SELECTIVE BECKMANN REARRANGEMENTS. PREPARATION OF ISOMERIC 2,6- AND 3,6-DIAZEPINOISOQUINOLINES AND -PYRIDOINDOLES

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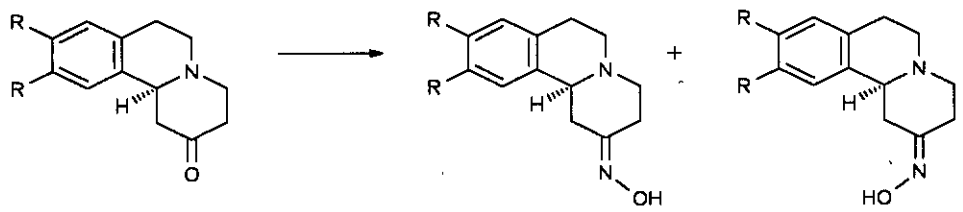
Abstract - *Z* and *E* oximes (**2**, **3**, **6**, **7**) of some benzoquinolizidones (**1**) and indoloquinolizidone were converted into isomeric diazepinoisoquinolines (**4**, **5**) and diazepinopyridoindoles (**8**, **9**), respectively, *via* Beckmann ring enlargement. The 1-isopropyl-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-2-one (**1c**) exhibits a *cis* "b" B/C ring junction.

The preparative use of 1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-2-ones in synthesis of the *ipecacuanha* alkaloid emetine[1-6] and other related heterocyclic compounds[7,8] is well documented. Their intriguing stereochemistry, especially its dependence on the C-1, C-3, C-4 substituents, was also thoroughly studied.[9-12] A mixture of oximes of **1b** was prepared earlier by Buzas *et al.*,[7] but their separation, identification and Beckmann rearrangements in separate trials will be described in this paper. In addition we synthesized the C-1-isopropyl derivative (**1c**) to study the influence of the bulky alkyl group on the *Z/E* ratio in the course of oxime formation. The same sequence of reactions was applied to 3,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-2(1*H*)-one[13] resulting in isomeric diazepinopyridoindoles (**8**, **9**) not published previously.

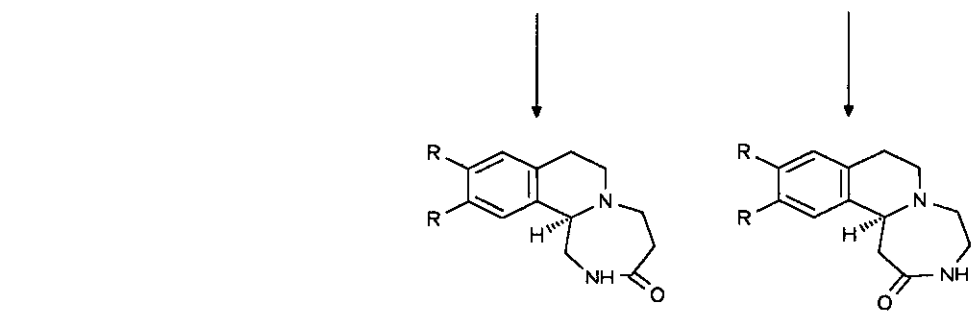
The oximes (**2**) and (**3**) prepared in the usual way (*E/Z* ratio 1:1) were separated by fractional crystallization or column chromatography. The *E* and Z position of the hydroxyl group was determined by ^{13}C nmr spectroscopy, taking into account the different upfield shift effect of the oxime group on the adjacent carbon atoms. This difference between the α,α' shifts in the case of cyclohexanone oxime amounts to 4.8 ppm[14] and seems to be strong enough to establish a firm stereochemical assignment. The ^{13}C nmr chemical shifts are shown in Table 1.



