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OXIDATIVE CYCLIZATION OF 2-PYRROLIDINYL-ACETAMIDE AND 2-PYRROLIDINYL-PROPIONAMIDE LOCAL ANAESTHETICS

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Abstract—2 - Pyrrolidinyl - acetamide and -propionamide local anaesthetics (**1a–d**) on oxidation with mercuric acetate, potassium hexacyanoferrate(III) and potassium permanganate underwent oxidative cyclization to give new bicyclic compounds, hexahydro - 1H - pyrrolo[1,2 - *a*]imidazolin - 2 - ones (**2a–d**). The propionamides (**1c–d**) yielded mixtures of the two possible diastereoisomers of **2c** and **2d**. These were separated; in solution and above their melting points they epimerized via ring opening and reclosure between the 7a-carbon and 1-nitrogen atoms.

As reported earlier,[1] aptocaine (**1d**) formed *in vitro* and *in vivo* a cyclic metabonate, 1 - (2 - tolyl) - 3 - methyl - hexahydro - 1H - pyrrolo[1,2 - *a*]imidazolin - 2 - one (**2d**). Thus cyclic metabonates are to be expected[2] in the metabolic transformation of compounds with similar structural features. In the present experiments we investigate the chemical oxidation of compounds **1a–d**, with the expectation of producing the cyclic compounds **2a–d**.

Some tertiary amines, which have a nucleophilic group in a favourable position in the molecule, undergo oxidative cyclization using suitable oxidative agents.[4–13]

Leonard *et al.* observed that the mercuric acetate oxidation of some cyclic tertiary aminoalcohols led not to the expected enaminoalcohols, but to bicyclic products.[4,5] The reaction was considered as a 2-electron oxidation leading to iminium ion intermediate, followed by an intramolecular nucleophilic addition by the hydroxy group onto the electron deficient α_N carbon atom of the iminium ion.

Möhrle *et al.* reported oxidative cyclization reactions by mercuric acetate, in the presence of EDTA, in 1% acetic acid solution involving hydroxy,[6] primary amino,[6–8] secondary and tertiary amino,[7] aromatic amino,[9,10] carbohydrazido, ureido, carbamoyl[11] and hydroxy-imino[12] groups as nucleophilic centres.

Audeh and Lindsay Smith[13] oxidized trialkylamino-alkanols and amines, as chemical models for biological processes, to cyclic oxaza- and diaza-compounds with potassium hexacyanoferrate(III) in 2N potassium hydroxide solution.

The above oxidative cyclization reactions however led mainly to overoxidation and hydrolysis and cyclic products from a 2-electron oxidation were only rarely obtained and in poor yield. A general pattern for the oxidative cyclization, overoxidation and solvolysis processes was proposed by Möhrle and Mayer.[7]

In the case of the local anaesthetics **1a–d** the phenyl-, tolyl-, or xylyl-substituted carbamoyl group should react as the intramolecular nucleophilic centre. Further oxidation of compounds **2** is unlikely, if we consider the steric requirements[3,14] of the oxidation reaction and the steric conditions of compounds **2**. To oxidize the α_N C–H bond, the leaving hydrogen must be *trans*-diaxial to the N-metal complex bond, i.e. the lone pair electrons of the tertiary nitrogen atom.[14] The ring fusion in compounds **2** is *cis* (see later), thus the bridgehead proton, which is the most reactive α_N-hydrogen,[3] is in the *cis* position to the lone pair electrons of the bridgehead tertiary nitrogen atom.

The results of the oxidation reactions are shown in Table 1. Oxidation by potassium hexacyanoferrate(III) in potassium hydroxide solution yielded the cyclic compounds **2** in good yield. It is probably the alkaline media, which by enhancing the weak nucleophilic power of the carbamoyl nitrogen, promoted the reaction. Potassium permanganate oxidation under physiological pH ones gave the cyclic compound in relatively good yield.

