Chemistry of Heterocyclic Compounds, Vol. 33, No. 5, 1997

OXIDATION REACTIONS OF AZINES. 3.* SYNTHESIS AND OXIDATION OF 1,2,3,6-TETRAHYDRO-4-([2.2]-PARACYCLOPHAN-4-YL)PYRIDINES

A. T. Soldatenkov, I. A. Bekro, Zh. A. Mamyrbekova, S. A. Soldatova, and A. I. Chernyshev

Condensation of 2-([2.2]paracyclophan-4-yl)propene with formaldehyde and amines gave 4-paracyclophanyl substituted γ-piperidols which were readily dehydrated to the corresponding tetrahydropyridines. N-Methyl substituted 4-paracyclophanyltetrahydropyridine has been oxidized to the corresponding piperidin-2-one.

In preceding work in this series [1, 3] we reported a novel oxidative ketodihydroxylation reaction of 4-aryl substituted tetrahydropyridines making possible a one-stage synthesis of lactamdiols which are difficult to prepare and also potentially biologically active. In connection with the introduction of three functional groups into the piperidine ring at one time, there arose the question of the order of the oxidative reactions. Previously we have proposed [1] that the first chemical event must be oxidation of the piperidine to an unsaturated lactam which is then hydroxylated. However, obtaining experimental confirmation has not so far proved possible even when exchanging the phenyl substituent at atom C_4 for a π-deficient pyridyl which might check the oxidation at the 2-ketopiperidine stage [3]). In this work we set the goal of studying a possible steric inhibition of the reaction of permanganate anion with the double bond of the proposed piperidine intermediate. [2.2]Paracyclophane was chosen as the bulky substituent at the piperidine C_4 atom (see compound I).

To synthesize piperidines Ia-c we used the condensation of 4-(propenyl-2)paracyclophane (II) [4] with formaldehyde and alkylamines (or with NH_3) which can lead to piperidols IIIa-c (under previously reported conditions [5]) and which can dehydrate upon heating in the presence of acid. In [5] it was noted that condensation of α-methylstyrenes with amines gave both 4-phenylpiperidols and the isomeric oxazines. We have found that analogous heterocyclization of II gives a mixture (1:1 according to PMR) of the corresponding 4-paracyclophanyl γ-piperidol III and its dehydration product (4-paracyclophanyl-1,2,3,6-tetrahydropyridine I). Oxazine derivatives were not found among the cyclocondensation products. Hence, exchange of methylstyrene for its π-excessive paracyclophane analog directs towards one reaction route besides influencing the stability of the obtained γ-piperidols IIIa-c (which are readily converted to the corresponding piperidines Ia-c by heating in HCl). Formation of a significant amount of the latter in acid catalyzed cyclocondensation conditions is evidently associated with the ready protonation of the OH group and stabilization of the oxonium cation by the neighboring paracyclophane "nucleophilic cleft" [4].

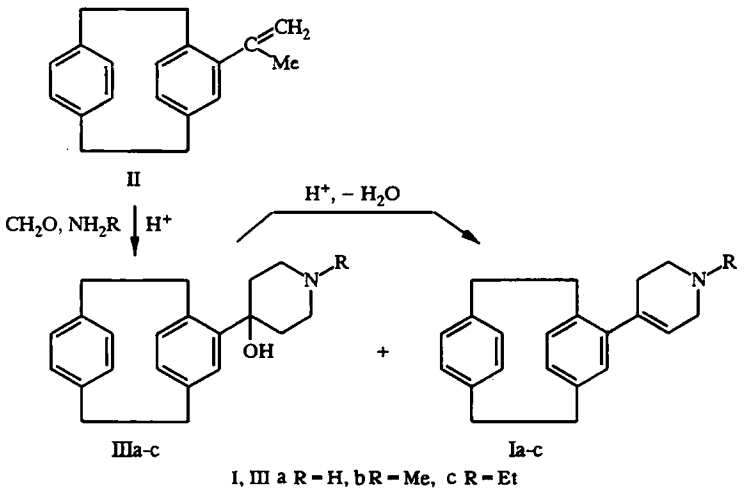
Piperidols IIIa, b and tetrahydropyridines Ib, c were separated pure using adsorption chromatography, and their structure confirmed via elemental analysis and spectral data (see Tables 1-3). The PMR spectrum ($CDCl_3$, 40°C) of the N-methyl substituted piperidol IIIb shows signals for the paracyclophane protons together with seven separate multiplets for the heterocyclic protons. A particular property of this part of the spectrum is the pairwise equivalence of the geminal (^2J = 13.7 and 11.9 Hz) and vicinal ($^3J_{aa}$ = 11.9, $^3J_{ae}$ = $^3J_{ee}$ = 2.8 Hz) coupling constants between protons 2-H_a, 2-H_e, 3-H_a, 3-H_e, and 6-H_a, 6-H_e, 5-H_a, and 5-H_e respectively indicating that the piperidine ring has a chairlike conformation, symmetrical rela-