1a R = H
1b R = OCH_3

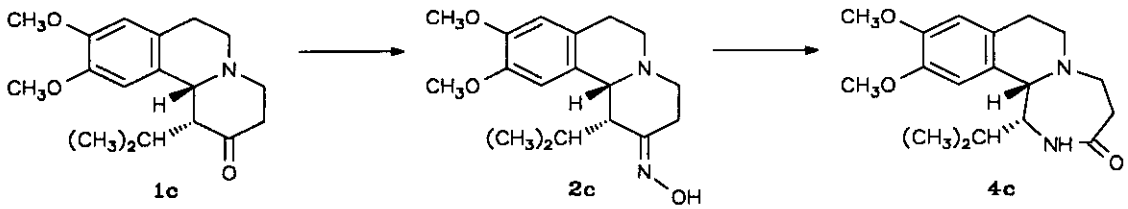
2a R = H
2b R = OCH_3

3a R = H
3b R = OCH_3

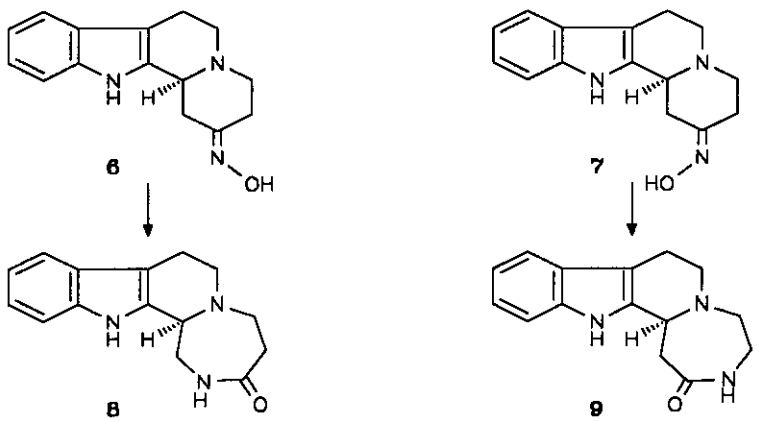


4a R = H
4b R = OCH_3

5a R = H
5b R = OCH_3



1c **2c** **4c**



6 **7** **8** **9**

It is worth mentioning that no signal appears in the 3.9-4.4 ppm region in the ^1H nmr spectra of **1a**, **1b**, **2a**, **2b**, **3a**, **3b** indicating the *trans* B/C ring junction.[9] The 1-isopropyl derivatives (**1c**) and (**2c**) showed, however, a

well distinguishable broad singlet for 11b-*H* at δ4.24 and 4.32 ppm and a signal for C-7 at 24.5 and 22.8 ppm, respectively, which can be attributed to a B/C *cis* structure of "b" type.[11] Because of the steric hindrance of the C-1 substituent the oxime (**2c**) was predominantly formed from **1c**, only a negligible by-product could be assumed to be traces of the other isomer.

Table 1

^{13}C Nmr shifts of compounds (**1a-5b**) ($CDCl_3$ or *DMSO-d_6 solutions)

compound	C-1	C-2	C-3	C-4	C-6	C-7	C-8a	C-8	C-9	C-10	C-11	C-11a	C-11b	R		CH	CH_3
1a	47 3	208.7	41.1	54.8	50.7	29.7	126 6	126.2	134.0	136.7	126.1	129.0	61.7				
1b	47.6	208.5	41.1	54.7	50 8	29.3	126 0	111.4	147.7	147.5	107.7	128.5	61.5	55.9	55.9		
1c	38.9	211 3	61.8	47.4	50.7	24.5	127.3	112.0	147.7	147.3	109 4	126 4	60 1	56.0	55.8	29.1	21.7, 20.0
2a	37.0	157.5	24.2	54 3	51 2	29.4	134 3	128.9	124.9	126.0	126.4	136.8	62.6	-	-		
2b*	36.9	155.0	23.9	53.9	50 8	28.6	129 3	112 0	147.4	147.2	108.9	126.4	62.0	55.8	55.5		
2c	28.0	157 1	42 0	45.3	50.4	22.8	125.7	111.6	147.9	147.5	109.4	125.5	59.0	55.8	55 8	27.1	21.5, 20 3
3a	31.0	157.5	29.8	55.7	51.5	29.5	134.3	128 9	125.1	126.0	126 4	137.1	61.3	-	-		
3b*	31.0	157.4	29.9	56.2	51.6	29.1	129 1	111 6	147.9	147.5	108.5	126.7	60.9	55.9	55.6		
4a	47.8	178.2	36.5	49.1	52.6	29.5	135 1	129 0	125.9	126.6	126.8	135.4	65.3	-	-		
4b*	46.3	178.4	35.3	48.4	51 6	28.3	127.2	111.2	147.6	147.1	109.7	126.3	64.0	55.7	55.4		
4c	37 0	177 2	59 7	44.0	52.0	24.0	127.1	111.9	147.7	147.3	110.0	126.3	58.3	56 0	55 8	29.0	19 7, 21 0
5a	45 4	177.3	41.5	59.1	50.1	29.4	134 7	128 7	126 1	126.3	127.2	137.4	59.8	-	-		
5b*	45.1	176.8	41 6	59.0	50.8	29.0	129.2	111.3	147.8	147.7	110.1	126.9	59.4	56.2	55.9		

The pure oximes were subjected to Beckmann rearrangement, resulting in the formation of only one of the possible 2,6- and 3,6-diazepinoisoquinolines. The **2** ⟶ **4** and **3** ⟶ **5** conversions correspond to the anticipated *trans* migration of the cationic intermediate involved.

