SYNTHESIS OF NEW BIHETEROCYCLIC ANALOGUES OF PYRIDOCARBAZOLES

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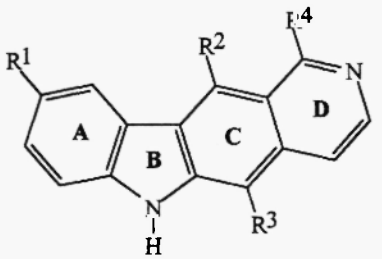
ABSTRACT : Pyridocarbazoles like ellipticine are known for their antitumor activity. Many heterocyclic analogues of these compounds have been synthesized. In this paper, the synthesis of new biheterocyclic analogues of ellipticine, by replacing rings B and C by other heterocycles, is described.

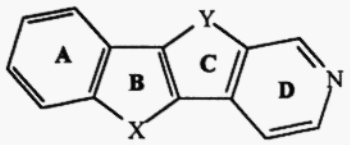
INTRODUCTION

Certain 6*H*-pyrido[4,3-*b*]carbazoles, for example, ellipticine, 9-methoxyellipticine and olivacine, occur in plants of the *Aspidosperma*, *Ochrosia* and *Tabernaemontana* genera of the family *Apocyanaceae*. These natural products, despite their apparent structural simplicity, are the subject of continuing interest firstly because of the controversy which surrounds their mode of biogenesis and secondly because of their anti-cancer activities (1).



Ellipticine	$R^1 = R^4 = H, R^2 = R^3 = CH_3$
9-Methoxyellipticine	$R^1 = OCH_3, R^2 = R^3 = CH_3, R^4 = H$
Olivacine	$R^1 = R^2 = H, R^3 = R^4 = CH_3$

Many studies toward the synthesis of these pyridocarbazoles have been made in recent years (2). Few examples of replacement of the carbazole nitrogen in these compounds by other heteroatoms like oxygen and sulfur have been described (3). In this paper, we present the results obtained by replacing rings B and C by different heterocycles like furane, thiophene and selenophene to prepare compounds of general structure I.



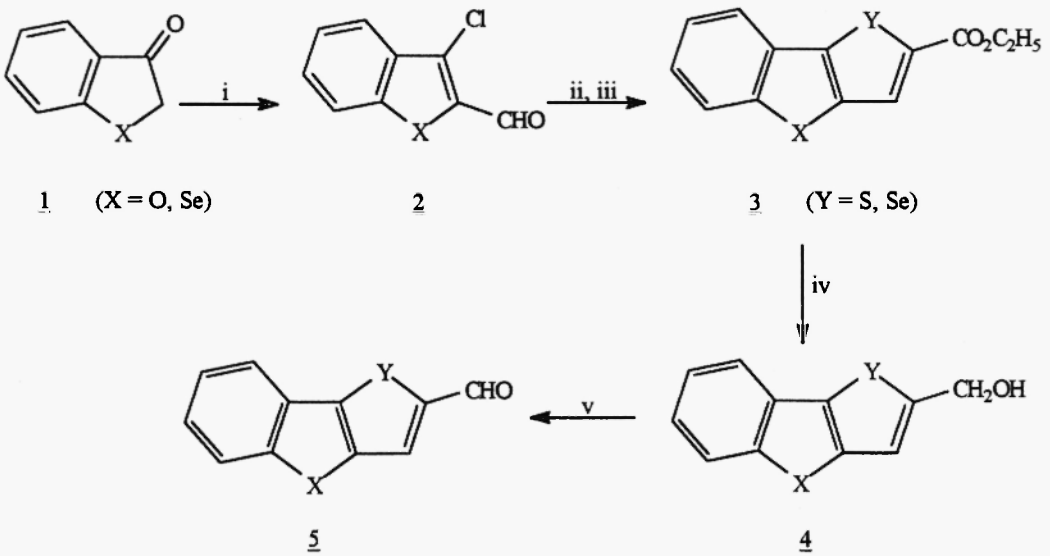
I X = O, Se
Y = S, Se

In our approach, the tricyclic ring system ABC is prepared first and the final sequence involves the construction of ring D.

Our stategy was based on the Pomeranz-Fritsch isoquinoline synthesis (4, 5). Of the many methods available for the preparation of isoquinoline alkaloids, including the well-known Bischler-Napieralski cyclisation (6a) (affords dihydroisoquinolines) and the Pictet-Spengler ring closure (6b) (yields tetrahydroisoquinolines), only the Pomeranz-Fritsch cyclisation provides a general and direct method for the construction of an isoquinoline ring.

RESULTS AND DISCUSSION

In our case, Pomeranz-Fritsch cyclisation will be applied onto tricyclic aldehydes 5. Compounds 5 were prepared starting from ketones 1 (7a, 7b, 8) (scheme 1).



1 (X = O, Se) 2 3 (Y = S, Se)

4 5

Reagents and conditions : i, $POCl_3$, DMF, 60° ; ii, Na_2Y (Y = S or Y = Se), DMF, $ClCH_2CO_2C_2H_5$; iii, H_2SO_4, ethanol abs., reflux ; iv, $LiAlH_4$, ether, reflux ; v, PCC, CH_2Cl_2.