The α_N carbon atoms of the pyrrolidine ring of **1a–d**

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Table 1. Oxidative cyclization of compounds **1a–c** by various oxidative agents

Oxidative agent	pH	Yield /%/ 2a	2b	2c	2d
1./ Potassium hexacyanoferrate$_{III}$ in 2N potassium hydroxide	12	67	85	77	86
2./ Potassium permanganate in water	7,4		46		
3./ Mercuric acetate + EDTA in 1% acetic acid	5		25		
4./ Mercuric acetate in 5% acetic acid	3		5		

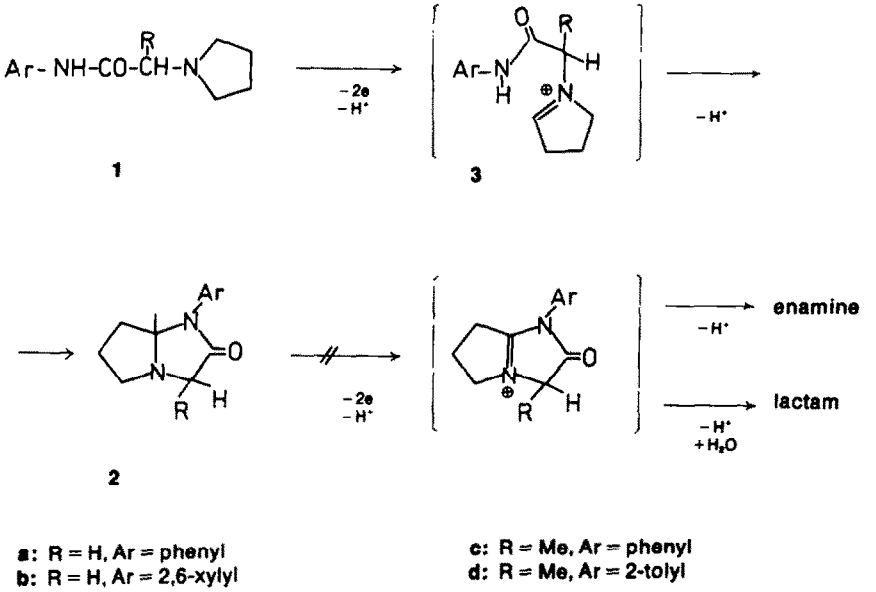


Fig. 1. Oxidative cyclization of compounds 1.

are prochiral because in oxidative cyclization one of them becomes the asymmetric bridgehead 7a-carbon atom. In the case of the propionamides **1c,d** which already have one asymmetric carbon atom, a second centre of chirality is formed in oxidative cyclization and thus diastereoisomers can be expected. Examination of products **2c** and **2d** (thick oils) by tlc and ^{1}H NMR indicated two isomers in a ratio of approximately 1:5. These were separated; ^{1}H-NMR investigation allowed configurational assignments to be made. Figure 2 shows the structure of the two possible diastereoisomers of **2c**. The isomer designated as "*cis*" contains the protons, belonging to the asymmetric 3 and 7a carbons, on the same side of the imidazolinone ring.

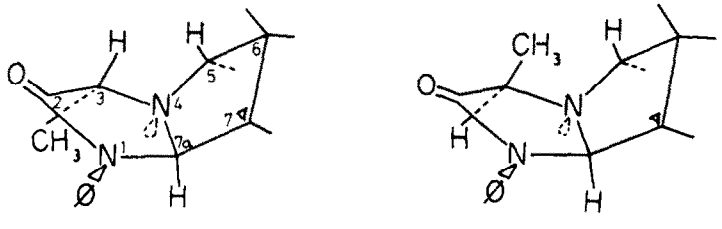
The minor products from both **2c** and **2d** were crystalline *cis* isomers, while the major products were thick oils of the *trans* isomers.

