Saturated Heterocycles. 57 [1,2]. Synthesis of 4-Substituted-9,10-dialkoxy-1,6,7,11b-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-2-ones

Jenő Kóbor

Chemical Department, Pedagogical Training College,
H-6720 Szeged, Április 4, u. 6., Hungary

Ferenc Fülöp, M. Sami El-Gharib, Gábor Bernáth*

Institute of Pharmaceutical Chemistry, University Medical School,
H-6720 Szeged, Eötvös u. 6., Hungary

Received May 25, 1983

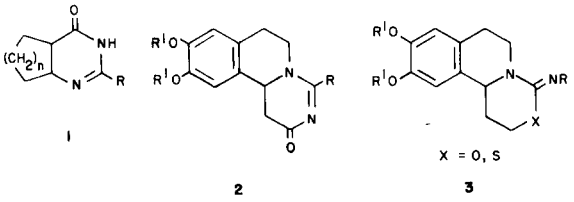
A large number of 4-substituted-9,10-dialkoxy-1,6,7,11b-tetrahydropyrimido[6,1-*a*]isoquinolin-2-ones were prepared by the reaction of 1-(ethoxycarbonylmethyl)-6,7-dialkoxy-1,2,3,4-tetrahydroisoquinolines with iminoethers. Reaction of the corresponding isoquinoline-1-acetic acid derivatives with iminoethers led to the formation of *N*-acyl-1,2,3,4-tetrahydroisoquinolin-1-acetamides. In the hydrolysis of the prepared 4-substituted-pyrimido[6,1-*a*]isoquinolin-2-ones, the corresponding *N*-acyl-1,2,3,4-tetrahydroisoquinolin-1-acetamides were obtained. While reduction of the 4-phenyl derivative resulted in the corresponding 1,3,4,6,7,11b-hexahydropyrimidinone. The steric structures of the tetrahydro- and hexahydropyrimido[6,1-*a*]isoquinolines were determined by nmr spectroscopy.

J. Heterocyclic Chem., **21**, 149 (1984).

Introduction.

We earlier reported [3] the synthesis of a large number of pyrimidin-4-one derivatives condensed with an alicyclic ring (**1**). Pharmacological examinations revealed the very favourable anti-inflammatory and analgetic effects of these compounds. Accordingly, we set out to synthesize analogous pyrimidinones condensed with an isoquinoline skeleton (Scheme 1).

Scheme 1



1 **2** **3**

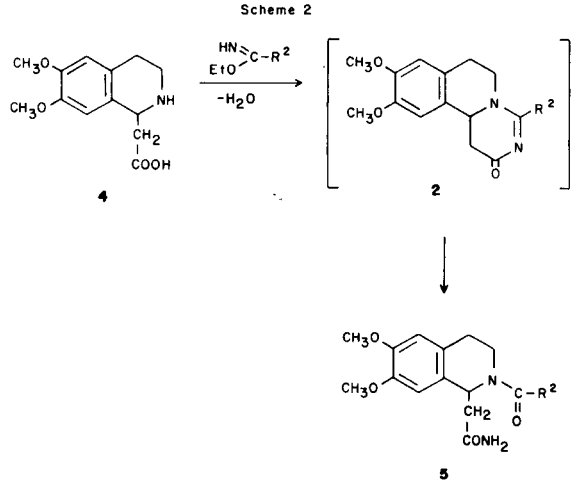
We recently described [4] the synthesis of isoquinoline derivatives condensed with 1,3-heterocycles of similar type.

The literature does not mention compounds of type **2**. However, pyrimido[6,1-*a*]isoquinolines with related structures [5-7], their dioxo derivatives, and other 3-substituted analogues have been prepared for pharmacological purposes [8-12]. Very varied (antihypertensive, bronchodilator, local anesthetic, anti-allergenic and anti-inflammatory) effects have been described for this family of compounds.

Synthesis.