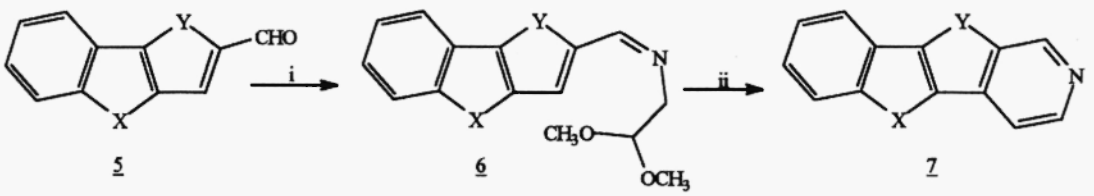
Scheme 1

The ketones 1, *via* a Vilsmeier-Haack-Arnold reaction (9), lead to derivatives 2, which by condensation with sodium sulfide (Y = S) or selenide (Y = Se) and ethyl chloroacetate, give compounds 3 (10) (Table I). Compounds 3 may be obtained with some acids from 2. Esterification allows to have only 3, easier to reduce.

Table I : Chemical data of compounds 3

X	Y	Mp (°C) (Lit.)	Yields (%)	Anal. Found / Calcd. (%)	
				C	H
O	S	91 (pet. ether)	75	63.58 63.41	4.06 4.06
O	Se	85 (ether)	67	53.48 53.24	3.52 3.41
Se	S	102 (97) (ether/pet.ether)	70	50.19 50.48	3.12 3.23
Se	Se	132 (135)	82	43.57 43.82	2.64 2.81

Reduction of 3 to alcohols 4 (table II) (11) followed by oxidation with pyridinium chlorochromate (12) allows the formation of aldehydes 5 (table III) which are used in the Pomeranz-Fritsch reaction for creating the isoquinoline ring (scheme 2).



5 6 7

Reagents and conditions : i, $NH_2CH_2CH(OCH_3)_2$, toluene, azeotropic reflux ; ii, polyphosphoric acid, 150°C.

Scheme 2

Table II : Chemical data of compounds 4

X	Y	Mp (°C)	Yields (%)	Anal. Found / Calcd. (%)	
				C	H
O	S	116 (ether)	89	64.53 64.70	3.84 3.92
O	Se	130 (ether)	55	52.40 52.58	3.14 3.18
Se	S	116 (chloroform/ pet. ether)	82	49.84 49.44	3.06 2.99
Se	Se	114	98	41.87 42.04	2.49 2.55

Table III : Chemical data of compounds 5

X	Y	Mp (°C)	Yields (%)	Anal. Found / Calcd. (%)	
				C	H
O	S	124 (ether/pet.ether)	86	65.32 65.34	3.11 2.97
O	Se	112 (ether)	79	53.00 53.01	2.34 2.41
Se	S	130 (ethylacetate/ pet.ether)	70	49.77 49.81	2.54 2.26
Se	Se	134	67	42.07 42.31	1.80 1.92

Reaction of aldehydes 5 with aminoacetaldehyde dimethylacetal gives the Shiff's bases 6 (table IV) which are cyclised under acidic conditions to give the tetracyclic compounds 7 (table V).

Different acidic conditions have been used : 85% phosphoric acid, sulfuric acid (concentrated and 76%) and polyphosphoric acid.

Only the cyclisation with polyphosphoric acid gave access to compounds 7 with moderate yields.

Table IV : Chemical data of compounds 6

X	Y	Mp (°C)	Yields (%)	Anal. Found / Calcd. (%)		
				C	H	N
O	S	85 (pet.ether)	90	62.21 62.28	5.04 5.19	4.73 4.84
O	Se	89 (ether/pet.ether)	86	53.49 53.57	4.22 4.46	4.20 4.16
Se	S	oil	92	not determined (pure by TLC and NMR)		
Se	Se	oil	95	not determined (pure by TLC and NMR)		

Table V : Chemical data of compounds 7

X	Y	Mp (°C)	Yields (%)	^{1}H NMR ($CDCl_3$)* δ (ppm) and multiplicity**
O	S	195	25	7.41 (2H, m, Ar-H); 7.64 (1H, d, Ar-H); 7.76 (1H, d, Ar-H); 7.81 (1H, d, Ar-H); 8.59 (1H, d, Ar-H); 9.11 (1H, s, CH = N).
O	Se	172	33	7.40 (2H, m, Ar-H); 7.66 (1H, d, Ar-H); 7.74 (1H, d, Ar-H); 7.85 (1H, d, Ar-H); 8.60 (1H, d, Ar-H); 9.11 (1H, s, CH = N).
Se	S	204	27	7.47 (2H, m, Ar-H); 7.68 (1H, d, Ar-H); 7.97 (2H, t, Ar-H); 8.60 (1H, d, Ar-H); 9.19 (1H, s, CH = N).
Se	Se	212	21	7.40 (2H, m, Ar-H); 7.70 (1H, d, Ar-H); 7.92 (1H, d, Ar-H); 8.03 (1H, d, Ar-H); 8.63 (1H, s, Ar-H); 9.22 (1H, s, CH = N).