*For communication 2, see [1]. This article is also communication 4 in the series "Synthesis, structure and biological activity of [2.2]paracyclophanes" (for communication 3, see [2]).

Russian University of National Friendship, Moscow 117198. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 653-658, May, 1997. Original article submitted July 22, 1996; revision submitted November 6, 1996.

 0009-3122/97/3305-0566$18.00

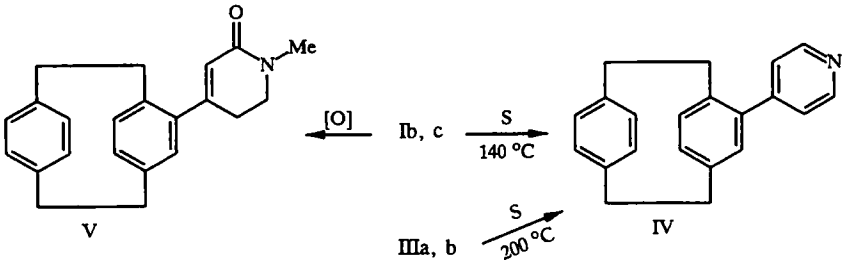
tive to the vertical plane passing through the N_1-C_4 bond. Hence, the bulky substituent at C_4 does not lead to a conformational anomaly in the heterocycle. A mutual comparison of the chemical shifts of the symmetrically placed axial and equatorial protons in positions 2,6 and 3,5 shows that the greatest shift difference is observed for protons 3-H_a and 5-H_a ($\Delta\delta$ = 0.32 ppm) which are placed nearer to the equatorial paracyclophane substituent. The axial orientation of the hydroxyl at C_4 is directly confirmed by the x-ray structural analysis of 3,4-dihydroxy-4-phenylpiperidin-2-one and its diacetate [3]. Signals for the axial and equatorial protons at positions 2 and 3 are shifted to low field of analogous signals for protons at 5 and 6. These facts point to a difference in the magnetic anisotropic effect of the paracyclophane substituent on the symmetrically placed protons of the piperidine ring and we can deduce that this substituent is placed asymmetrically to the vertical plane of the piperidol fragment passing through the N_1-C_4 axis.



The mass spectrum of piperidol IIIb shows a low intensity molecular ion peak M^+ at 321 (11%). The maximum peak occurs for the ion peak $[M-H_2O]^{+\cdot}$ with m/z 303 confirming the ready dehydration of the piperidol. The mass spectra of the piperidols I show a high intensity or maximum peak for the M^+ ion. In addition, compounds IIIa, b and Ib, c under electron impact show paraxylylene ion fragments with m/z 105 and 104, typifying the breakdown of a mono substituted paracyclophane radical [4].

The ^1H NMR spectrum of Ib shows a signal for the 3-H proton at 5.82 ppm, confirming the presence of a double bond in the heterocyclic fragment. It has a triplet structure due to interaction with two neighboring protons at C_2. Assignment of the signals of the piperidine 2, 5, and 6 protons was difficult because they were obscured by the complex multiplets for the methylene group protons of the paracyclophane substituent in the region 2.5-3.5 ppm.