In contrast with the ring-closure of alicyclic β-aminocarboxylic acids with iminoethers, which leads to pyrimidinones [3], the condensation of 1,2,3,4-tetrahydroisoquinoline-1-acetic acid (**4**) and the iminoethers under similar conditions did not give the desired result. When the reaction was attempted at the boiling point of the solution in chlorobenzene, only the unchanged aminocarboxylic acid **4** and the *N*-acylisoquinolin-1-acetamide derivatives **5** could be isolated from the reaction mixture (Scheme 2). The formation of carboxamide **5** is explained by the hydrolytic cleavage of the desired tricycle **2** by the water eliminated under the ring-closure conditions.

Scheme 2

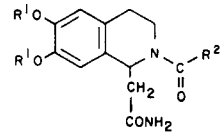


4 **2** **5**

In accordance with this, successful ring-closure could be achieved if the starting compounds was not the carboxylic acid **4**, but the corresponding 1-[(ethoxycarbonyl)methyl]-1,2,3,4-tetrahydroisoquinoline (**6**) [13,14], and if acid catalysis was applied (Scheme 3). Yamazaki *et al.* [15] prepared 8,13-diazasteroid derivatives by the ring-closure of **6a** and lactim ethers with various ring sizes.

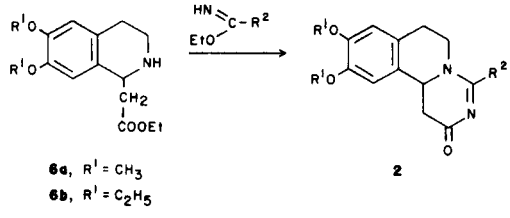
Table 1

Physical Properties of *N*-Acyl-1,2,3,4-tetrahydroisoquinoline-1-acetamide Derivatives **5a-5l**



No.	R^1	R^2	Mp, °C Recrystallization Solvent	Yield %	Molecular Formula	Analyses Calcd. (Found) C	H	N	IR ν max, cm^{-1}
5a	CH_3	CH_3	188-189 Ethanol	69	$C_{15}H_{20}N_2O_4$ (292.33)	61.62 (61.76)	6.89 (6.80)	9.98 (9.56)	1625, 1695
5b	CH_3	CH_2CH_3	187-189 Benzene	68	$C_{16}H_{22}N_2O_4$ (306.35)	62.72 (62.85)	7.23 (6.90)	9.14 (9.20)	1635, 1680
5c	CH_3	$CH_2CH_2CH_3$	170-172 Benzene	61	$C_{17}H_{24}N_2O_4$ (320.37)	63.73 (63.67)	7.55 (7.47)	8.74 (8.61)	1635, 1700
5d	CH_3	C_6H_6	195-196 Ethanol	72	$C_{20}H_{22}N_2O_4$ (354.39)	67.76 (67.96)	6.42 (6.30)	7.90 (8.00)	1615, 1685
5e	CH_3	$C_6H_4CH_3(p)$	191-192 Ethanol	62	$C_{21}H_{24}N_2O_4$ (368.41)	68.45 (68.24)	6.56 (6.30)	7.60 (7.46)	1600, 1670
5f	CH_3	$C_6H_4CH_3(m)$	183-185 Ethanol	78	$C_{21}H_{24}N_2O_4$ (368.41)	68.45 (68.37)	6.56 (6.84)	7.60 (7.89)	1640, 1690
5g	CH_3	$C_6H_4Cl(p)$	195-196 Ethanol	57	$C_{20}H_{21}ClN_2O_4$ (388.85)	61.77 (61.48)	5.44 (5.61)	7.20 (7.33)	1610, 1665
5h	CH_3	$C_6H_4Br(p)$	204 Ethanol	60	$C_{20}H_{21}BrN_2O_4$ (433.30)	55.43 (55.29)	4.84 (5.01)	6.46 (6.31)	1640, 1700
5i	CH_3	$C_6H_4Br(m)$	189-191 Ethanol	61	$C_{20}H_{21}BrN_2O_4$ (433.30)	55.43 (55.30)	4.84 (5.10)	6.46 (6.64)	1640, 1690
5j	CH_3	$C_6H_4OCH_3(p)$	214-215 Ethanol	64	$C_{21}H_{24}N_2O_5$ (384.43)	65.60 (65.80)	6.30 (6.54)	7.28 (7.46)	1605, 1675
5k	CH_3	$C_6H_4NO_2(p)$	222-224 Ethanol	54	$C_{20}H_{21}N_3O_6$ (399.40)	60.14 (60.41)	5.29 (5.52)	10.52 (10.45)	1645, 1670
5l	CH_3	$CH_2C_6H_4Cl(p)$	183-184 Ethanol	49	$C_{21}H_{23}ClN_2O_4$ (402.87)	62.60 (62.41)	5.75 (5.39)	6.96 (6.87)	1630, 1680