The intermediate indoloquinolizidone,[13] was also subjected to ring enlargement reactions in the same way described above. Due to the poor solubility of the oximes obtained in an *E/Z* ratio of 1:1, the entire separation of **6** and **7** failed either by chromatography or by crystallization. The corresponding lactams obtained from the oximes (**6** and **7**) were almost indistinguishable by tlc, however repeated crystallization of the mixture led to an enrichment of **8** and **9** respectively. After all, the isomers were characterized by ^{13}C nmr unambigously (Table 2).

Table 2

^{13}C Nmr shifts of compounds **6-9** (DMSO-d_6 solutions)

compound	C-1	C-2	C-3	C-4	C-6	C-7	C-7a	C-7b	C-8	C-9	C-10	C-11	C-11a	C-12a	C-12b
6	35.7	154.5	24.6	53.5	52.1	21.7	126.7	106.8	117.7	118 6	120.7	111.2	136.4	135.0	59.6
7	31.3	154.2	28.9	54.9	52.4	21 7	126.7	106.8	117.7	118.6	120.7	111.3	136.4	135.1	58 3
8	44.8	176.7	37.4	51.9	51.9	21.5	126.7	108.4	117.8	118 6	121.0	111.9	136.4	133.0	62.6
9	42 7	174.7	41.4	59.5	52.7	21.6	126 6	107 8	113.7	118.5	120.8	111 3	136 4	135.0	56.8

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EXPERIMENTAL

Melting points were determined on a Büchi SMP 20 apparatus and are uncorrected. The ir spectra were recorded with a Perkin-Elmer FT 1605 instrument. ^{1}H and ^{13}C nmr spectra were obtained with a Bruker AM300 and 400 instruments in $CDCl_3$ or DMSO-d_6 solutions. For tlc analyses, Merck silica plates F254 were used. All compounds were characterized by elemental analyses run on a Heraeus Mikro Rapid CHN apparatus.

1-Isopropyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-benzo[a]quinolizin-2-one (**1c**): 12.5 g (0.05 mol) of 6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride and 8.65 g (0.055 mol) of 1-dimethylamino-5-methylhexan-3-one hydrochloride, prepared by Mannich condensation of 4-methyl-2-pentanone, dimethylamine and formaldehyde, were dissolved in 35 ml of water. It was left at room temperature for 8 h. The precipitated crystalline substance (3.0 g) proved to be a dimeric product (mp 197-198 °C). The mother liquor was then made alkaline with a 5% sodium carbonate solution, and was extracted three times with dichloromethane. The combined extracts were dried over sodium sulfate and evaporated at reduced pressure. 9 g of an oil was obtained, which was dissolved in ethanol and converted into its hydrochloride with dry HCl in ether. 8.5 g (50%) of **1c**.HCl was separated, filtered and recrystallized from ethanol.

General procedure for the preparation of the oximes: The ketone was dissolved in methanol, and hydroxylamine hydrochloride and sodium acetate were added to it in 20% molar excess in a water solution. The mixture was then cooled and the crystalline solid precipitated was filtered. The yields were between 85-90 %. To obtain the pure *E* and *Z* isomers they were recrystallized several times and/or separated by coloumn chromatography.

General procedure for the Beckmann rearrangement: 6.2 mmol of oxime was dissolved in 60 ml of acetone, and 60 ml of 5% sodium carbonate solution was added to it. To this stirred solution, 9.3 mmol of *p*-TsCl in 30 ml of acetone was added dropwise. The mixture was then stirred for 8 h at room temperature and filtered. The acetone was evaporated under reduced pressure, and the water solution was extracted with dichloromethane to obtain the regioisomeric mixture of lactams in about 45-50 % yield.