In the IR spectrum of compounds **2a–d**, the carbonyl group appeared in a high absorption region (ν_{CO} = 1698–1715 cm^{-1}) which is consistent with the five-membered ring structure.[15] Each product exhibited a characteristic ^{1}H NMR spectrum with a multiplet appearing in the region of δ = 5.10–5.50 for the methine proton on the bridgehead 7a-carbon. This multiplet, as well as the doublet, appearing in the spectrum of **1a,b** for the diastereotopic 3-methylene protons, are proof for the cyclic structure. One of the 3-methylene protons, which is on the same side as the lone pair electrons of the bridgehead nitrogen (downfield methylene proton), gives long range coupling with the 7a-methine proton ($^4J_{7aH\text{-}3Hcis}$ = 0.5–1.0 Hz), indicating the *cis* fusion of the rings. The same type of long range coupling occurs in the spectrum of the *cis* diastereoisomers of **2c** and **2d**, while it is absent in the spectrum of the *trans* diastereoisomers.

According to a Dreiding model the imidazolinone ring of **2a–d** must be nearly planar, and the pyrrolidine ring may exist in two main conformations: "A" and "B" respectively (see Fig. 3). In conformation "A" the 7a-H and *trans* 7-H atoms are *trans*-diaxial, while in conformation "B" the 7a-H is gauche to both of the 7-methylene protons. The small and similar values of the coupling constants ($^3J_{7aH\text{-}7Hcis}$ = 3–6 Hz and $^3J_{7aH\text{-}7Htrans}$ = 2.0–2.4 Hz) refer to gauche relations and the predominance of conformation "B".

The main physical and spectroscopic characteristics of compounds 2 are shown in Table 2.

Freshly made solutions of the separated *cis* and *trans* diastereoisomers, on investigation by tlc and ^{1}H-NMR contained one diastereoisomer, with only a small amount (according to ^{1}H-NMR less than 10%) of other isomer.



trans **2c**
oil, major product

cis **2c**
crystal, minor product

Fig. 2. Diastereoisomers of compound **2c**.

Table 2. The main physical and spectroscopic characteristics of compounds **2a–d**

Compound 2	mp (C°)	^{1}Hnmr ($CDCl_3$) δ (ppm) 3-Hcis	3-Htr	3-CH_3cis	3-CH_3tr	7a-H	J (Hz) $^2J_{3Hcis\text{-}3Htr}$	$^3J_{7aH\text{-}7Hcis}$	$^3J_{7aH\text{-}7Htr}$	$^4J_{7aH\text{-}3Hcis}$	IR (KBr) ν CO (cm^{-1})
a	55–8	3,70d	3,48d	-	-	5,30–5,50m	16,4	4,0	2,4	0,5	1705
b	81–2	3,79d	3,46d	-	-	5,15–5,33m	16,6	5,6	2,0	1,0	1710
							$^3J_{3Me\text{-}3H}$				
c (cis)	106–8	3,76q	-	-	1,48d	5,25–5,42m	7,2	5,0	2,0	0,7	1698
c (trans)	oil	-	3,48q	1,37d	-	5,28–5,47m	6,4	6,0	2,0	-	1702[x]
d (cis)	106–9	3,85q	-	-	1,46d	5,16–5,32m	7,0	4,0		0,6	1703
d (trans)	oil	-	3,44q	1,42d	-	5,10–5,30m	6,6	3,0		-	1703[x]
2·HCl											
c (trans)	164–6	-	4,16q	1,91d	-	6,1m	7,4	6,0	3,5	-	1712

[x] in liquid film

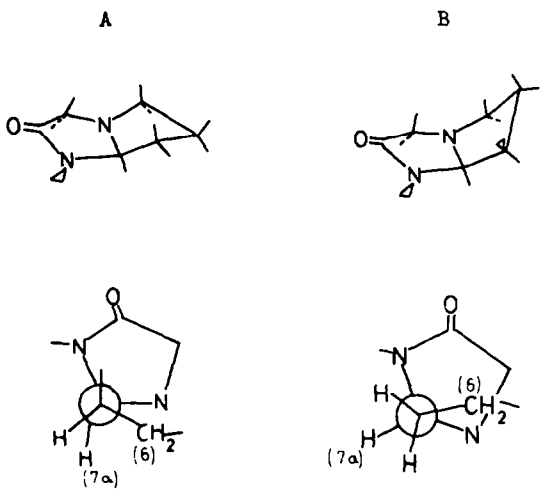


Fig. 3. Conformation of compounds 2.

