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NEW SYNTHESIS OF 1,4 BENZODIAZEPINE-2,5-DIONES BY MEANS OF HCL GAS CATALYST.

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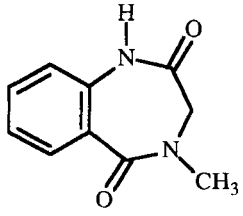
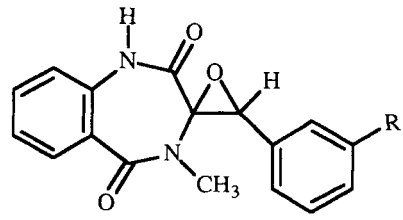
Abstract : A new synthesis of 1,4- benzodiazepinediones **4** *, particularly 1,4-dihydro1H-1,4-benzodiazepine-2,5-dione,***4c** *key intermediate of metabolites cyclopenin* **9**, *cyclopenol* **10**, *cyclopeptine* **11** *and dehydrocyclopeptine* **12** *, was achieved by action of dry HCl gas in DMF on compound* **3** *prepared from anthranilic acid derivative* **1** *and amino ester* **2**.

Biosynthetic studies by Luckner have established that cyclopenin **5** and cyclopenol **6** metabolites of *Penicillium cyclopium* Westling, incorporate anthranilic acid and phenylalanine efficiently (1). Tracer experiments (2) and related studies (3) have shown that the compounds **5** and **6** are formed biosynthetically via cyclopeptine **7** and dehydrocyclopeptine **8** which are reversibly interconverted in vivo (4).

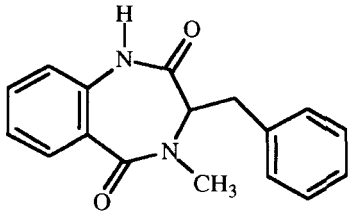


4c



5 : R = H
6 : R = OH

* To whom correspondence should be addressed



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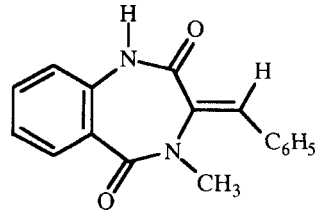

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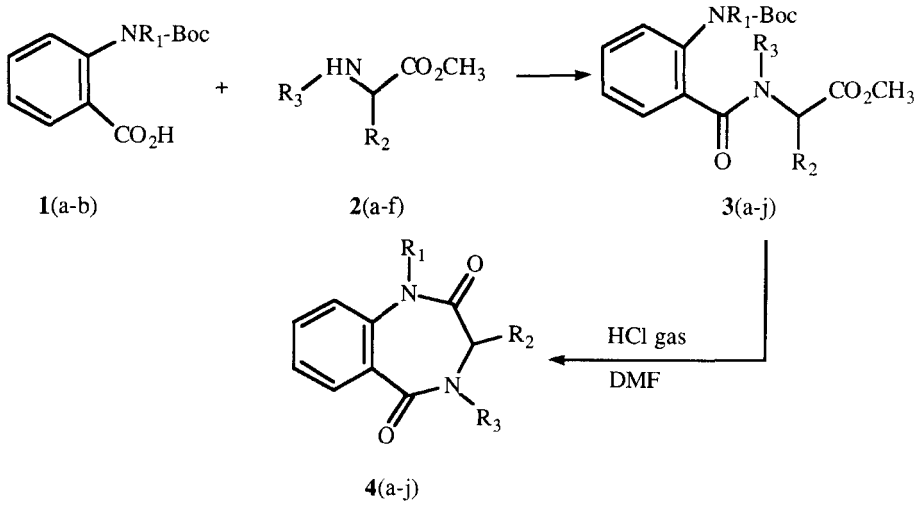
Our interest in this area prompted us to explore synthetic methods to prepare the benzodiazepinediones, key intermediates for the synthesis of these diazepine metabolites (5).

In our previous reports, we have reported a new synthetic method for 1,4-benzodiazepine-2,5 diones (BZDs) by application of amino acid N-carboxy anhydrides (NCAs) (6).

In the present study we describe a continuation of our work, we have been particularly interested in exploration of a new route for the synthesis of 1- and/or 4-substituted benzodiazepinediones **4**(a-j)scheme1.