* With TMS as internal standard

** Abreviations have their usual significance

Table VI : Elemental analyses of compounds 7

X	Y	Anal. Found / Calcd. (%)		
		C	H	N
O	S	69.63	3.30	6.11
		69.33	3.11	6.22
O	Se	57.46	2.82	5.08
		57.35	2.57	5.14
Se	S	54.02	2.62	5.03
		54.16	2.43	4.86
Se	Se	46.52	2.33	4.35
		46.56	2.08	4.17

EXPERIMENTAL

All the melting points were determined on a Kofler Bench and were uncorrected. ^1H NMR spectra were recorded on a Brucker 250 MHz spectrometer ($CDCl_3$, TMS as internal standard).

Compounds 1, 2, 3 were prepared by known methods (7a, 7b, 8, 9, 10).

Preparation of alcohols 4

To a solution of 0.025 mol (2.50 equivalents) of lithium aluminium hydride in 30 ml of dry ether was added, 0.01 mol (1 equivalent) of ester 3, at a rate such as to keep a gentle reflux. The mixture was refluxed for 3 hours. After cooling to room temperature, water was added dropwise with cooling. The mixture was then poured onto an ice cooled solution of 20% H_2SO_4. Extraction with ether, washing with water and drying, gave, after evaporation, the crude product which was purified by recrystallisation (Table II).

Preparation of aldehydes 5

A solution of compound 4 (0.01 mol) in CH_2Cl_2 (26 ml) was added in one portion to a stirred suspension of PCC (0.01 mol) in CH_2Cl_2 (26 ml) and the mixture was stirred at room temperature for 2-3 hours. 50 ml of ether was added and the solution decanted from the residue. The residue was extracted 2 or 3 times with 50 ml of ether. The combined extracts were filtered on silica gel. Evaporation gave the crude product 5 which was purified by recrystallisation (Table III).

Preparation of Schiff's bases 6

Aldehyde 5 (0.04 mol) was dissolved in dry toluene (100 ml) and aminoacetaldehyde dimethylacetal (0.042 mol) was added. The solution was refluxed (Dean-Stark) until no further water was evolved (usually 5-7 hours). Removal of the solvant under reduced pressure gave the Schiff's base 6. Purification was carried out by recrystallisation or by distillation (Table IV). Yields are almost quantitative.

Preparation of the tetracyclic compounds 7

A mixture of 6 (1 g) and polyphosphoric acid (80 g) was heated at 130°-150°C for 3 hours with stirring. The reaction mixture was stirred at room temperature overnight and poured into ice-water , basified with a 20% sodium hydroxide solution and extracted with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4, filtered and evaporated to produce the crude product 7, purified by chromatography on silica gel using dichloromethane:ethylacetate (8:2) as eluent.

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REFERENCES

1. P. A. Cranwell and J. E. Saxton, J. Chem. Soc., Perkin Trans. 1, 3482 (1962); R. B. Woodward, G. A. Iacobucci and F. A. Hochstein, J. Am. Chem. Soc., 81, 4434 (1959); M. Sainsbury, Synthesis, 437 (1977).

2. A. H. Jackson, P. R. Jenkins and P. V. R. Shannon, J. Chem. Soc., Perkin Trans. 1, 1698 (1977); J. R. Dormoy and A. Heymes, Tetrahedron, 49, 2885 (1993).

3. A. N. Fujiwara, E. M. Acton and L. Goodman, J. Heterocycl. Chem., 5, 853 (1968); Ibid., 6, 379 (1969).

4. R. Adams (Ed.), Organic Reactions, John Wiley, New York, 6, 191 (1959).

5. A. J. Birch, A. H. Jackson and P. V. R. Shannon, J. Chem. Soc., Perkin Trans. 1, 2185 (1974); J. M. Bobbitt, K. L. Khanna and R. Ebermann, J. Org. Chem., 30, 2247 (1965).

6. a- R. Adams (Ed.), Organic Reactions, John Wiley, New York, 6, 74 (1959); b- Ibid., 6, 151 (1959).

7. a- L. Perrin, Ph. D. Thesis, Metz, 1973.
b- G.Kirsch, Ph. D. Thesis, Metz, 1973.

8. C. Hansch and H. G. Lindwall, J. Org. Chem., 10, 381 (1945); G. M. Badger, D. J. Clark and K. T. H. Farrer, J. Chem. Soc., 2624 (1957).

9. Z. Arnold, J. Zemlicke, Collect. Czech. Chem. Comm., 24, 2385 (1959).

10. G. Kirsch and D. Prim, F. Leising and G. Mignani, J. Heterocycl. Chem., 31, 1005 (1994).

11. R. F. Nystrom and W. G. Brown, J. Am. Chem. Soc., 69, 1197 (1947).

12. E. J. Corey and J. W. Suggs, Tetrahedron Lett., 2647 (1975)

13. M. C. Liu, T. S. Lin and A. C. Sartorelli, J. Med. Chem., 38, 4234 (1995).

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