The ratio of the isomers however gradually changed, until an equilibrium was attained, with a *cis–trans* isomeric ratio of approximately 1:5. The *trans* isomers changed into the equilibrium mixture in the absence of solvents. The *cis* isomers were stable in the solid phase, but above their melting points changed rapidly into the equilibrium mixtures.

At equilibrium, the *trans* isomers predominate over the *cis* isomers indicating the greater thermodynamical stability of the former. Smalter non-bonding interactions occur between the *trans*-3 and *trans* - 5 - hydrogen atoms in the *trans* diastereoisomers, than between the *trans* - 3 - methyl group and *trans* - 5 - hydrogen atom in the *cis* isomer (see Fig. 2).

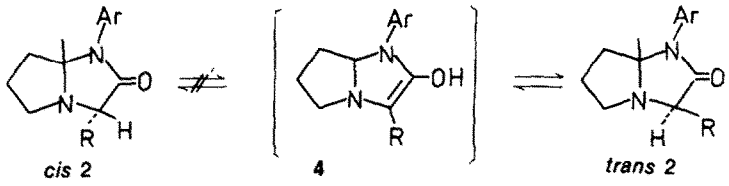
The rate of the epimerization in dilute solutions of *cis* **2c** in various solvents at room temperature was investigated by tlc; the time interval, required to obtain a 50:50% *cis–trans* isomeric ratio was noted. The epimerization proceeded rapidly in protic solvents, but more slowly in aprotic ones, the rate being dependent on the ε value (polarity). The presence of acids lowered greatly, while bases enhanced slightly, the reaction rate (see Table 3).

^{1}H-NMR spectroscopy indicated that *cis* **2c** and *cis* **2d** in $CDCl_3$ solution equilibrated in 21 and 14 days respectively, while in CD_3OD the same reaction proceeded in 1 hr.

Three mechanisms for the epimerization, as shown in Fig. 4 are possible.

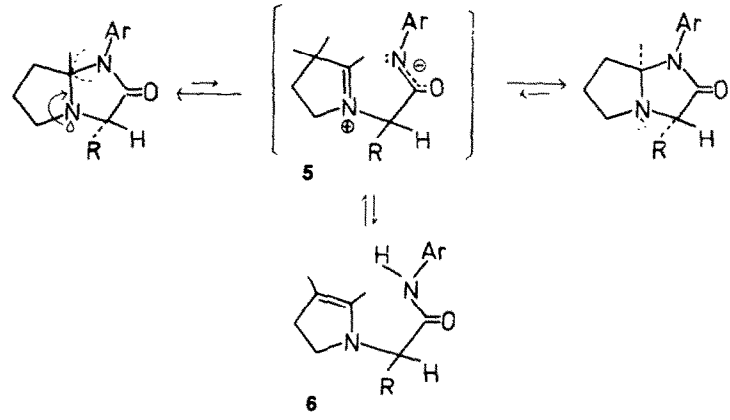
Mechanism "a" could be excluded on the basis of the deuteration experiments. On addition of CF_3COOD or D_2O the 3-CH_2 protons of **2a,b** and the 3-CH proton of **2c,d** were not exchanged, while the 7-CH_2 protons were fully exchanged within one week. Exchange of the 7-CH_2 protons can be explained in terms of both mechanisms "b" and "c", if we suppose that the iminium forms **5** or **7** are in equilibrium with the enamines **6** or **8**. We have no real evidence to decide between mechanisms "b" and "c". By tlc or ^{1}H-NMR only compounds **2** were detected and no sign of the enamines **6** or **8** was evident. Some observations, however support mechanism "b"; ^{1}H-NMR of the base and the hydrochloride of **2** (Table 2) indicates that the salt is protonated at the bridgehead N_4 atom; thus the epimerization should be promoted by acids if it follows mechanism "c", and hindered if it

a: Epimerization at the 3-carbon atom, through oxo-enol tautomerism.



