5.85 g (0.042 mole) piperidone (I), and the experiment carried out in a similar manner to the preceding. From the ether extract there was obtained 3.5 g residue in which TLC (the same system) showed two compounds with R_f 0.72 and 0.69. The residue was crystallized from heptane, yielding 2.98 g (31%) compound III, mp 160-161°C; R_f 0.69. Found, %: N 6.0; M^+ 231. $C_{15}H_{21}NO$. Calculated, %: N 6.1; M^+ 231.

1,2,5-Trimethyl-4-(4-hydroxy-2-methylphenyl)-Δ^3-tetrahydropyridine (IV) was prepared by a similar condensation of piperidone (I) with m-cresol using the same molar proportions of reactants, the yield being 3.05% of (IV), mp 120-121°C from heptane; R_f 0.51. Found, %: N 6.1; M^+ 231. $C_{15}H_{21}NO$. Calculated, %: N 6.1; M^+ 231.

LITERATURE CITED

1. D. M. Zimmerman, R. Nikander, J. S. Horng, and D. T. Wong, Nature, 275, 332 (1978).
2. M. M. A. Hassan and A. F. Casy, Org. Magn. Reson., 2, 197 (1970).
3. M. Karplus, J. Chem. Phys., 30, 11 (1959).
4. M. Barfield and B. Chakrabarti, Chem. Rev., 69, 757 (1969).
5. F. A. L. Anet and I. Yavari, J. Am. Chem. Soc., 99, 2794 (1977).
6. M. Anteunis, Bull. Soc. Chim. Belg., 75, 413 (1966).
7. F. R. Jensen and C. H. Bushweller, Adv. Alicyclic Chem., 3, 139 (1971).

SYNTHESIS OF 1,5-METHANO-2-BENZAZOCINES FROM 3-HYDROXY-1,3-DIMETHYL-6-PHENYL-4-PIPERIDONE

G. V. Pshenichnyi, V. A. Mashenkov, and L. S. Stanishevskii

UDC 547.823:543.422

Reaction of 3e-hydroxy-1e,3a-dimethyl-6e-phenyl-4-piperidone with cyanoacetic ester affords 6e,8a-dimethyl-2-oxo-5e-phenyl-3-cyanofuro[2,3-c]piperidine, the epoxide of which undergoes intramolecular cyclization on treatment with 80% H_2SO_4 to give 1,2,5,6-tetrahydro-2-endo-4-dimethyl-1,5-methano-6-oxo-2-benzazocin-3-ene. It has been found that the latter is formed via the intermediate 3-hydroxy-6e,8a-dimethyl-2-oxo-5e-phenylfuro[2,3-c]piperidine.

1,5-Methano-2-benzazocines have so far received little attention as a result of the lack of satisfactory methods for their preparation. Compounds of this type have been obtained by adding amidines to di-, tri-, and tetranitronapthalenes [1]. We have developed a new method for the synthesis of 1,5-methano-2-benzazocines based on the acid-catalyzed reaction of the epoxy-lactone (II). The latter compound was obtained by condensing the α-ketol (I) with ethyl cyanoacetate.

The conversion of the epoxylactone (III) into the ketone (V) evidently involves hydrolysis of the cyano-group and the epoxide ring, decarboxylation, and dehydration to give the intermediate lactone (IV). Subsequent intramolecular reactions of the lactone (IV) involve opening of the lactone ring, decarbonylation, and dehydration (see scheme on following page).

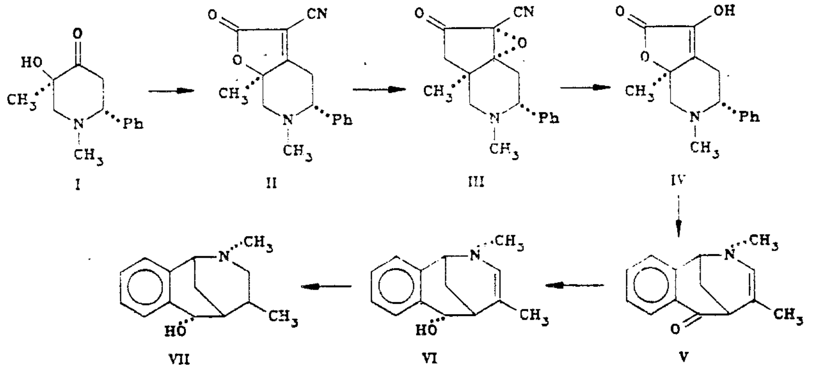
Reduction of the ketone (V) with complex hydrides of aluminum and boron showed that attack on the carbonyl group by the hydride ion takes place from the sterically more accessible exo-position, subsequent reduction of the double bond with sodium borohydride in ethanol taking place from the endo-position.

The structures of all the compounds obtained were confirmed by their elemental analyses and their IR, PMR, and mass spectra. For example, in the PMR spectra of (II-IV), the protons of the piperidine ring are seen as two spin systems, AMX and AX, examination of which shows

---

V. I. Lenin Belorussian State University, Minsk 220080. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1371-1374, October, 1986. Original article submitted May 31, 1985; revision submitted December 2, 1985.