Scheme 3



6a, $R^1 = CH_3$
6b, $R^1 = C_2H_5$

2

The yields in the reaction **6** → **2** varied considerably, depending on the iminoether substituent and the reaction conditions.

Ring-closure in chlorobenzene gave satisfactory yields only with alkyl-substituted compounds. When the ring-closure was performed in the melt (4 hours, 130°), the yield was 25-30%. Both a longer reaction time and a higher temperature favoured decomposition.

With acetic acid catalysis in benzene, the aryl-substituted derivatives too could be prepared with satisfactory yields (Table 2).

The prepared compounds of type **2** are labile. In air, in solvents containing acid traces, the pyrimidinone ring opens rapidly. In a study of the stability of similar, condensed-skeleton pyrimidinone derivatives, Armarego [16] observed that the 1-substituted dihydropyrimidinones decompose *via* rapid ring-opening.

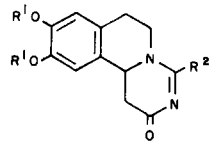
Hydrolysis of derivative **2d** in aqueous acidic solution led to the acetamide **5d** in good yield. This lends support to our hypothesis (Scheme 2) that, although the ring-closure occurs when β-aminoacids are used, the pyrimidinone ring is opened by water under the conditions employed.

The structure of the acetamides **5** was confirmed by benzoylation of **6a** to **9**, followed by amidation, or amidation of **6a** to **8**, followed by benzoylation (Scheme 4).

On reduction of **2d** with sodium borohydride, the corresponding hexahydropyrimidinone **7** was isolated in good yield. The structure of **7** was proved by ^{1}H-nmr spectroscopy and by hydrolysis, which resulted in benzaldehyde and the isoquinolin-1-acetamide **8**.