R = H, Me, Ar = Ph, 2-tolyl, 2,6-xylyl

b: Epimerization at the 7a-carbon atom, through ring opening and reclosure between 7a–C and 1–N atoms.



c: Epimerization at the 7a-carbon atom, through ring opening and reclosure between 7a–C and 4–N atoms.

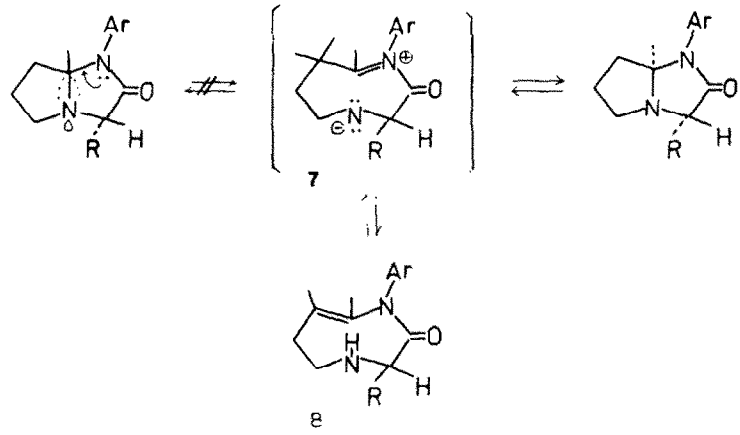


Fig. 4. Possible mechanisms for the epimerization of compounds **2**.

follows mechanism "b". As has been shown (Table 3) the epimerization proceeds much more slowly in the presence of acids.

Hydrogenation of compounds **2** was carried out by sodium tetrahydroborate and by formic acid. Both reactions gave compounds **1** in good yield. The formation of compounds **1** may be the result of the saturation of the iminium compounds **5** or the enamines **6** which are present if mechanism "b" applies, but they cannot be derived from compounds **7** or **8**.

In protic solvents the zwitter ion **5** is likely to exist in its protonated form **3**. Ring opening reactions to **3**-type iminium ions were reported[4] for tricyclic oxazolidines in aqueous and alcoholic solutions and supposed[12] for bicyclic oxaza) and diaza-compounds in aqueous solutions.

In aprotic solvents (although the presence of protons cannot be excluded) the heterolytic fission of compounds **2** to the zwitterions **5** must be assumed which is helped by the polar character of the solvent, as indicated by the fairly direct ratio between the rate of epimerization and the polarity of the solvent (Table 3).

Table 3. Epimerization of compound *cis*-**2c** in various solvents and in alkaline and acidic media

	Solvent	ϵ_{25}	Time interval required for cis2c to interchange into a cis-trans diastereoisomeric mixture of a ratio of 1:1 *		
			days	houre	minutes
apolar	benzene	2,27	39		
	chloroform	4,64	20		
	pyridine	12,3	10		
polar	acetone	20,3	7		
	nitrobenzene	34,8		68	
	dimethylformamide	37,0		44	
	dimethylsulphoxide	46,6		18	
protic	acetic acid	6,17		18	
	ethanol	24,3		4,5	
	methanol	32,6		1	
	water +20% acetone	78,4			20
	0,05 M NaOH +20% acetone				<20
	25% NH_4OH	"			<20
	0,05 M acetic acid	"		1	
	0,05 M HCl	"		120	

* 3 mg/ml solutions were chromatographed using 2x5 cm plates and solvent system 1.

EXPERIMENTAL

IR spectra were measured for KBr pellets with a Zeiss UR-20 spectrometer, ^{1}H-NMR spectra with a Perkin–Elmer R-32 spectrometer. For tlc, silicagel 60 F_{254} pre-coated 20 × 20 cm aluminium sheets (layer thickness 0.2 mm) were used in solvent systems (1) petrolether (40–60°)–diethylamine = 4:1 (2) benzene–methanol = 4:1 (3) chloroform–methanol–petrolether (40–60°) = 95:5:100.

