SATURATED HETEROCYCLES, 47.[1] SYNTHESIS OF SOME TETRAHYDROISOQUINOLINE CONDENSED 1,3-HETEROCYCLES

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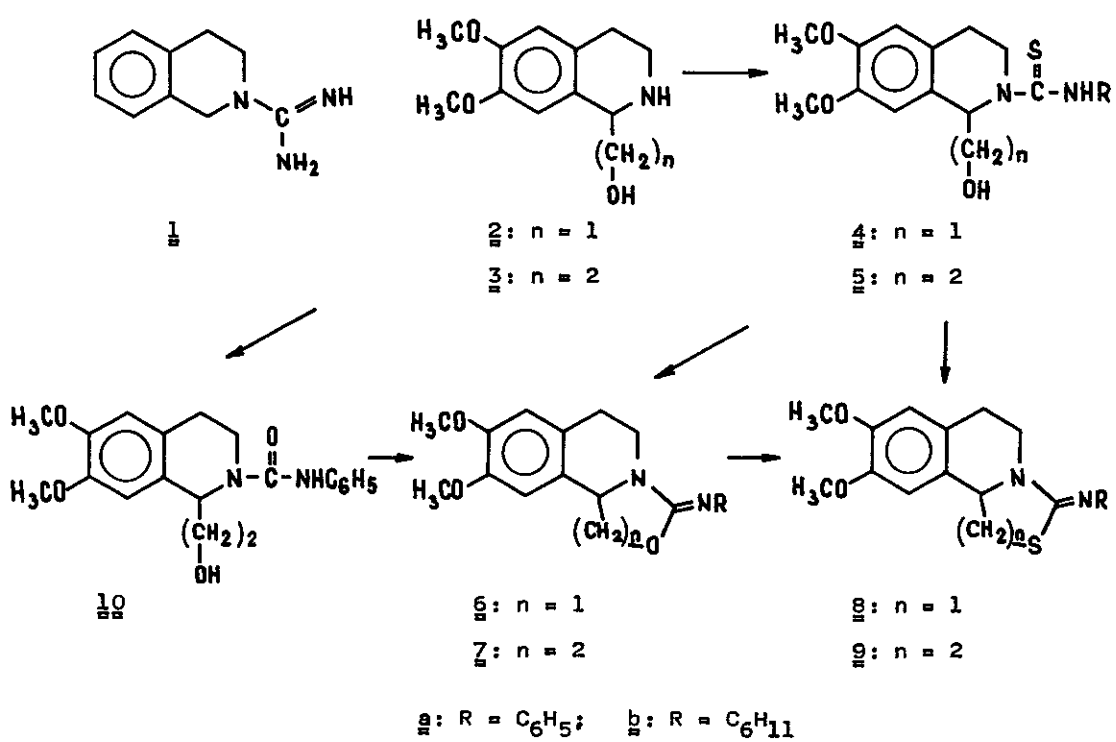
Abstract - Calycotomine (2) and homocalycotomine (3) reacted with isothiocyanates to give the corresponding thiocarbamides (4, 5). The latter were treated with methyl iodide, and subsequent elimination of methyl mercaptan on treatment with alkali afforded 1,3-oxazolo[4,3-a]-isoquinolines (6) and 1,3-oxazino[4,3-a]isoquinolines (7). 1,3-Thiazolo[4,3-a]isoquinolines (8) and 1,3-thiazino[4,3-a]isoquinolines (9) were prepared from 4 and 5 with hydrogen chloride. Compound 7a was also synthesized by the reaction of 3 with phenyl isocyanate, followed by the elimination of water; 9a was obtainable from 7a by treatment with P_4S_{10}. The structures of compounds 6-9 were confirmed by ^1H NMR.

In recent decades several guanidine derivatives have found medical use (e.g. Debrisoquine, Guanethidine, Clonidine).[2] Substitution of one of the guanidine nitrogens by a bioisosteric atom (O, S) gives compounds of high and varied pharmacological activities. Of the heterocyclic derivatives in this group, the main objects of research were the 2-imino-substituted 1,3-thiazoles, 1,3-thiazines, 1,3-oxazoles and 1,3-oxazines.[3-7]

Detailed studies have been carried out in this laboratory concerning the ring-closure reactions of alicyclic 1,3-aminoalcohol derivatives, such as 2-(amino-methyl)-1-cyclanols and 2-(hydroxymethyl)-1-cycloalkylamine (see e.g. ref.[8-10]). The present report is concerned with the synthesis of 1,3-thiazolidine, 1,3-oxazolidine, 1,3-thiazine and 1,3-oxazine derivatives fused with the tetrahydro-isoquinoline skeleton (6-9); these compounds are obtainable by the cyclization of aminoalcohols of the isoquinoline series, such as 1-(α-hydroxymethyl)- (2) and 1-(β-hydroxyethyl)-tetrahydroisoquinolines (3). Though these products are closely related cyclic analogues of Debrisoquine (1), their syntheses have not been reported.