1(a-b) **2**(a-f) **3**(a-j)

4(a-j)

Scheme 1

Subsequently, we attempted to synthesize the key compound **4c** intermediate for the synthesis of diazepine metabolites : 3,10 dehydro - cyclopeptine **8** , cyclopeptine **7** , cyclopenin **5** and cyclopenol **6** , by this method.

Although the synthesis of these four compounds has been achieved by several groups (2,7), the present syntheses of these compounds were effected by preparation of the key intermediate 1,4-dihydro-1H BZD **4c** .

As shown in scheme 1, the synthesis started with the protected anthranilic acid derivatives **1**. The resulting acid **1a** was then coupled with sarcosine methyl ester **2** . The reaction was accomplished under standard peptide coupling conditions with dicyclohexylcarbodiimide and 4,4-dimethyl aminopyridine catalyst to give the dipeptide **3c** in 87%yield.

Several methods were explored to cyclize **3c** to compound **4c**. After removal of the tert-butyloxycarbonyl group by TFA in CH_2Cl_2 the cyclisation to BZD was tempted using NEt_3 in different solvents : CH_2Cl_2, CH_3CN, toluene, without success ; cyclization to BZD **4c** was accomplished in 87% yield by heating **3c** in DMF at 60°C in the presence of hydrogen chloride gas catalyst.

In connection with this work we report the development of a versatible method for the synthesis of 1 and /or 4-substituted BZDs **4**(a-j) as shown in scheme 1. The yields and melting points of the products are summarised in table 1.

In conclusion, this route allowed us to prepare mono or disubstituted benzodiazepine-2,5-diones in good overall yields and in few steps from readily available starting materials.

Experimental section

Melting points were obtained on a Electrothermal melting point apparatus and are uncorrected. IR spectra (KBr,cm^{-1}) were recorded with a Shimadzu IR-435 spectrometer. ^{1}HNMR spectra were obtained on VARIAN EM-360(60MHz) and BRUCKER (250MHz) instruments, TMS as internal

Table 1 : Characterization of BZDs 4

Amino ester 2	R_1	R_3	BZD	Yield %	mp °C *	formula
2a Gly	H	H	**4a**	59	328 [a]	$C_9H_8N_2O_2$/176
	CH_3	H	**4b**	69	194 [b]	$C_{10}H_{10}N_2O_2$/190
2b Sar	H	CH_3	**4c**	87	250-252 [c]	$C_{10}H_{10}N_2O_2$/190
	CH_3	CH_3	**4d**	87	153 [d]	$C_{11}H_{22}N_2O_2$/204
2c Ala (L) or (D, L)	H	H	**4e**	64	336 [a]	$C_{10}H_{10}N_2O_2$/190
	CH_3	H	**4f**	80	245-246 [d]	$C_{11}H_{12}N_2O_2$/204
2d Phe (L) or (D, L)	H	H	**4g**	62	268-270 [a]	$C_{16}H_{14}N_2O_2$/266
	CH_3	H	**4h**	72	224-225 [e]	$C_{17}H_{16}N_2O_2$/280
2e Pro (L)	H	/	**4i**	82	216-218[a]	$C_{12}H_{12}N_2O_2$/216
2f Glu (L)	H	H	**4j**	55	190 [a]	$C_{13}H_{14}N_2O_4$/262

*: Solvent of recrystallization : a)EtOH, b)$CHCl_3$, c)Acetone, d)$CHCl_3$/Hex., e)EtOAc/Hex.

standard, chemical shifts in δ ppm, splitting patterns designated as follows : s, singlet ; d, doublet ; t, triplet ; q, quartet ; m, multiplet; br ; broad. Coupling constants are reported in hertz. Mass spectra (MS) were measured on a JEOL-JMS-DX 300 FAB or EI.

Preparation of dipeptides **3**. *GENERAL PROCEDURE.* 4,4-dimethylaminopyridine (0,1eq.,1mmol.) was added to a cold (0°c) stirred

mixture of amino methyl ester hydrochloride (1eq.,10mmol.), Boc-anthranilic acid(1eq.,10mmol.) and triethylamine (1,1eq.,11mmol.) in 35 ml of dry dichloromethane under nitrogen. After 5 min., solid dicyclohexylcarbodiimide (1,1eq., 11mmol.) was added. The mixture was allowed to warm to ambient temperature after 2 hours and stirred an additional 16 hours. Dicyclohexylurea was filtered off, the filtrate was concentrated and partitioned between ethyl acetate and saturated $NaHCO_3$ solution. The organic layer was washed with a second portion of saturated $NaHCO_3$, dried on Na_2SO_4 and concentrated. The residue was subjected to column chromatography(Silica gel, EtOAc/Hex. eluant) to afford **3** in satisfactory yields.