Additional confirmation of formation of I and III was carried out via aromatization by heating with sulfur. It is known that a similar reaction of δ-piperidols needs quite a high temperature (190-200°C) both with an unsubstituted NH group and in the case of N-methyl derivatives [6, 7]. Since it is known that the [2.2]paracyclophane strained system is liable to fission of the methylene bridges at temperatures greater than 200°C [8], we carried out a preliminary experiment of heating the unsubstituted [2.2]paracyclophane with sulfur. It was found that it did not undergo a marked change in the range 50-150°C but that heating to 180-200°C caused an almost complete conversion to a polymericlike material from which no kind of pure material could be separated. Also, introduction of the piperidol substituent slightly stabilizes the paracyclophane system. Thus, when piperidols IIIa,b are treated with sulfur at 180-200°C (at lower temperatures these alcohols are stable) up to 10% of 4-(γ-pyridyl)paracyclophane IV is obtained, accompanied by tarring of the starting material. Change of the piperidyl substituent for tetrahydropyridyl (compounds Ib, c) results in ready aromatization even at 140°C and leads to a preparation of pyridine IV in preparatively useful yield (60%). The ^1H NMR spectrum shows multiplets for paracyclophane protons at 2.4-3.5 and 6.2-6.7 ppm together with a pair of two proton multiplets at 8.6 (AA′ system) and 7.3 ppm (BB′) for the α- and β-heterocyclic protons with a vicinal spin-spin coupling of about 5.6 Hz, unambiguously pointing to formation of a fully aromatic γ-substituted pyridine ring.



The obtained paracyclophanyl substituted tetrahydropyridine Ib was also used in an oxidative reaction carried out under ketodihydroxylation conditions (potassium permanganate in aqueous acetonitrile medium) by a known method [1, 3]. From the reaction medium in about 50% yield there was isolated one compound which was analyzed for the structure 1,2,5,6-tetrahydro-2-oxo-4-([2.2]-paracyclophan-4-yl)pyridine (V). The IR spectrum showed absorption bands at 1654 and 1609 cm^{-1}, assigned to the amide carbonyl and olefinic bond respectively. The change from tetrahydropyridine Ib to 2-oxo derivative V is indicated by the PMR spectrum of the latter, in which a 0.66 ppm shift to low field is seen in the methyl group protons when compared with Ib. The 3-H proton singlet is also shifted to low field (by 0.4 ppm) due to the effect of the oxygen atom. Double doublet signals for the two protons at position 6 are seen at 3.85 and 3.64 ppm (spin-spin coupling ^2J = 12.8, ^3J = 4.6 and 2.0 Hz). The decrease in the value of the vicinal constant is a result of a significant flattening of the tetrahydropyridine fragment in molecule V. The amide C_2 carbonyl signal is found at 163.7 ppm in the low field region of the ^{13}C NMR spectrum of lactam V (DMSO-D_6, 30°C). In the region 120-155 ppm, typical for sp^2 hybridized carbon atoms, there are found six signals for quaternary and eight for methine carbon atoms. The signals for the C_5 and C_6 atoms in the lactam ring were observed at 47.73 and 59.47 ppm respectively. In the region 33.8-34.7 ppm there were found the four methylene signals for the paracyclophane ring. The ^{13}C NMR signal for the NMe group was seen at 33.73 ppm. Combination of this data showed that only one of the three methylene groups present in the starting Ib is oxidized, in fact the methylene in the allylamine fragment. The mass spectrum of lactam V shows low intensity ion peaks for M^+ and $[M-H]^{+\cdot}$ and ion peaks with m/z 213 and 212 formed as a result of separation of a paraxylylene fragment (ions m/z 105 and 104) which are characteristic of paracyclophane derivatives and also serve to confirm the structure of this compound.

Hence introduction of the bulky paracyclophane substituent at piperidine position 4 generated, as expected, a powerful steric hindrance towards hydroxylation at the olefinic bond and halted the stepwise oxidation process of the allylamine fragment at the intermediate tetrahydropyridin-2-one stage. This result can be considered as a first experimental confirmation of our previous proposal [1, 3] for the order of the oxidative polyfunctionalization of tetrahydropyridines to lactams occurring in one reaction vessel.

