Synthesis of Vinca Alkaloids and Related Compounds. XLVI. [1]. Formation of a New Ring System

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In the Pictet-Spengler reaction of indole-3-propanamine **1** and diethyl-(2-formyl-cyclopropane-1,1-dicarboxylate) **2** the formation of ethyl (1a,2,4,5,6,11,11b,11c-octahydro-2-oxo-1*H*-cycloprop[3',4']pyrrolo[1',2':1,2]-azepino[3,4-*b*]indole-1a-carboxylates) **3** and **4** was observed. Compounds **3** and **4** represent a new ring system.

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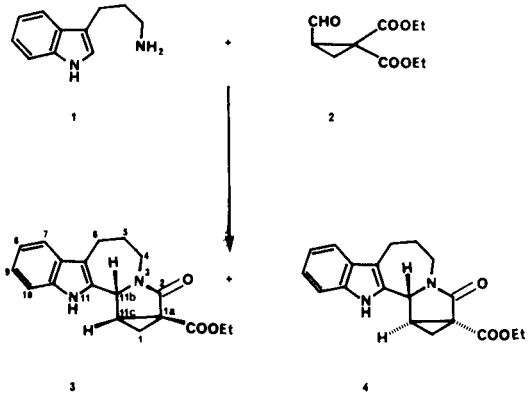
Investigating the synthesis of vincamine, Winterfeldt *et al.* in 1977 reported a route [2] *via* cycloprop[1,2]indolizino[8,7-*b*]indoles. Since that time indole derivatives containing a fused cyclopropane ring have attracted further attention [3-8].

The cycloprop[1,2]indolizino[8,7-*b*]indoles are prepared [8] by the Pictet-Spengler condensation of tryptamine and Warner's aldehyde **2** [9]. As a generalization of this principle, a homologue of tryptamine, indole-3-propanamine **1** was reacted with an equimolar amount of Warner's aldehyde **2**. From the reaction mixture the lactams **3** (0.4%) and **4** (0.4%) were isolated (Scheme 1). In the case of the analogous cycloprop[1,2]indolizino[8,7-*b*]indoles, the yields were significantly higher (16% and 2.3% respectively) [8]. The very low yield in this case may be attributed to the well-established fact that formation of a seven-membered ring is handicapped when compared with the development of a six-membered one.

Scheme 1



On the other hand, some derivatives of another closely related ring system, the pyrido[1',2':1,2]azepino[3,4-*b*]-indole were synthetized in the seventies and proved to have diuretic activity [10-14].

The structure of **3** and **4** was proved by spectroscopic methods, making use of the analogies [4,8]. The fact that the 4α proton shows an upfield shift in both compounds due to the anisotropic magnetic field of the lactam carbonyl group provides an evidence for the conformation of the azepine ring. The ring atoms are placed on two intersecting plane: the atoms 6, 6a, 11a, 11b, and 3 are approximately coplanar, as well as the atoms 3, 4, 5, and 6.

The lactams **3** and **4** are derivatives of a new ring system, cycloprop[3',4']pyrrolo[1',2':1,2]azepino[3,4-*b*]indole.

EXPERIMENTAL

Relative configuration is described according to the CIP rules [15]. The ir spectra were recorded with a Karl Zeiss SPECORD 75 IR instrument. The ^{1}H nmr spectra were obtained on a Varian XL-100 spectrometer at 100.1 MHz. Mass spectra were taken on an AEI MS 902 instrument.

Condensation of 1*H*-Indole-3-propanamine (**1**) and Diethyl (2-Formylcyclopropane-1,1-dicarboxylate) (**2**).

Amine **1** (12 g, 0.0709 mole) and aldehyde **2** (10 g, 0.0709 mole) were heated in acetic acid (100 ml) at 50° for 24 hours. The resulting mixture was poured in a citric acid solution (300 ml, 3.6%) and extracted with dichloromethane (4 x 50 ml). The extract was dried over sodium sulfate, the solvent was removed and the residue was chromatographed over silica gel (column length: 0.6 m, diameter: 0.05 m, eluent: toluene-ethyl acetate 1:1). The crude lactams **3** and **4** were recrystallized from ethyl acetate-hexane.

Ethyl (1a,2,4,5,6,11,11b,11c-Octahydro-2-oxo-1*H*-cycloprop[3',4']-pyrrolo[1',2':1,2]azepino[3,4-*b*]indole-1a-carboxylate) (1a-11b u, 1a-11c l) (**3**).

