recorded at 100 MHz with a JEOL PS-100 spectrometer, with tetramethylsilane as internal standard.

cis-1,2,3,4,4a,6,7,8,9,11a-*Decahydropyrido*[2,1-b]*quinazolin*-11-*one* (3b).—*Method* (*a*). Powdered *cis*-2-aminocyclohexanecarboxylic acid (0.72 g, 5 mmol) and *O*-methyl-δ-valerolactim (0.57 g, 5 mmol) were heated in refluxing chlorobenzene (20 ml) until the amino-acid had dissolved (4—6 h). The mixture was evaporated to dryness, the residue was extracted with dry acetone (4 × 20 ml), and the solution was evaporated to dryness, to give the product (3b), m.p. 67—69 °C (0.91 g, 88%). Physical and analytical data for (3b) and for compounds (3a) and (3c—f) which were prepared similarly are given in Table 1.

Method (*b*). *cis*-7-Azabicyclo[4.2.0]octan-8-one (6b) (1.25 g, 10 mmol) and *O*-methyl-δ-valerolactim (1.13 g, 10 mmol) were heated for 5 h in refluxing chlorobenzene (20 ml), the solution was evaporated to dryness, and ethanolic hydrogen chloride was added to give the hydrochloride of (3b). The base obtained on addition of dilute aqueous sodium carbonate was identical with the product obtained by method (a). Physical and analytical data for (3b),HCl and (3g),HCl prepared similarly are in Table 1.

Method (*c*). *O*-Methyl-δ-valerolactam (0.99 g, 10 mmol) was heated for 15 min on a water-bath, in refluxing benzene (50 ml)–phosphoryl chloride (15 ml). *cis*-2-Aminocyclohexanecarboxylic acid (1.57 g, 11 mmol) was then added, and refluxing on a water-bath was continued for 6 h more. The cooled mixture was neutralized with 1M ammonium hydroxide solution. The separated aqueous phase was extracted with chloroform, and the combined organic phases were dried and evaporated to dryness. The fractions obtained by chromatography of the yellow residue on aluminium oxide of activity II (30 g) (eluant : light petroleum) were examined by t.l.c. (silica gel; benzene–ethanol, 4 : 1), and the appropriate fractions were evaporated to yield the product (3b) (0.18 g, 8.7%; m.p. 68—70 °C), the properties of which corresponded to those of the product obtained by methods (a) and (b).

cis-2-(3,4,5,6-*Tetrahydropyridin*-2-*ylamino*)*cyclohexanecarboxylic acid* (5).—*cis*-2-Aminocyclohexanecarboxylic acid (0.72 g, 5 mmol) and *O*-methyl-δ-valerolactim (0.57 g, 5 mmol) were heated in refluxing ethanol (20 ml) for 15 min. The white crystals obtained by evaporation of the solution to dryness were triturated with ether and filtered off (0.91 g, 81%; m.p. 186—190 °C). Crystallization from ethanol–ether gave the *amidine* (5), m.p. 188—191 °C (Found: C, 64.3; H, 9.0; N, 12.5. $C_{12}H_{20}N_2O_2$ requires C, 64.2; H, 8.9; N, 12.5%).

Preparation of cis-1,2,3,4,4a,6,7,8,9,11a-*Decahydropyrido*-[2,1-b]*quinazolin*-11-*one* (3b) *from the Amidine* (5).—The amidine (5) (0.45 g, 2 mmol) was heated for 3 h in refluxing ethanol (20 ml), and the solution was then evaporated to dryness. The residue (0.37 g, 91%) was recrystallized from ether to yield crystals of (3b), m.p. 68—70 °C, the spectroscopic data for which agree with those of the product obtained by method (a).

trans-1,2,3,4,4a,5,5a,6,7,8,9,11a-*Dodecahydropyrido*-[2,1-b]*quinazolin*-11-*one* (4c).—A solution of compound (3d) (206 mg, 1 mmol) in methanol (10 ml) was shaken, and sodium borohydride (76 mg, 2 mmol) in water (10 ml) was added. The mixture was set aside for 2 h, and then worked up in the usual way; methanol was evaporated off, and the aqueous residue was extracted with ether (3 × 20 ml). The ether extract was dried and evaporated to dryness to give (4c) (160 mg, 77%; m.p. 175—177 °C). Physical and analytical data for (4c) and compounds (4a, b, and d) prepared similarly are in Table 2.

This work was supported by the CHINOIN Pharmaceutical and Chemical Works, Budapest.