Starting materials **1a–d**

Pyrrocaine, N - 2.6 - xylyl) - 2 - pyrrolidinyl - acetamide (**1b**) and Aptocaine, N - (2 - tolyl) - 2 - pyrrolidinyl - propionamide (**1d**) were obtained from Graham Chemical Corp., U.S.A. and Pharmaceutical Manufacturing Co., Surrey, England respectively. **1a** and **1c** were prepared for the present investigation at the Chinoin Pharm. and Chemical Works Budapest, Hungary.

N - Phenyl - 2 - pyrrolidinyl - acetamide (**1a**)

N - Phenyl - 2 - chloro - acetamide[16] (18.45 g, 0.1 mol), and pyrrolidine (35.56 g = 0.5 m) were refluxed in toluene (150 ml) for 5 hr. The solvent was distilled off; the residue was mixed with water (50 ml) and extracted with chloroform. The chloroform extract was dried, evaporated, to give 38.5 g (94%) of **1a**, white crystals, m.p. = 57–60°; calc for $C_{12}H_{16}N_2O$ (204.273) C, 70.56; H, 7.89; N, 13.71; found C, 70.50; H, 7.85; N, 13.65%; ν cm^{-1}: 3186 (NH); 1660 (amide I); 1508 (amide II): δ (ppm): 2.23 (2 s 2-CH_2); 4.66 (4 m –CH_2–N–CH_2–); 6.90–7.08 (5 m Ar–H); 9.08 (1 broad a NH); R_f: 1. 0.33; 2. 0.29; 3. 0.18. **1a** HCl: white crystals, m.p. 204–6°.

N - Phenyl - 2 - pyrrolidinyl - propionamide (**1c**)

N - Phenyl - 2 - chloro-propionamide (17.35 g, 0.1 mol) and pyrrolidine (35.36 g; 0.5 mol) were treated as above, to obtain 15.53 g (73%) of **1c**, white crystals (from acetone), m.p. 80–81°; calc for $C_{13}H_{18}N_2O$ (218.300); C, 71.53; H, 8.31; N, 12.83; found C, 71.45; H, 8.28; N, 12.76%; ν (cm^{-1}): 3200 (NH); 1670 (amide I); 1510 (amide II); (ppm): 3.04 (1 q 2H); 1.36 (3 d 2-CH_3); 1.80 (4 m –CH_2–N–CH_2–); 2.62 (4 m –CH_2–CH_2–); 6.9–7.7 (5 m Ar–H); 8.93 (1 broad s NH); $^3J_{2H\text{-}2CH_3}$ = 7.0 Hz; R_f: 1. 0.40; 2. 0.25; 3. 0.14. **1c** HCl: white crystals, m.p. 212–4°.

Oxidative cyclizations; General procedures

6.58 g (0.02 mol) $K_3[Fe(CN)_6]$ in 40 ml of 2N KOH was added to the solution of 0.01 mol **1** in methanol (30 ml). After 1 h of stirring at room temperature the precipitated $K_4[Fe(CN)_6]\cdot 3H_2O$ was filtered off, and the methanol was distilled off from the filtrate. The aqueous solution was extracted with chloroform. The chloroform extract was washed several times with 1% acetic acid, then dried and evaporated and the resideu crystallised from ethanol, to obtain **2**. From the 1% acetic acid phase the unchanged **1** was obtained after neutralization and extraction. For **1b** 2.5% acetic acid was used.

0.11 g (1.3 mmol) $KMnO_4$ in 5 ml of water was added to 0.54 g (2 mmol) **1b** in 1 ml of acetone. The mixture was stirred at room temperature for 30 min; MnO_2 was filtered off, the filtrate was extracted with chloroform, and treated as above.