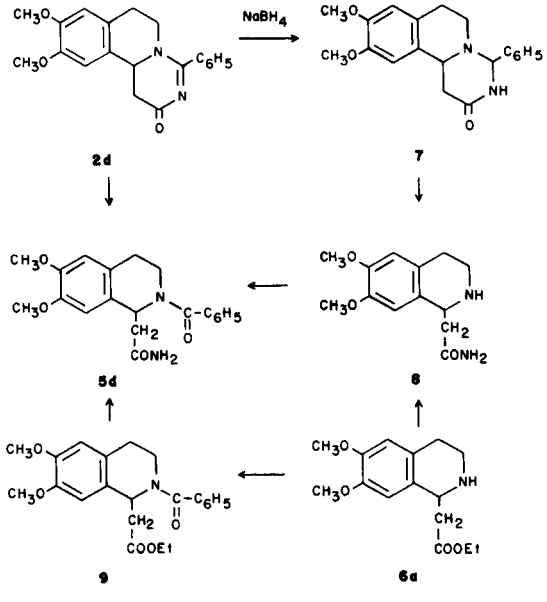
Table 2

Physical Properties of Pyrimido[6,1-*a*]isoquinoline Derivatives **2a-2n**



No.	R^1	R^2	Mp, °C Recrystallization Solvent	Yield, % Method A	B	C	Molecular Formula	Analyses Calcd. (Found) C	H	N	IR ν max, cm^{-1}
2a	CH_3	CH_3	196-198 Benzene	50			$C_{15}H_{16}N_2O_3$ (274.31)	65.67 (65.25)	6.61 (6.48)	10.21 (9.89)	1510, 1670
2b	CH_3	CH_2CH_3	205-206 Benzene	58		70	$C_{16}H_{20}N_2O_3$ (288.34)	69.69 (69.50)	6.99 (6.83)	9.71 (10.04)	1510, 1660
2c	CH_3	$CH_2CH_2CH_3$	162-164 Benzene	50	28		$C_{17}H_{22}N_2O_3$ (302.36)	67.52 (67.73)	7.33 (7.41)	9.26 (9.48)	1525, 1680
2d	CH_3	C_6H_5	180-181 Benzene	25	30	65	$C_{20}H_{20}N_2O_3$ (336.38)	71.40 (71.17)	5.99 (6.38)	8.33 (8.32)	1510, 1660
2e	C_2H_5	C_6H_5	165-167 Ethyl acetate	42		60	$C_{22}H_{24}N_2O_3$ (364.65)	72.52 (72.84)	6.63 (6.78)	7.68 (7.80)	1510, 1670
2f	CH_3	$C_6H_4Cl(m)$	213-214 Ethanol	28	25	65	$C_{20}H_{19}ClN_2O_3$ (370.82)	64.78 (64.64)	5.16 (5.30)	7.55 (7.28)	1510, 1680
2g	CH_3	$C_6H_4Br(p)$	204 Ethanol			65	$C_{20}H_{19}BrN_2O_3$ (415.29)	57.83 (57.62)	4.61 (4.80)	6.71 (6.82)	1510, 1670
2h	CH_3	$C_6H_4CH_3(p)$	164-165 Ethanol			40	$C_{21}H_{22}N_2O_3$ (350.40)	71.97 (71.90)	6.33 (6.27)	7.99 (7.90)	1500, 1660
2i	C_2H_5	$C_6H_4CH_3(p)$	180-181 Ethanol			44	$C_{23}H_{26}N_2O_3$ (378.47)	72.99 (72.52)	6.92 (7.25)	7.40 (7.11)	1510, 1660
2j	C_2H_5	$C_6H_4CH_3(m)$	175-176 Ethyl acetate			64	$C_{23}H_{26}N_2O_3$ (378.47)	72.99 (72.38)	6.92 (7.06)	7.40 (7.25)	1500, 1665
2k	C_2H_5	$C_6H_3(CH_3)_2(m,p)$	210-211 Ethyl acetate			39	$C_{24}H_{28}N_2O_3$ (392.47)	73.44 (73.48)	7.19 (6.94)	7.14 (7.05)	1500, 1665
2l	CH_3	$C_6H_4CF_3(m)$	206-208 Ethanol			50	$C_{21}H_{19}F_3N_2O_3$ (404.39)	62.37 (62.48)	4.73 (4.56)	6.92 (7.19)	1510, 1670
2m	C_2H_5	$C_6H_4CF_3(m)$	213-216 Ethanol			51	$C_{23}H_{23}F_3N_2O_3$ (432.43)	63.88 (63.80)	5.36 (5.68)	6.47 (6.68)	1505, 1665
2n	CH_3	$CH_2C_6H_4Cl(p)$	192-194 Ethanol			42	$C_{21}H_{21}ClN_2O_3$ (384.86)	65.53 (65.40)	5.50 (5.33)	7.28 (7.61)	1510, 1660

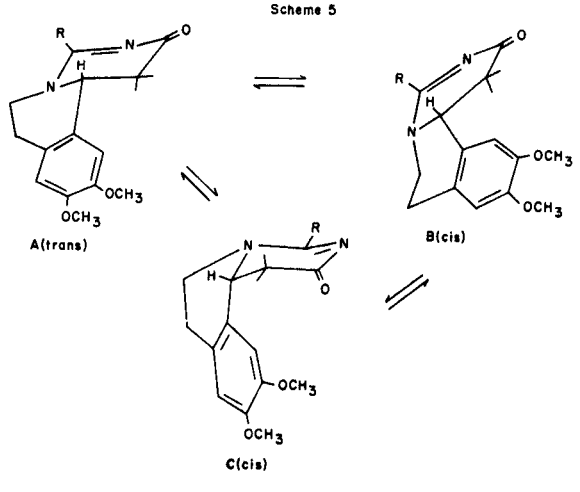
Scheme 4



Structural Examinations.