Table 3

mp's, ir and ^{1}H nmr data of the prepared compounds

Compound	Formula	mp °C (cryst. solv)	ir (KBr pellets, ν, cm^{-1})	^{1}H nmr (CDCl$_3$ or *DMSO-d_6 solutions)
1c	$C_{18}H_{26}NO_3Cl$ Calcd C63.61, H7.71, N4.12 Found C63.54, H7 92, N4 43	160-161 (HCl) (EtOH)	2970, 2512, 2358, 1714, 1523, 1283, 1221, 1108, 992, 851	0.98 (d, J=6.7 Hz, 3H, CH_3); 1.15 (d, J=6.6 Hz, 3H, CH_3); 2.28-2 37 (m, 1H, CH_2); 2.38-2.50 (m, 1H, CH_2); 2.54-2.73 (m, 3H, CH_2, CH); 2.92-3.17 (m, 3H, CH_2); 3 14-3 29 (m, 2H, CH_2); 3.84 (s, 3H, OCH_3); 3.86 (s, 3H, OCH_3); 4.24 (br s, 1H, 11b-H); 6.58 (s, 1H, ArH); 6 69 (s, 1H, ArH)
2a	$C_{13}H_{16}N_2O$ Calcd C72.19, H7.46, N12.95 Found C72 59, H7 60, N12 69	151-152 (iPrOH)	3176, 3066, 2817, 1493, 1367, 1298, 1101, 939, 741	2 16-2.63 (m, 4H, CH_2), 2.72-2.80 (m, 1H, CH_2); 2.98-3.40 (m, 6H, CH_2, CH); 7.10-7.30 (m, 4H, ArH); 8.88 (br s, 1H, OH)
2b	$C_{15}H_{20}N_2O_3$ Calcd C65 20, H7 30, N10 14 Foud C65.02, H7.08, N10.39	208-209 (MeOH)	3059, 2826, 1521, 1466, 1361, 1260, 1222, 1134, 1010, 949, 772	1.82-3.22 (m, 11H, CH_2, CH); 3.70 (s, 3H, OCH_3); 3.73 (s, 3H, OCH_3); 6 64 (s, 1H, ArH); 6.73 (s, 1H, ArH); 10.37 (s, 1H, OH) (*)
2c	$C_{18}H_{27}N_2O_3Cl$ Calcd C60.92, H7.67, N7.89 Found C60.63, H7.69, N7.68	155-156 (HCl) (EtOH)	3089, 2963, 1521, 1462, 1413, 1279, 1213, 1183, 1108, 666	0.92, (d, J=6.7 Hz, 3H, CH_3), 1.10 (d, J=6 4 Hz, 3H, CH_3), 2 31-3.42 (m, 9H, CH_2), 3.68 (d, J=10.4 Hz, 1H, CH), 3 84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.32 (br s, 1H, CH_2), 6.56 (s, 1H, ArH), 6 93 (s, 1H, ArH), 8.65 (br s, 1H, OH)
3a	$C_{13}H_{16}N_2O$ Calcd C72.19, H7.46, N12.95 Found C72 01, H7.69, N12.83	179-180 (iPrOH)	3177, 3068, 2804, 1494, 1355, 1298, 1102, 922, 744	1.90-1.98 (m, 1H, CH_2), 2.40-2.64 (m, 4H, CH_2), 2 72-2 80 (m, 1H, CH_2), 3 03-3.26 (m, 3H, CH_2), 3 32 (dd, J=11.6 and 3.3 Hz, 1H, CH_2), 3 96 (ddd, J=14.5, 3.8 and 1.9 Hz, 1H, 1-H_{equ}), 7.08-7 30 (m, 4H, ArH), 9.03 (s, 1H, OH)
3b	$C_{15}H_{20}N_2O_3$ Calcd C65.20, H7.30, N10.14 Found C64.95, H7.64, N9.81	182-183 (MeOH)	3071, 2805, 1525, 1461, 1361, 1260, 1229, 1136, 1009, 925, 768	1 87-3.36 (m, 11H, CH_2, CH), 3.85 (s, 3H, OCH_3), 3 88 (s, 3H, OCH_3); 6 58 (s, 1H, ArH); 6.70 (s, 1-H, ArH); 8.88 (br s, 1H, O-H) (*)
4a	$C_{13}H_{16}N_2O$ Calcd C72.19, H7.46, N12 95 Found C71 86, H7.59, N12.63	190 (EtOAc)	3181, 3086, 2922, 1671, 1457, 1437, 1340, 1095, 748, 584	2 42-2 49 (m, 1H, CH_2); 2.70-2.84 (m, 2H, CH_2); 2 97-3 18 (m, 5H, CH_2), 3.34-3.41 (m, 1H CH_2); 3.69-3.76 (m, 1H, CH_2); 3.85 (d, J=8 7 Hz, 1H, 11b-H); 6 88 (br s, 1H, NH); 7.07-7.2 (m, 4H, ArH)
4b	$C_{15}H_{20}N_2O_3$ Calcd C65 20, H7 30, N10.14 Found C65.12, H7.61, N10 32	184-185 (EtOAc)	3198, 3072, 2914, 1675, 1521, 1462, 1437, 1260, 1227, 1142	2.20-3.98 (m, 12H, CH_2, CH, NH); 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3); 6 58 (s, 1H, ArH); 6.63 (s, 1H, ArH) (*)
4c	$C_{18}H_{26}N_2O_3$ Calcd C67.90, H8 23, N8.80 Found C67.78, H8 58, N8.55	165-166 (EtOAc)	3208, 3061, 2931, 1665, 1518, 1437, 1261, 1212, 1117, 1091	0.99 (d, J=6 6 Hz, 3H, CH_3); 1.02 (d, J=6.7 Hz, 3H, CH_3); 2.34-3.37 (m, 10H, CH_2); 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.26 (brs, 1H, 11b-H); 6.59 (s, 1H, ArH); 6 62 (s, 1H, ArH); 7.28 (br s, 1H, NH)
5a	$C_{13}H_{16}N_2O$ Calcd C72.19, H7.46, N12 95 Found C72 08, H7.40, N12.68	149 (EtOAc)	3210, 3062, 2946, 1658, 1487, 1436, 1357, 1108, 739, 609	2.69-2.92 (m, 4H, CH_2); 2 96-3.21 (m, 5H, CH_2); 3 62-3 72 (m, 1H, CH_2), 3.96 (d, J=9.6 Hz, 1H, 11b-H), 6.75 (br s, 1H, NH); 7.04-7 33 (m, 4H, ArH)
5b	$C_{15}H_{20}N_2O_3$ Calcd C65.20, H7 30, N10.14 Found C65.18, H7 41, N10 01	187-188 (EtOAc)	3195, 3060, 2912, 1674, 1525, 1461, 1438, 1261, 1227,1142	2.56-3 75 (m, 11H, CH_2); 3.83 (s, 3H, OCH_3); 3 86 (s, 3H, OCH_3); 6.46 (br s, 1H, NH), 6.56 (s, 1H, ArH); 6.73 (s, 1H, ArH) (*)