EXPERIMENTAL

^1H NMR spectra were recorded on a Bruker WM-400 spectrometer (400 MHz) for solutions in $CDCl_3$. The ^{13}C NMR spectrum of V was taken in DMSO-D_6 on a Bruker WP-200 (50.29 MHz). Chemical shifts were measured relative to TMS internal standard (^1H, δ, 0.00 ppm) or DMSO-D_6 solvent (^{13}C, δ, 39.5 ppm). IR spectra were measured on a UR-20 instrument for KBr tablets. Mass spectra were obtained on an LKB-2091 instrument with direct introduction of the sample into the ion source (electron ionization energy 70 eV). The course of the reactions and purities of the compounds prepared were monitored using TLC on Silufol UV-254 plates with iodine vapor visualization.

The parameters and spectral data for the new compounds are given in Tables 1-3.

Cyclocondensation of 1-Methyl-1-([2.2]paracyclophan-4-yl)-ethylene (II) with Formaldehyde and Alkylamines. A mixture of ammonium chloride (or alkylamine hydrochloride) (3 mmole), 40% formaldehyde (12 mmole), and compound II (3 mmole) was vigorously stirred on a water bath at 80-90°C for 5 h. The reaction product was cooled to room temperature, water added (10 ml), and extracted with benzene. The aqueous layer was basified with 50% NaOH to pH 10-12 and extracted with benzene. The extract was dried with $MgSO_4$. After removal of solvent, the residue containing a 1:1 mixture of the corresponding piperidol IIIa-c and piperidine Ia-c was chromatographed on a silica gel column using ether eluant. The following products were separated: 4-hydroxy-4-([2.2]paracyclophan-4-yl)piperidine (IIIa) (R_f 0.2, eluant chloro-

TABLE 1. Parameters for Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	IR spectrum, ν, cm^{-1}	Yield, %
		C	H	N			
Ib	$C_{22}H_{25}N$	87.22 87,13	8.54 8,25	4.56 4,62	94...96	1640	15*
Ic	$C_{23}H_{27}N$	87.19 87,06	8.35 8,52	4.55 4,42	Oil	1637	50
IIIa	$C_{21}H_{25}NO$	81.87 82,08	8.33 8,14	4.72 4,56	104...106	3360 br , 3310 sh	35
IIIb	$C_{22}H_{27}NO$	82.31 82,24	8.56 8,41	4.51 4,36	Oil	3360 br	30
IV	$C_{21}H_{19}N$	88.50 88,40	6.42 6,67	4.83 4,91	110...112		60
V	$C_{22}H_{23}NO$	75.26 75,21	7.26 7,12	4.31 4,28	210...212	1654 vs 1609 s	50

*Yield of cyclocondensation product.