The conformations of the benzo[*a*]quinolizidines, which can be regarded as near analogues of the synthesized pyrimido[6,1-*a*]isoquinolines, have been investigated in detail

Scheme 5

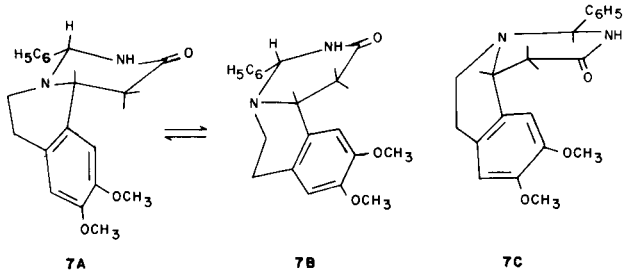


in recent years (see *e.g.* [17]). Crabb *et al.* [7] studied the conformations of 3-methyl-1,2,3,4,7,11b-hexahydro-6*H*-pyrimido[6,1-*a*]isoquinoline, and established that there is a conformational equilibrium between three of the six possible conformers. At the same time, O- (or S-) *inside cis*-conformation predominates in the 1,3-oxazino- or 1,3-thiazino[4,3-*a*]isoquinolines [6,18].

In the synthesized compounds of type **2**, one *trans* and two *cis* conformers are possible because of the conformational instability of the bridgehead nitrogen (Scheme 5). In the structural examinations, detailed studies were made on derivative **2d**. The choice between the three possible structures was made as follows. Since only weak Bohlmann bands are to be found in the ir spectrum, the **A** *(trans)* structure can be excluded. In the ^{1}H-nmr spectrum the 11b methine proton shows a double doublet and the 14 and 6 Hz couplings point to the presence of the **B** *(cis)* form.

The hexahydro derivative **7** obtained by reduction from **2d** contains a new asymmetry centre. The relative conformation of the phenyl group must therefore be established here. Dreiding model examinations indicate that three possible arrangements are conceivable in which the phenyl group is *equatorial* (Scheme 6). Forms **7A** and **7B** are in conformational equilibrium; in these forms the phenyl group is *trans* to the anellation hydrogen 11b, while in diastereomer **7C** the phenyl group is *cis*. Similarly as for compound **2d**, weak Bohlmann bands are to be found in the ir spectrum of compound **7**; this excludes the presence of form **7A**. The dd multiplicity and coupling constants (9

Scheme 6



7A **7B** **7C**

and 3 Hz) of the 11b proton likewise point to the presence of the form **7B**. In the synthesis of the 1,3-oxazino- and 1,3-thiazino[4,3-*a*]isoquinolines, achieved by ring-closure of the corresponding aminoalcohols with *p*-nitrobenzaldehyde, Crabb similarly found the *trans* configuration of the *p*-nitrophenyl ring [18].

EXPERIMENTAL

The ir spectra were recorded on a Specord 75 IR instrument in potassium bromide pellets, or for 0.2 *M* solutions in deuteriochloroform using 0.2 mm matched cells. The nmr spectra were recorded on a Bruker WH-250 Ft spectrometer at 250 MHz in deuteriochloroform, TMS being used as internal standard. Melting points are uncorrected.

4-Phenyl-9,10-dimethoxy-1,6,7,11b-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-2-one (**2d**).

Method A.

1-[(Ethoxycarbonyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**6a**) [13] (2.79 g, 0.01 mole) was boiled for 24 hours with 0.011 mole (1.69 g) of ethyl benzimidate in 50 ml of chlorobenzene. Crystals of **2d** separated out after standing for 2 days.

Method B.

A mixture of 0.01 mole of aminoacid ester **6a** and 0.15 mole of imidate was kept at 140° for 4 hours. The imidate excess was distilled off from the reaction mixture under vacuum, the residue was triturated with ether, and **2d** was obtained in the crystalline state.