Characterization of Boc-antraniloyl amino methylesters 3

-Boc MeAnt-Gly-OMe (3b) : Yield = 62% ; Rf : 0.42 (EtOAc/Hex.2/3); ^{1}HNMR ($CDCl_3$) δ ppm : 1.44 (s, 9H); 3.23 (s, NCH_3); 3.76(s, OCH3); 4.17(d,1H , J=5.8 Hz); 6.89-8.25 (m, 4H arom + NH); MS: (M+1) = 323 .

-Boc Ant- Sar- OMe (3c) : Yield = 87% ; Rf : 0.44 (EtOAc/Hex. 2/3) ; mp : 90°C ; ^{1}HNMR ($CDCl_3$) δ ppm : 1.48 (s, 9H) ; 2.99 (s, NCH_3) ; 3.78 (s,3H) ; 4.26(s, 2H); 6.80- 7.40 (m,3H arom.) ; 7.84 (s, NH) ; 8.12 (d, 1H arom., J=8.63Hz,) ; MS: (M+1) =323 ; Anal. Calc. for $C_{16}H_{22}N_2O_5$ C = 59.63, H = 6.83, N = 8.69 found : C = 59.71, H = 6.71, N = 8.61.

-Boc Me Ant-Sar-OMe (3d) : Yield = 70% ; Rf : 0.34 (EtOAc/Hex. 2/3); mp : 96°C ; ^{1}HNMR ($CDCl_3$) δ ppm : 1.30 , 1.41 (two s, 9H, t- Boc) ; 2.87, 3.01 , 3.11 , 3.64 , 3.71 (five s, 6H, NCH_3,OCH_3) ; 4.20 (s,2H) ; 7.20-7.30(m, 4H arom.) ; MS : (M+1)= 337 (305, 281, 237. . .) .

-Boc-Ant-Phe-OMe (L) or (D,L) (3g) : Yield = 62% ; Rf: 0.45(EtOAc/Hex. 1/4) ; ^{1}HNMR ($CDCl_3$) d ppm : 1.52(s,9H) ; 3.23(m,2H) ; 3.78 (s, 3H) ; 5.04 (m,H) ; 6.62 (d, NH, J=6Hz) ; 6.64 -7.43(m, 8H arom.) ; 8.35(d, 1H arom., J=8.63Hz) ; 10.02(s, NH) ; MS: (M+1)= 399 .

-Boc MeAnt-Phe-OMe (L) or (D,L) (3h) : Yield = 67% ; Rf : 0.47 EtOAc/Hex. 1/4) ; ^{1}HNMR : ($CDCl_3$) δ ppm : 1.48(s, 9H) ; 3.23(m, 2H) ; 3.25(s,3H) ; 3.80(s,3H) ; 5.10(m,1H) ; 6.72(d, NH,J=6Hz); 6.66-7.45(m, 8H arom.) ; 8.12(d, 1H arom., J=8.63Hz) ; MS : (M+1)= 413 .

-Boc Ant- (L) Pro-OMe (3i) : Yield = 65% ; Rf : 0.46(EtOAc/Hex. 2/3) ; ^{1}HNMR : ($CDCl_3$) δ ppm : 1.48(s, 9H) ; 1.81-2.30(m, 4H) ; 3.41-3.60(m, 2H) ; 3.78(s, 3H) ; 4.15(m,1H) ; 6.80-7.40(m, 3H arom.) ; 7.84(s, NH) ; 8.12(d, 1H arom., J=8.60Hz) ; MS: (M+1)= 349 .

-Boc Ant-(L)-Glu-OMe : (3j) : Yield = 56%, Rf : 0.52 (EtOAc/Hex. 2/3) ; mp : 94°C ; ^{1}HNMR ($CDCl_3$) δ ppm 1.49(s, 9H) ; 2.15(m, 2H) ; 2.46(m, 2H) ; 3.65(s, 3H) ; 3.77(s, 3H) ; 4.75(m, 1H) ; 6.96(t, 1H arom, J=8.50 Hz) ; 7.16 (d, NH, J=7.30Hz) ; 7.43(t, 1H arom., J=8.50Hz) ; 7.52(m, 1H arom. , J=8.50Hz) ; 8.35(d, 1H arom., J=8.50Hz) ; 10.15(s, NH) ; MS: (M+1)= 395.