TABLE 2. PMR spectra of Compounds Synthesized

Compound	Chemical shift,* δ, ppm, spin-spin coupling (J), Hz		
	heterocyclic protons	paracyclophane protons	other protons
Ib	2,05...3,25 (6H,m, $3CH_2$); 5,82 (1H, br. s, 3-H)	2,55...3,20 (7H,m, $3CH_2$ and2-H); 3,50 (1H,m, 2-H); 6,25...6,45 (4H,m, H_{arom}); 6,55...6,70 (3H,m, H_{arom})	2,44 (3H, s, CH_3)
Ic	2,25...3,40 (6H,m, $3CH_2$); 5,75 (1H, br. s, 3-H)	2,80...3,40 (8H,m, $4CH_2$); 6,05...6,45 (4H,m, H_{arom}); 6,50...6,70 (3H,m, H_{arom})	1,50 (3H, t, CH_3); 2,55 (2H, q, CH_2CH_3)
IIIa	1,95 (2H,m, 3-H_e, 5-H_a); 2,44 (1H,m, 5-H_e); 2,80...2,95 (3H,m, 3-H_a, 2- and 6-H_e); 3,70 (2H,m, 2- and 6-H_a)	2,80...3,25 (7H,m, $3CH_2$and 2-H); 3,80 (1H,m, 2-H); 6,10...6,50 (4H,m, H_{arom}); 6,50...6,65 (3H,m, H_{arom})	2,35 (1H, s, OH); 4,00 (1H, br. s, NH)
IIIb	1,77 (1H, d.d.d.d , 5-H_e); 1,93 (1H, d.d.d.d , 3-H_e); 1,95 (1H, d.d.d, 5-H_a); 2,27 (1H, d.d.d, 3-H_a); 2,43 (1H, d.d.d, 6-H_a); 2,49 (1H, br. d.d.d , 6-H_e); 2,77 (1H, br. d.d.d, 2-H_e); $J_{5a,5e} = J_{3a,3e} = 13,7$; $J_{2a,2e} = J_{6a,6e} = J_{2a,3a} = = J_{5a,6a} = 11,9$; $J_{2e,3a} = = J_{2e,3e} = J_{2a,3e} = J_{3e,5e} = = J_{5a,6e} = J_{5e,6e} = J_{5e,6a} = 2,8$	2,85...3,25 (7H,m, $3CH_2$and 2-H); 3,83 (1H,m, 2-H); 6,30 (1H, d, $J = 8$, 8-H); 6,36 (2H,m, 12- and 13-H); 6,48 (1H, d, $J = 8$, 7-H); 6,55 (1H, s, 5-H); 6,62 (2H,m, 15- and16-H)	1,75 (1H, br. s , OH); 2,32 (3H, s, CH_3)
IV	7,30 (2H, d.d., $J = 5,6$ and 1,4; 3- and 5-H); 8,60 (2H, br. d.d , 2- and 6-H)	2,40...3,50 (8H,m, $4CH_2$); 6,25...6,70 (7H,m, H_{arom})	
V†	2,70...3,20 (2H,m, 5-H_e, 5-H_a); 3,64 (1H, d.d, $J = 12,8$ and 2,0, 6-H_e); 3,85 (d.d, $J = 12,8$ and 4,6, 6-H_a); 6,20 (1H, s, 3-H)	2,70...3,25 (7H,m, $3CH_2$and 2-H); 3,41 (1H, t, $J = 10,1$, 2-H); 6,41 (1H, br. s , 5-H); 6,41 and 6,66 (2H,m, ABX); 6,49 (1H), 6,52 (1H), 6,57 (1H) and 6,60 (1H) (four multiple AA' and BB' system)	3,08 (3H, s, CH_3)

*For narrow multiplet signals the center of the multiplet is given.

†^{13}C NMR spectrum of V: 33.7 (CH_3); 34.66, 34.6, 34.2, and 33.9 (paracyclophane CH_2 groups); 47.7 and 59.47 (piperidine CH_2 groups); 122.5, 128.7, 130.75, 132.0, 132.1, 133.1, 133.7, 135.34 (=CH groups); 136.85, 138.4, 138.8, 139.2, 139.5, 153.35 (C_{quat}), 163.74 (NC=O).

TABLE 3. Mass Spectra of Compounds Synthesized, m/z, (I, %)

IIa	M^+ 307(55), [M-MeCHOH] 262(34)
IIb	M^+ 321(11), $[M-H_2O]^+$ = Φ_1 303 (100), $[M-103]^{+\cdot}$ 218(16), $[M-104]^{+\cdot}$ 217(22), $[\Phi_1-104]^{+\cdot}$ = Φ_2 199(50), $[\Phi_1-105]^{+\cdot}$ 198(39), $[\Phi_2-CH_2CH=NH_2]^{+\cdot}$ 155(72), 105(55), 104(72), 103(12)
IIIb	M^+ 303(86), $[M-Me]^{+\cdot}$ 288(4), $[M-104]^{+\cdot}$ 199(79), 105(43), 104(100)
IIIc	M^+ 317(100), $[M-H]^{+\cdot}$ 316(60), $[M-Me]^{+\cdot}$ 302(22), $[M-104]^{+\cdot}$ = Φ_1 213(30), $[\Phi_1-H]^{+\cdot}$ 215(15), 198(5), $[\Phi_1-CH_3CH=NH_2]^{+\cdot}$ 169(4), $[\Phi_1-CH=NH-CH]^{+\cdot}$ 155(10), $[\Phi_1-MeCH=NHEt]^{+\cdot}$ 141(20), 104(5)
IV	M^+ 285(50), $[M-104]^{+\cdot}$ 181(75), 104(100)
V	M^+ 317(8), $[M-H]^{+\cdot}$ 316(29), 243(17), $[M-C_6H_3]^{+\cdot}$ 242(34), 224(7), $[M-C_8H_8]^{+\cdot}$ 213(7), 212(11), 211(12), 199(12), 167(11), 156(39), 141(34), 128(30), 105(53), $[C_8H_8]^{+\cdot}$ 104(87), 91(9), 78(22), 51(17), 44(100)