Method C.

The aminoacid ester **6a** (0.01 mole) was boiled with 0.11 mole of imidate in 15 ml of absolute benzene, 2 drops of acetic acid being added as catalyst. After 14 hours, the reaction mixture was allowed to stand, and the crystals separating out were filtered off. Further product could be obtained by evaporation of the mother liquor; nmr (deuteriochloroform): δ 2.7 (m, H_2-7, 2H), 3.1 (m, H_2-1, 2H), 3.32, 4.12 (2 × m, H_2-6, 2H), 5.00 (2 × d, H-11b, 1H, $J_{1d,11b}$ = 6 Hz, $J_{1a,11b}$ = 14 Hz), 6.67, 6.71 (2 × s, H-8, H-11, 2H), 7.4-7.6 (m, phenyl, 5H).

The compounds obtained by methods A, B, and C had identical melting points and ir spectra. Table 2 contains the physical data on products **2a-n**, and the yields.

2-Benzoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-acetamide (**5d**).

Method A.

Powdered 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-acetic acid (**4**) [19] (2.43 g, 0.01 mole) was suspended in 25 ml of chlorobenzene, 1.64 (0.011 mole) of ethyl benzimidate was added, and the mixture was boiled for 20 hours. The unchanged aminoacid was filtered off from the boiling solution, and the filtrate was evaporated under vacuum. Portions of benzene were repeatedly poured onto the residue, and the evaporation was resumed; in this way, crystals were obtained.

The data on **5d** and on **5a-5l**, which were prepared in a similar manner, are given in Table 1.

Method B.

Pyrimidoisoquinoline (**2d**) (0.5 g) was boiled for 2 hours in 50 ml water. After standing overnight, 0.37 g (70%) of **5d** crystallized out, mp 193-195°.

If 2-3 drops of acetic acid are added to an aqueous solution of pyrimidoisoquinoline (**2d**) and the mixture was allowed to stand for 24 hours at room temperature, **5d** was formed in a yield of more than 80%, mp 193-196°.

Method C.

One g of 1-[(ethoxycarbonyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**6a**) was benzoylated with benzoyl chloride by the Schotten-Baumann method, and the product **9** was allowed to stand for 3 days with methanolic ammonia. After evaporation, crystals of **5d** were obtained, mp 194-195°. A similarly good yield of **5d** was obtained if the amidation preceded the benzoylation, mp 194-195°.

The samples of **5d** prepared by methods A, B and C have the same mp, their mixture does not exhibit a mp depression and their ir spectra are identical.

cis-4-Phenyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-6*H*-pyrimido-[6,1-*a*]isoquinolin-2-one (**7**).

4-Phenyl-9,10-dimethoxy-1,6,7,11b-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-2-one (**2d**) (1.82 g, 0.005 mole) was dissolved in 30 ml or methanol, and 0.38 g (0.01 mole) of sodium borohydride dissolved in 15 ml of water was added during stirring. After stirring for 2 hours, the methanol

was evaporated off and the aqueous part was extracted with chloroform. After evaporation and drying, 1.45 g (86%) of crystalline **7** was obtained. It was recrystallized from chloroform-petroleum ether, mp 244-245°; nmr (deuteriochloroform): δ 2.3, 2.55, (2 × m, H_2-7, 2H), 2.6, 3.3 (2 × m, H_2-1, 2H), 2.8 (m, H_2-6, 2H), 3.84, 3.86 (2 × s, OCH_3, 6H), 3.95 (2 × d, H-11b, 1H, $J_{1e,11b}$ = 3 Hz, $J_{1a,11b}$ = 9 Hz), 4.8° (s, H-4, 1H), 6.25 (s, NH, 1H), 6.57, 6.61 (2 × s, H-8, H-11, 2H), 7.4-75. (m, phenyl, 5H).

Anal. Calcd. for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.28. Found: C, 71.13; H, 6.64; N, 8.34.