Synthesis of 1,4-benzodiazepine-2,5-diones. *GENERAL PROCEDURE*

To a stirred solution of dipeptide **3**(1,5mmol) in dry/DMF (40ml) the dry hydrogen chloride gas was bubbled over 15 to 20min. The resulting reaction mixture was stirred and heated to 60°C, the reaction was monitored by TLC. After completion of the reaction (7 to 24h.), the mixture was concentrated, the residue was triturated with H_2O (20 ml) and dried to give 4 (white solids). Characteristics of these compounds are reported in table1.

Spectral data of BZDs 4 :
4b: R_1= CH_3 , R_2= R_3= H

^{1}HNMR ($DMSO_{d_6}$)δ ppm : 3.42(s, NH3) ; 3.96(m, 2H) ; 6.62(br, NH) 7.20-7.32(m, 2H arom.) ; 7.54(t, 1H arom., J=7.75Hz) ; 7.85(d, 1H arom. , J=7.75Hz) ; IR(KBr, cm^{-1}) ; 3290, 1695, 1668.

4c : R_1= R_2= H, R_3= CH_3

^{1}HNMR ($DMSO_{d_6}$)δ ppm : 3.12(s, NH3) ; 3.85(s, 2H) ; 7.10(d, 1H arom, J=7.80 Hz) ; 7.21 (t, 1H arom, J=7.80Hz) ; 7.48(t, 1H arom., J=7.80Hz) ; 7.74(d, 1H arom. , J=7.80Hz) ; 10.48(s, NH), IR(Kr, cm^{-1}) : 3248, 1700, 1633. Anal. Calc. C=63.16 ; H=5.26 ; N=14.73 found : C=63.24 ; H=5.39 ; N=14.66; MS: EI (M^+)= 190.

4d : R_1= R_3= CH_3 , R_2= H

^{1}HNMR : ($CDCl_3$) δ ppm : 3.17(s, NCH_3) ;3.29(s, NCH_3) ; 3.78(syst.AB, J=15.76Hz) ; 7.10(d, 1H arom., J=7.80Hz) ; 7.19(t,1H arom., J=7.80Hz) ; 7.61 (t,

1H arom, J=7.80Hz) ; 7.75(d, 1H arom,J=7.80Hz) ; IR(KBr, cm^{-1}) : 1667, 1634 ; MS: (M+1)= 205.

4g : R_1= R_3= H , R_2= CH_2Ph (L) or (D,L)

^{1}HNMR : ($DMSO_{d6}$)δ ppm : 3.10(m, 2H) ; 3.92(m, 1H) ; 7.1-7.7(m, 9H arom.) ;8.59(d, 1Harom., J=7.80Hz) ; 10.48(s,NH); IR(KBr,cm^{-1}) : 3250 3120, 1700, 1660 ; SM : EI : (M^+)= 266.

4h: R_1= CH_3, R_2= CH_2 Ph , R_3= H

^{1}HNMR : ($CDCl_3$)δ ppm : 3.04(dd,1H, J=14.57Hz, J=8.25Hz);3.42(s,3H); 3.43(dd,1H, J=14.57Hz, J=8.25Hz) ; 4.02(m, 1H); 6.62(d, NH, J=5Hz) ; 7.20-7.35(m,7H arom.) ; 7.56(t, 1H arom., J=7.74Hz) ; 7.83(d,1H arom., J=7.74Hz); IR(KBr, cm^{-1}) : 3260, 1698, 1685 ; SM : EI: (M^+)= 280.

4i : R_1= H , R_2, R_3= -$(CH_2)_3$-

^{1}HNMR : ($CDCl_3$-$DMSO_{d6}$)δ ppm : 1.81-2,42(m,4H) ; 3.34-3.90(m,3H); 7.35-7.67(m,4H) ; 10.08(s,NH) ; IR(KBr, cm^{-1}) : 3230, 1665, 1610.

4j: R_1= R_3= H , R_2= CH_2-CH_2-CO_2-CH_3.(L).

^{1}HNMR : ($CDCl_3$ -$DMSO_{d6}$)δ ppm : 1.95-2.83(m,4H) ; 3.67(s,3H) ; 3.73(m,1H) ; 6.98-8.30(m, H arom., NH) ; 10.18(s, NH).

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