The synthetic pathway is shown in the Scheme. The general procedure is a modification of the method developed earlier[3] for the preparation of 1,3-oxazines and 1,3-thiazines. Calycotomine (2) or homocalycotomine (3) (prepared by described methods[11,12]) was refluxed in benzene for 1 h with an equivalent amount of isothiocyanate to obtain the corresponding thiocarbamides (4, 5) in nearly quantitative yield. Mp's 4a: 171-172°C; 4b: 105-107°C; 5a: 185-188°C; 5b: 186-188°C (All compounds were recrystallized from EtOH[13]).



Compounds 4 and 5 were allowed to stand for 1 h at room temperature with excess methyl iodide to give the thiuronium salts. In one case, when starting from 5a, the thiuronium salt was isolated (mp 154-156°C, from EtOH[13]). The residue obtained on evaporation of the methyl iodide-containing reaction mixture was stirred at room temperature in methanol containing 3 N potassium hydroxide. After methyl mercaptan had been completely expelled (2-4 h), the reaction mixture was evaporated. When R = C_6H_5, the residue was mixed with water and the crystalline product was filtered off; in the case of R = C_6H_{11}, the product was isolated by extraction of the evaporation residue with hot benzene. Both methods of work-up gave the 1,3-oxazolo[4,3-a]isoquinolines (6) and 1,3-oxazino[4,3-a]-isoquinolines (7), respectively, in good yields.

Refluxing of 4 and 5 for 15 min in ethanol containing 20% dry hydrogen chloride gave, after evaporation and neutralization, 1,3-thiazolo[4,3-a]isoquinolines (8) and 1,3-thiazino[4,3-a]isoquinolines (9), respectively.

The mp, IR and ^{1}H NMR data on the synthesized compounds are shown in the Table.

The 1,3-oxazine 7a was also prepared from homocalycotomine (3) and phenyl isocyanate via the urea derivative 10 (mp 167-168°C, from EtOH[12]), by treatment with thionyl chloride; however, the yield was only 17%.

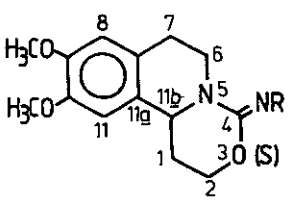
The 1,3-thiazine (9a) was synthesized in an alternative route[14] by heating 7a with phosphorus pentasulphide for 2 h at 150°C; the product (9a) was obtained in 31% yield.

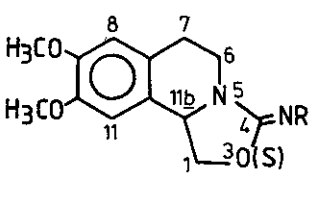
Crabb and Mitchell[15] synthesized and made a detailed ^{1}H NMR study of the closely analogous compounds, cis-4-(p-nitrophenyl)-1,6,7,11b-tetrahydro-2H,4H-1,3-oxazino[4,3-a]isoquinoline (11) and cis-4-(p-nitrophenyl)-1,6,7,11b-tetrahydro-2H,4H-1,3-thiazino[4,3-a]isoquinoline (12). In the oxazino 11 and in the related thiazino derivative 12 Bohlmann bands were absent and the NMR spectrum indicated predominance of the O (or S) inside form as concerns the two possible B/C cis conformers.