This compound was obtained as colorless prisms and yielded 95 mg (0.4%), mp 249-250°; ir (potassium bromide): 3413, 3300, 1707, 1667 d cm^{-1}; ms: [70 eV, 150°, m/e (%)], 325 (21) (M + 1), 324 (100) (M), 323 (33), 310 (0.3), 295 (2.9), 279 (6.2), 278 (4.1), 277 (2.6), 267 (1.7), 251 (48), 250 (5.7), 249 (3.2), 239 (1.0), 223 (4.3), 222 (3.8), 221 (3.2), 197 (3.8), 195 (4.8), 194 (4.3), 184 (3.6), 183 (4.3), 181 (3.6), 180 (3.8), 169 (3.6), 168 (6.4), 167 (5.2), 157 (3.1), 156 (8.0), 155 (2.3), 154 (3.3), 143 (3.3), 139.5 (2.6), 139 (1.5), 130 (8.3); ^{1}H-nmr (deuteriochloroform + DMSO-d_6): δ, ppm 9.79 (1H, bs, NH), 7.25-7.55 (2H, m, C7-H, C10-H), 6.9-7.25 (2H, m, C8-H, C9-H), 5.22 (1H, d, $J_{11b,11c}$ = 6 Hz, C11b-H), 4.28 (1H, m, C4-H$_\alpha$), 4.26 (2H, q, J = 7 Hz, OCH_2), 2.98 (1H, ddd, J_{trans} = 5 Hz, J_{cis} = 8 Hz, C11c-H), 2.6-3.15 (3H, m, C4-H$_\beta$ + C6-H_2), 1.7-2.2 (2H, m, C5-H_2), 1.83 (1H, dd, J_{gem} = −5 Hz, C1-H$_\beta$), 1.32 (3H, t, CH_3), 1.07 (1H, dd, C1-H$_\alpha$).

Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.63. Found: C, 70.14; H, 6.06; N, 8.92.

Ethyl-(1a,2,4,5,6,11,11b,11c-Octahydro-2-oxo-1*H*-cycloprop[3',4']-pyrrolo[1',2':1,2]azepino[3,4-*b*]indole-1a-carboxylate) (1a-11b l, 1a-11c l) (**4**).

This compound was obtained as colorless prisms and yielded 96 mg (0.4%); mp: 224-225°; ir (potassium bromide): 3316, 1719, 1659 cm^{-1}; ms: [70 eV, 150°, m/e (%)], 325 (23), 324 (100), 323 (17), 310 (0.6), 295 (1.7), 297 (10.4), 278 (21), 277 (5.3), 267 (0.9), 251 (29), 250 (10), 249 (5.4), 239 (1.7), 223 (4.1), 222 (6.3), 221 (8.3), 197 (3.5), 195 (4.6), 194 (6.1), 184 (4.6), 183 (4.8), 181 (9.2), 180 (5.8), 169 (5.1), 168 (11), 167 (8.5), 157 (5.2), 156 (15), 155 (4.2), 154 (4.1), 143 (4.6), 139.5 (3.5), 139 (9.3), 130 (9.3); ^1H nmr (deuteriochloroform): δ, ppm 8.44 (1H, bs, NH), 7.0-7.6 (4H, m, aromatic CH protons), 4.81 (1H, s, C11b-H), 4.28 (1H, m, C4-H_α), 4.17 (2H, q, J = 7 Hz, OCH_2), 2.7-3.1 (3H, m, C4-H_β + C6-H_2), 2.69 (1H, dd, J_{trans} = 5 Hz, J_{cis} = 8 Hz, C11c-H), 1.8-2.3 (2H, m, C5-H_2), 2.01 (1H, dd, J_{gem} = −5 Hz, Cl-H_α), 1.27 (1H, dd, Cl-H_β), 1.20 (3H, t, CH_3).

Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.63. Found C, 70.25; H, 6.36; N, 8.86.

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REFERENCES AND NOTES

[1] For Part **XLV**. see Zs. Kardos-Balogh, F. Sóti, M. Incze, M. Kajtár-Peredy and Cs. Szántay: A New Heterocyclic Ring System, *Heterocycles*, **29**, 1589 (1989).

[2] F. Klatte, U. Rosentreter and E. Winterfeldt, *Angew. Chem.*, **89**, 916 (1977).

[3] E. Winterfeldt and U. Rosentreter, *German Offen.* 27 53 730 (1979); *Chem. Abstr.*, **91**, 123730z (1979).

[4] R. Becker, G. Benz, M. Rösner, U. Rosentreter and E. Winterfeldt, *Chem. Ber.*, **112**, 1879 (1979).

[5] H. Hammer, M. Rösner, U. Rosentreter and E. Winterfeldt, *Chem. Ber.*, **112**, 1889 (1979).

[6] M. Mailand and E. Winterfeldt, *Chem. Ber.*, **114**, 1926 (1981).

[7] H. Hammer and E. Winterfeldt, *Tetrahedron*, **37**, 3609 (1981).

[8] A. Dancsó, Gy. Kalaus, M. Kajtár-Peredy, L. Szabó and Cs. Szántay, *Acta Chim., Acad. Sci. Hung.*, in press.

[9] D. T. Warner, *J. Org. Chem.*, **24**, 1536 (1959).

[10] D. R. Herbst and H. Smith, *German Offen.* 20 04 356 (1971); *Chem. Abstr.*, **76**, 3414g (1972).

[11] D. R. Herbst and H. Smith, *German Offen.* 20 33 631 (1971); *Chem. Abstr.*, **76**, 113061h (1972).

[12] D. R. Herbst, H. Smith, *S. African* Patent 70 00 530 (1971); *Chem. Abstr.*, **77**, 34373d (1972).

[13] A. G. Terzyan, S. P. Avakyan and G. T. Tatevosyan, *Arm. Khim. Zh.*, **24**, 509 (1971).

[14] A. G. Terzyan, L. A. Manucharowa and G. T. Tatevosyan, *Arm. Khim. Zh.*, **29**, 342 (1976).

[15] V. Prelog and G. Helmchen, *Angew. Chem.*, **94**, 614 (1982).