3.18 g (10 mmol) $Hg(OAc)_2$ and EDTA-disodium salt 3.72 g (0.01 mol) was added to 0.54 g (2 mmol) of **1b** HCl in 10 ml of 1% acetic acid, and the solution was heated under reflux for 2 hr. The precipitated mercurous acetate and mercury were filtered off and the filtrate was extracted with chloroform. The chloroform extract was treated as above, while the acidic aqueous layer was neutralized with Na_2S, filtered, and extracted with benzene, to obtain further amount of the unchanged **1b**.

6.38 g (0.02 mol) of $Hg(OAc)_2$ and 0.01 mol of **1** were dissolved in 20 ml of 5% acetic acid, heated at reflux temperature for 5 hr and treated as above.

Separation of the diastereoisomers of **2c** *and* **2d**

3.0 g of **2c** (1:5 mixture of *cis*-**2c** and *trans*-**2c**) was dissolved in 4 ml of Et_2O and the solution was kept in a fridge for several days. The crystals were collected, washed with cold ether, to obtain 0.4 g of *cis*-**2c**. The first filtrzte was evaporated *in vacuo*, to give 1.9 g of *trans*-**2c**, as a thick oil. 1.13 g of **2d** (1:5 mixture of *cis*-**2d** and *trans*-**2d**) was dissolved in 2 ml of ether and treated as above to yield 0.14 g of *cis*-**2d**, as white crystals and 0.7 g *trans*-**2d**, as a thick oil.

The hydrochlorides of the separated diasteroeisomers were prepared by dissolving the separated bases in cold, dried acetone and immediately passing dry HCl, until the solution was slightly acidic, the salts precipitated.

Oxidation products **2a–d**

1 - *Phenyl - hexahydro* - 1H - *pyrrolo*[1,2 - a]*imidazolin* - 2 - *one* (**2a**). M.p. 55–58°; calc for $C_{12}H_{14}N_2O$ (202.257) C, 71.26; H, 6.98; N, 13.85; found C, 71.18; H, 6.91; N, 13.77%; δ (ppm) (see

also Table 2), 3.10–3.40 (1 m *cis*-5H); 2.55–2.85 (1 m *trans*-5H); 1.9–2.1 (3 m 6-CH_2, *cis*-7H); 2.05–2.35 (1 m *trans*-7H); R_f: 1. 0.20; 2. 0.31; 3. 0.20. **2a** HCl, white crystals, m.p. 182–184°.

1 - (2,6 - *Xylyl*) - *hexahydro* - 1H - *pyrrolo*[1,2 - a]*imidazolin* - 2 - *one* (**2b**). M.p. 82°; calc for $C_{14}H_{18}N_2O$ (230.311); C, 73.01; H, 7.88; N, 12.16; found C, 73.00; H, 7.85; N, 12.11%; δ (ppm) (see also Table 2), 3.15–3.41 (1 m *cis*-5H); 2.65–3.02 (1 m *trans*-5H); 1.5–2.1 (4 m 6-CH_2, 7-CH_2); 2.23 (6 broad s Ar$(CH_3)_2$; 7.12 (3 broad s ArH); R_f: 1. 0.18; 2. 0.19; 3. 0.43. **2b** HCl white crystals, m.p. 187°.

1 - *Phenyl* - 3 trans-7aH *methyl* - *hexahydro* - 1H - *pyrrolo*[1,2 - a]*imidazolin* - 2 - *one* (cis **2c**). White needles, m.p. (94)—106–109° (contains < 10% *trans* **2c**) δ (ppm) (see also Table 2), 2.86–3.10 (1 m *cis*-5H); 2.50–2.85 (1 m *trans*-5H); 1.67–2.10 (3 m 6-CH_2, *cis*-7H); 2.10–2.40 (1 m *trans*-7H); 7.0–7.57 (5 m Ar–H); R_f: 1. 0.30; 2. 0.39; 3. 0.28. *cis*-**2c** HCl: white needles, m.p. 157–9° (pure *cis* isomer) ν (cm^{-1}): 1730 (CO). Picrate of *cis* **2c** bright yellow crystals, m.p. 174–7°.