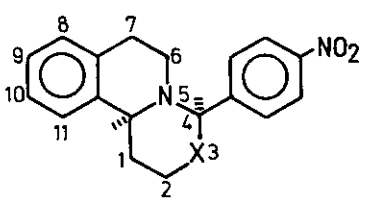
The ^{1}H NMR spectra of the compounds 6-9 synthesized in the present work are in good agreement with the data measured by Crabb (cf. Table). As the lone electron pair of 5-N is considerably conjugated with the near-by hetero atoms, the appearance of Bohlmann bands cannot be expected. The presence of $\overset{\displaystyle N-C=N}{\underset{\displaystyle O}{|}}$ or $\overset{\displaystyle N-C=N}{\underset{\displaystyle S}{|}}$ groups makes the conformation of the hetero ring near-planar. This is

No	Mp (^{o}C)[b]	IR[16] ν_{max} (cm^{-1})	^{1}H NMR[17] data[a] Chemical shifts (ppm) OCH_3	$-CH_2-O$(s)	H-11b	H-11	H-8	Coupling constants (Hz) $J_{11b,1ax}$	$J_{11b,1eq}$
6a	129-130	1680	3,82	4,6	4,15	6,47	6,65	7,5	4,0
6b	104-105	2910, 1675	3,83	4,7	4,15	6,55	6,65	7,5	4,0
7a	115-118	1585, 1550	3,82	4,6	4,15	6,6	6,66	8,0	4,0
7b	128-129	2910, 1620	3,84	4,5	4,15	6,61	6,64	8,0	4,5
11[c]	145-147			4,03	4,17			11,9	4,0
8a	147-148	1625	3,83	4,7	3,5	6,6	6,68	10,0	6,0
8b	134-135	2905, 1605	3,82	4,7	3,55	6,62	6,65	10,0	6,0
9a	158-160	1575	3,84	4,7	4,40	6,63	6,67	9,0	4,5
9b	111-112	2915, 1575	3,84	4,6	4,35	6,61	6,66	9,0	5,0
12[c]	114-116			4,15	4,24			11,5	3,5

[a] In order to facilitate comparison, the numbering of compounds 6-12 in the Table is as follows:







11: X = O; 12: X = S

[b] All compounds were recrystallized from ethanol.

[c] Compounds synthesized and studied by Crabb and Mitchell.[15]

supported by the higher chemical shifts of the CH_2-O(S) protons as compared with the corresponding protons in compounds **11** or **12**, and also by the $J_{11b,1ax}$ values, which are significantly smaller than in usual diaxial couplings.

Results of the current investigation of some reactions of **6**-**9** and a high-resolution NMR study of these compounds will be described in a forthcoming publication.

REFERENCES AND NOTES

1. Part 46.: G. Bernáth, J. Lázár, L. Gera, Gy. Göndös and Z. Ecsery: Acta Chim. Acad. Sci. Hung., in press. At the same time this paper forms Stereochemical Studies, Part 63. Part 62.: P. Pflegel, Ch. Kühnstedt, F. Fülöp, G. Bernáth: Pharmazie, in press.
2. A. Kleemann and J. Engel: "Pharmazeutische Wirkstoffe" Georg Thieme Verlag, Stuttgart, 1978.
3. P. L. Ovechkin, L. A. Ignatova, A. E. Gechman and B. V. Unkovskii: Khim. Get. Soed., 1974, 357.
4. G. Tóth and A. Almásy: Org. Magnetic Resonance, 1982. **19**, 219.
5. L. Toldy and J. Lipták: Tetrahedron Letters, 1970, 4319.
6. A. R. Katritzky, R. T. Langthorne, R. C. Patel and G. Lhommet: Tetrahedron, 1981, **37**, 2383.
7. T. Okawara, K. Nakayama and M. Furukawa: Heterocycles, 1982, **19**, 1571.
8. G. Bernáth, Gy. Göndös, K. Kovács and P. Sohár: Tetrahedron, 1973, **29**, 981.
9. F. Fülöp and G. Bernáth: Synthesis, 1981, 628.
10. G. Stájer, A. E. Szabó, F. Fülöp, G. Bernáth and P. Sohár: Heterocycles, 1982, **19**, 1191.
11. J. Kóbor and K. Koczka: Szegedi Tanárképző Főiskola Tud. Közl., 1969, 179. (Chem. Abstr., 1972, **77**, 151861.)
12. L. Dúbravková, I. Ježo, P. Šefčovič and Z. Votický: Chem. Zvesti, 1959, **13**, 16. (Chem. Abstr., 1959, **53**, 17162e.)
13. All prepared compounds gave satisfactory elemental (C, H, N, S) analyses.
14. A. I. Meyers: J. Org. Chem., 1960, **25**, 1147.
15. T. A. Crabb and J. S. Mitchell: Org. Magnetic Resonance, 1976, **8**, 258.
16. IR spectra were recorded with a SPECORD 75 IR instrument in KBr pills.
17. ^{1}H NMR spectra were recorded at 60 MHz with a JEOL C60 spectrometer at room temperature in $CDCl_3$ solution with TMS as internal standard.

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