form–alcohol, 1:1); N-methyl-4-hydroxy-4-([2.2]paracyclophan-4-yl)piperidine (IIIb) (R_f 0.11, eluant alcohol–ether, 1:1); N-methyl-4-([2.2]para-cyclophan-4-yl)-1,2,5,6-tetrahydropyridine (Ib) (R_f 0.44, eluant chloroform–alcohol, 1:1) and N-ethyl-4-([2.2]paracyclophan-4-yl)-1,2,5,6-tetrahydropyridine (Ic) (R_f 0.54, eluant ether–alcohol, 5:2).

Dehydration of Piperidol IIIb. A solution of piperidol IIb (0.88 g, 2.75 mmole) in 18% HCl (30 ml) was stirred for 4 h at 90-95°C. The mixture was cooled to room temperature and HCl distilled off *in vacuo* using a water pump. A saturated aqueous solution of sodium carbonate was added to pH 10 and stirring continued for 2 h at 50°C. The cooled product was extracted with ether and the extract dried over magnesium sulfate to give Ib (0.36 g, 40%) as a pale yellow oil.

Aromatization of Piperidol IIIa and Piperidine Ib. A mixture of Ib (0.093 g, 0.31 mmole) or IIIa (0.095 g, 0.31 mmole) and sulfur (0.02 g. atom) was thoroughly stirred and held for 0.5 h at 140°C (180-200°C in the case of the piperidol). The mixture was then cooled and extracted with ether. After distillation of ether, the extract was purified on a silica gel column (eluant ether) to give 4-([2.2]paracyclophan-4-yl)pyridine (IV) as light yellow crystals with R_f 0.25 (ether). The yield was 0.01 g (10%) from alcohol IIIa and 0.06 g (60%) from Ib.

Oxidation of Piperidine Ib. Piperidine Ib (3 mmole) was oxidized by a known method [1,3] to give 1,2,5,6-tetrahydro-1-methyl-2-oxo-4-([2.2]paracyclophan-4-yl)pyridine (V) as colorless crystals from ether. R_f 0.12 (ether). Yield 0.45 g (50%).

This work was supported by the Russian Fund for Basic Research (project 96-03-33432a) and GKRF at VO NTP "Fine Organic Synthesis" (grant FT-15).

REFERENCES

1. I. A. Bekro, A. T. Soldatenkov, A. I. Stash, N. Yu. Chernikova, and A. I. Chernyshev, Khim. Geterotsikl. Soedin., No. 10, 1372 (1996).
2. D. Lozinskaya, S. Siaka, Zh. A. Mamyrbekova, B. N. Anisimov, and A. T. Soldatenkov, Khim.-Farm. Zh., No. 3, 42 (1994).
3. A. T. Soldatenkov, I. A. Bekro, S. A. Soldatova, A. Temesgen, N. D. Sergeeva, L. N. Kuleshova, and V. N. Khrustalev, Khim. Geterotsikl. Soedin., No. 2, 222 (1996).
4. Zh. A. Mamyrbekova, I. A. Bekro, S. A. Soldatova, E. A. Ageev, V. N. Guryshev, and A. T. Soldatenkov, Khim.-Farm. Zh., No. 3, 52 (1994).
5. C. J. Schmidle and R. C. Mansfield, J. Am. Chem. Soc., 77, 5698 (1955).
6. V. Baliah and A. Ekambaram, Indian J. Chem., 32, 274 (1955).
7. N. S. Prostakov, V. O. Fedorov, and A. T. Soldatenkov, Khim. Geterotsikl. Soedin., No. 8, 1098 (1979).
8. D. J. Cram, Accounts Chem. Res., 4, 204 (1971).