1 - *Phenyl* - 3 cis-7aH *methyl* - *hexahydro* - 1*H* - *pyrrolo*[1,2 - a]*imidazolin* - 2 - *one* (trans **2c**). Thick oil (contains < 10% *cis* **2c**); δ (ppm) (see also Table 2), 3.10–3.35 (1 m *cis*-5H); 2.50–2.90 (1 m *trans*-5H); 1.60–2.05 (3 m 6-CH_2, *cis*-7H); 2.10–2.30 (1 m *trans*-7H); 7.00–7.50 (5 m ArH); R_f: 1. 0.24; 2. 0.34; 3. 0.25. *trans*-**2c** HCl: white crystals, m.p. 164–6° (pure *trans* isomer); ν (cm^{-1}): 1712 (CO); δ (ppm) (in $CDCl_3$ see also Table 2); 3.40 (1 m *cis*-5H); 4.05 (1 m *trans*-5H); 2.0–2.6 (4 m 6-CH_2, 7-CH_2); 7.3–7.5 (5 m ArH); in DMSO 1.64 (3 d 3-CH_3); 4.46 (1 q 3-H); 3.60 (2 m 5-CH_2); 1.8–2.5 (4 m-CH_2, 7-CH_2); 6.02 (1 q 7a-H); 7.2–7.7 (5 m ArH); 13.3 (1 broad NH); $^3J_{7aH\text{-}7Htrans} = 4.5$ Hz, $^3J_{7aH\text{-}7Hcis} = 6.0$ Hz; in TFA 2.03 (3 d 3-CH_3); 4.61 (1 q 3H); 3.82 (1 m *cis*-5H); 4.23 (1 m *trans*-5H); 2.3–2.7 (4 m 6-CH_2, 7-CH_2); 6.36 (1 m 7aH); 7.35–7.65 (5 m ArH); 10.10 (1 broad NH); Picrate of *trans* **2c** bright yellow crystals, m.p. 144–7°C.

1 - (2 - *Tolyl*) - 3 trans-7*aH methyl* - *hexahydro* - 1*H* - *pyrrolo*[1,2 - a]*imidazolin* - 2 - *one* (cis **2d**). White needles, m.p. (96)—106–108° (contains < 10% *trans* **2d**); δ (ppm) (see also Table 2), 2.10–3.15 (2 m 5-CH_2); 1.18–2.10 (4 m 6-CH_2, 7-CH_2); 2.21 (3 s Ar-CH_3); 6.85–7.40 (4 m ArH); R_f: 1. 0.28; 2. 0.36; 3. 0.25.

1 - (2 - *Tolyl*) - 3 cis-7aH *methyl* - *hexahydro* - 1*H* - *pyrrolo*[1,2 - a]*imidazolin* - 2 - *one* (trans **2d**). Thick oil (< 10% *cis* **2d**); δ (ppm) (see also Table 2), 3.05–3.35 (1 m *cis*-5H); 2.50–2.95 (1 m *trans*-5H); 1.55–2.05 (4 m 6-CH_2, 7-CH_2); 2.21 (3 broad s Ar-CH_3); 6.90–7.28 (4 m ArH); R_f: 1. 0.34; 2. 0.42; 3. 0.34. 1:5 mixture of *cis* **2d** and *trans* **2d**: thick oil, b.p. 180° (0.4 mm Hg).

Reduction of the cyclic products **2a–d**

With $NaBH_4$. **2** (0.5 mmol) was dissolved in methanol (0.2 ml) and $NaBH_4$ (38 mg; 1 mmol) in water (2 ml) was added dropwise. The mixture was stirred at room temp for 3 hr. The solution was acidified with 5% HCl solution, than neutralized with 5% NaOH solution, and extracted with chloroform. Separation of **1** and **2** was carried out as above. Yield of **1** 55–60%.

With formic acid. **2** (0.5 mmol) and formic acid (98–100%) 23 mg, (0.5 mmol) were heated at 120°C for 1.5 h. The thick reaction mixture was dissolved in water, neutralized with 5% NaOH solution, and extracted with chloroform. Separation of **1** and **2** was carried out as above. Yield of **1** 80–85%.

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