[8/970 *Received*, 24*th May*, 1978]

REFERENCES

[1] Part 29, B. Ribár, D. Lazar, A. Kálmán, J. Kóbor, and G. Bernáth, *J.C.S. Perkin II*, 1977, 1141.
[2] This paper is also considered to be Part 7 of the series Saturated Heterocycles. For previous parts of this series, see refs. 3, 4, 7, 8, 5, and 1, respectively.
[3] G. Bernáth, K. L. Láng, K. Kovács, and L. Radics, *Acta Chim. Acad. Sci. Hung*, 1972, **73**, 81.
[4] G. Bernáth, Gy. Göndös, L. Gera, M. Török, K. Kovács, and P. Sohár, *Acta Phys. et Chem. Szeged.*, 1973, **19**, 147.
[5] B. Ribár, D. Lazar, A. Kálmán, S. Sasváry, G. Bernáth, and L. Hackler, *Cryst. Struct. Comm.*, 1977, **6**, 671.
[6] G. Bernáth, L. Gera, K. L. Láng, L. Hackler, and P. Sohár, presented in part at a Meeting of the Hungarian Chemical Society, Debrecen, 23—26 August, 1977. See p. 69 of the Proceedings of this meeting.
[7] G. Bernáth, Gy. Göndös, K. Kovács, and P. Sohár, *Tetrahedron*, 1973, **29**, 981.
[8] P. Sohár and G. Bernáth, *Org. Magnetic Resonance*, 1973, **5**, 159.
[9] G. Bernáth, Gy. Göndös, L. Gera, F. Fülöp, Z. Ecsery, and P. Sohár, presented in part at the International Symposium on Stereochemistry, Kingston, Ontario, Canada, 28 June, 1976. See Abstract M4 of the symposium.
[10] G. Bernáth and F. Fülöp, presented in part at a Meeting of the Hungarian Chemical Society, Debrecen, 23—26 August, 1977. See p. 30 of the proceedings of this meeting.
[11] I. Hermecz, F. Fülöp, Z. Mészáros, G. Bernáth, and J. Knoll, *Hung. P. Appl.*, 19th August, 1977.
[12] G. Bernáth, F. Fülöp, Z. Mészáros, I. Hermecz, and G. Tóth, *J. Heterocyclic Chem.*, submitted for publication.
[13] W. L. F. Armarego, 'Stereochemistry of Heterocyclic Compounds,' Wiley, New York, 1977.
[14] I. J. Ferguson, A. R. Katritzky, and D. M. Read, *J.C.S. Perkin II*, 1977, 818.
[15] T. A. Crabb and J. S. Mitchell, *J.C.S. Perkin II*, 1977, 1592.
[16] F. G. Riddell and A. J. Kidd, *J.C.S. Perkin II*, 1977, 1816.
[17] H. Booth, D. V. Griffiths, and M. L. Jozefowicz, *J.C.S. Perkin II*, 1976, 895.
[18] W. L. F. Armarego, 'Quinazolines,' Part I, in 'Fused Pyrimidines,' ed. A. Weissberger, Interscience, New York, 1967.
[19] G. Devi, R. S. Kapil, and S. P. Popli, *Indian J. Chem.*, 1976, **14B**, 354.
[20] R. G. Glushkov and V. G. Granik, *Adv. Heterocyclic Chem.*, 1970, **12**, 185.
[21] S. Rajappa and B. G. Advani, *Tetrahedron*, 1973, **29**, 1299.
[22] S. Petersen and E. Tietze, Ger. P. 1,088,968/1960.
[23] E. Nativ and P. Rona, *Israel J. Chem.*, 1972, **10**, 971.
[24] H. Bestian, H. Biener, K. Clauss, and H. Heyn, *Annalen*, 1968, **718**, 94.
[25] D. Bormann, *Chem. Ber.*, 1970, **103**, 1797.
[26] G. Tóth, K. Horváth-Dóra, O. Clauder, and H. Duddeck, *Annalen*, 1977, 529.
[27] Kh. M. Shakhidoyatov, A. Irisbaev, L. M. Yun, E. Oripov, and Ch. Sh. Kadyrov, *Khim. geterotsikl. Soedinenii*, 1976, 1564.
[28] F. Bohlmann and D. Schumann, *Tetrahedron Letters*, 1965, 2435.
[29] R. Cahill and T. A. Crabb, *Org. Magnetic Resonance*, 1972, **4**, 823.