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-acetamide (**8**).

cis-4-Phenyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-6*H*-pyrimido-[6,1-*a*]isoquinolin-2-one (**7**) (0.5 g) was boiled for 2 hours in 25 ml ethanol containing 5% hydrochloric acid. On cooling, the hydrochloride of **8** separated out as plate-like crystals. The solution had the characteristic smell of benzaldehyde. The hydrochloride was filtered off and the base **8** was liberated with sodium carbonate and 0.3 g (81%) of a white crystalline product was obtained. It was recrystallized from benzene, mp 179-180°, lit [5] mp 171.5-172°. The product did not give a mp depression when mixed with **8** prepared from **6a** by amidation.

Acknowledgements.

The authors express their thanks to Professor Pál Sohár (Spectroscopic Department, EGYT Pharmacochemical Works, Budapest) for the 250 MHz nmr recordings, and to Mr. Z. Gombos for participation in certain of the experiments.

REFERENCES AND NOTES

[1] Part **56**: A. Kapor, D. Lazar, S. Loboda, S. Djuric and G. Bernáth, *Rev. Res. Fac. Sci. Novi Sad.*, **12**, 69 (1982).

[2] At the same time this paper is regarded as Part **70**, of the series "Stereochemical Studies", Part **69**: ref [1] and as part of the series of "Investigation in Isoquinoline Derivatives" previous part: J. Kóbor, M. S. El-Gharib, G. Bernáth, *Juhász Gyula Tanárképzö Föiskola Tudományos Közleményei* (Proceedings of the Juhász Gyula Pedagogical Training College, Szeged), 135 (1980); *Chem. Abstr.*, **97**, 144869 (1982).

[3] G. Bernáth, L. Gera, Gy. Göndös, M. Hermann, M. Szentiványi, Z. Ecsery and E. Janvári, German Patent 2,643,384 (1977); *Chem. Abstr.*, **87**, 168078 (1977).

[4] F. Fülöp, M. S. El-Gharib, A. Sohajda, G. Bernáth, J. Kóbor and Gy. Dombi, *Heterocycles*, **20**, 1325 (1983).

[5] J. G. Lombardino, J. I. Bodin, G. F. Gerber, W. M. McLamore and G. D. Lauback, *J. Med. Pharm. Chem.*, **3**, 504 (1969).

[6] J. G. Lombardino, W. M. McLamore and G. D. Lauback, U. S. Patent 3,021,331 (1961); *Chem. Abstr.*, **57**, 786 (1962).

[7] T. A. Crabb, J. S. Mitchell and R. F. Newton, *J. Chem. Soc., Perkin Trans. II*, 370 (1977).

[8] M. D. Nair and S. R. Mehta, *Indian J. Chem.*, **7**, 684 (1969).

[9] V. P. Arya and S. J. Shenoy, *ibid.*, **148**, 784 (1976).

[10] P. Lal, A. D'sa, H. Dornauer and N. J. De Sonza, German Patent 2,847,693 (1980); *Chem. Abstr.*, **93**, 220770 (1980).

[11] P. Kiss and S. Holly, *Chem. Ber.*, **114**, 61 (1981).

[12] K. Harsányi, P. Kiss and D. Korbonits, *J. Heterocyclic Chem.*, **10**, 435 (1973).

[13] A. R. Battersby, H. T. Openshaw and H. C. S. Wood, *J. Chem. Soc.*, 2463 (1963).

[14] A. Buzas, F. Cossais and J. P. Jacquet, *Bull. Soc. Chim. France*, 693 (1974).

[15] H. Takahata, M. Ishikura, K. Nagai, M. Nagata and T. Yamazaki, *Chem. Pharm. Bull.*, **29**, 366 (1981).

[16] W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc., (C)*, 238 (1971).

[17] M. Sugiura, N. Takao, H. Fujiwara and Y. Sasaki, *Chem. Pharm. Bull.*, **26**, 2555 (1978).

[18] T. A. Crabb and J. S. Mitchell, *Org. Magn. Reson.*, **8**, 258 (1976).

[19] J. Kóbor and G. Bernáth, *Acta Phys. Chem., (Szeged)*, **22**, 127 (1976).