7	$C_{15}H_{17}N_3O$ Calcd C70.56, H6.71, N16.46 Found C70.46, H6 92, N16.51	259-260 (MeOH)	3290, 3054, 2922, 2823, 1454, 1371, 1346, 1258, 1234, 1119, 918, 740	1.95 (dd, J=14.5 and 11.9 Hz, 1H, CH_2); 2 40-2.77 (m, 5H, CH_2); 2.95-3.19 (m, 3H, CH_2); 3.30-3.37 (m, 1H, CH); 3.98 (ddd, J=14 6, 3.5 and 1.9 Hz, 1H, 1-H_{equ}), 6.97-7.09 (m, 2H, ArH); 7.32-7.44 (m, 2H, ArH); 10 54 (s, 1H, OH); 10.95 (s, 1H, NH) (*)
8^+	$C_{15}H_{17}N_3O$ Calcd C70.56, H6.71, N16.46 Found C70.11, H6.80, N16.19	263-264 (EtOH)	3293, 2906, 1661, 1452, 1186, 743	2.20-3.18 (m, 7H, CH_2); 3 30-3 68 (m, 4H, CH_2); 6.90-7 06 (m, 2H, ArH); 7.24-7.39 (m, 2H, ArH); 7.84 (br s, 1H, CONH); 10.91 (s, 1H, NH) (*)
9^+	$C_{15}H_{17}N_3O$ Calcd C70.56, H6 71, N16.46 Found C70 21, H7.03, N16.11	223-224 (EtOH)	3301, 2905, 1663, 1456, 1047, 749	2.43-3.12 (m, 9H, CH_2); 3.35-3.50 (m, 1H,CH_2); 3 61 (d, J=9.0 Hz, 1H, 12b-H); 6.88-7.06 (m, 2H, ArH); 7.20-7.39 (m, 2H, ArH); 7.73 (br s, 1H, CONH); 10.98 (s, 1H, NH) (*)

$^+$ Major component of a mixture of **8** and **9**.

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