0009-3122/86/2210-1110$12.50 © 1987 Plenum Publishing Corporation



that the ring has the chair conformation, the methyl group at nitrogen being equatorially oriented [2]. The observed marked nonequivalence of the protons of the aromatic nucleus in (V-VII) is due to their presence in a ring with a neighboring electron acceptor. A particularly large paramagnetic shift is experienced by the proton in the 7-position. The PMR and IR spectra of the lactone (IV) show that this compound exists solely in the enol form, whether in solution in CCl_4 or $CHCl_3$, or in the solid state, in agreement with data for bicyclic α-ketolactones [3]. That the hydroxyl group occupies the endo-position in the benzazocines (VI) and (VII) is confirmed by the weak IHB ($\Delta\nu$ = 30 cm^{-1}) in (VI) between the hydroxyl hydrogen and the π-electrons of the double bond [4], and by the value of the coupling constant between the 5-H and 6-H [5]. The exo-position of the 4-CH_3 group in the benzazocine (VII) is confirmed by the value of the coupling constant between 4-H and the protons at $C_{(3)}$ and $C_{(5)}$. Experiments utilizing the nuclear Oberhauser effect (NOE) showed clear dipole-dipole interactions between the 2-CH_3 and 10-H protons in benzazocines (V) and (VII), indicating that the N-methyl group occupies the endo-position in these compounds.

Thus, the method of preparation of 1,5-methano-2-benzazocines which has been developed is adequately simple in use, and can be employed as a preparative method of synthesis of these difficultly-accessible compounds.

EXPERIMENTAL

The IR spectra of the compounds in solution in CCl_4, $CHCl_3$, and C_2Cl_4, and in KBr disks, were obtained on Specord-75 IR and UR-20 instruments. The PMR spectra of 5-10% solutions in $CDCl_3$ were obtained on Tesla BS-567A (100 MHz) and Bruker WM-360 (360 MHz) spectrometers, and the NOE experiments were carried out by differential spectroscopy, internal standard HMDS. Mass spectra were obtained on a Varian MAT-311 mass spectrometer at 70 eV. Carbon monoxide was measured with a CO-0,2 indicator tube. The properties of the compounds obtained are given in Table 1. In the mass spectra of all the compounds, the molecular ion peaks are in agreement with the calculated molecular masses.

6e,8a-Dimethyl-2-oxo-5e-phenyl-3-cyanofuro[2,3-c]piperdine (II). To a solution of 2.19 g (10 mmoles) of the piperidone (I) [6] in 5 ml of ethanol was added 1.70 g (15 mmoles) of ethyl cyanoacetate and 0.34 g (5 mmoles) of sodium ethoxide. The mixture was kept for 30 min at 20°C, and the lactone (II) which separated was filtered off and washed with cold ethanol.

6e-8a-Dimethyl-2-oxo-5e-phenyl-3-cyano-3,9e-epoxyfuro[2,3-c]piperidine (III). To a solution of 5.36 g (20 mmoles) of the lactone (II) in 200 ml of benzene was added 40 ml of 15% H_2O_2 and 1 g of tetrabutylammonium hydroxide. The mixture was stirred vigorously for 2 h at 20°C, the aqueous layer separated, and the benzene layer washed with water, dried over K_2CO_3, and passed through a thin layer of silica gel grade L40/100. After evaporation of part of the benzene, the residue was crystallized from a 1:1 mixture of benzene and hexane.

3-Hydroxy-6e,8a-dimethyl-2-oxo-5e-phenylfuro[2,3-c]piperidine (IV). A solution of 1.7 g (6 mmoles) of the lactone (III) in 50 ml of 25% sulfuric acid was boiled for 36 h, and the mixture cooled, treated with 10% sodium hydroxide to pH 8-9, extracted with benzene, and the extract dried over Na_2SO_4. The solvent was then partially evaporated, and the residue crystallized from 2:1 mixture of benzene and hexane.

1,2,5,6-Tetrahydro-2-endo-4-dimethyl-1,5-methano-6-oxo-2-benzazocin-3-ene (V). The lactone (III) or (IV) (10 mmoles) was dissolved in 10 ml of 80% sulfuric acid, and the mixture kept for 3.5 h at 140-150°C. After cooling, the mixture was poured into 100 ml of 10%

TABLE 1. Properties of Compounds (II-VII)

Compound	mp, °C	PMR spectrum, ppm (J, Hz)	IR spectrum, ν, cm-1	Found, %			Empirical formula	Calculated, %			Yield, %
				C	H	N		C	H	N	
II	152—153	1,79 (s, 8-CH_3); 2,06 (s 6-CH_3); 2,24 (d, J_{gem}=11,0, 7a-H); 2,72 (d.d. $J_{4e,4a}$=13,5, $J_{4a,5a}$=10,0, 4a-H); 3,06 (d.d, $J_{4e,5a}$=3,0, 5a-H); 3,15 (d.d., 4e-H); 3,37 (d, 7e-H); 7,22—7,41 (5H, m, H_{arom})	1650 (C=C), 1770 (C=O), 2235 (C≡N)	71,5	5,9	10,5	$C_{16}H_{16}N_2O_2$	71,6	6,0	10,4	93
III	95—96	1,68 (s, 8-CH_3); 1,89 (d.d. $J_{4a,4e}$=14,3, $J_{4e,5a}$=3,5, 4e-H); 2,04 (s, 6-CH_3); 2,25 (d, Jgem=12,0, 7a-H); 2,48 (d. d. $J_{4a,5a}$=11,5, 4a-H); 3,19 (d.d. 5a-H); 3,24 (d, 7e-H); 7,24—7,40 (5H, m H_{arom})	1800 (C=O), 2250 (C≡N)	67,2	5,7	9,9	$C_{16}H_{16}N_2O_3$	67,6	5,7	9,9	73
IV	163—164	1,68 (s, 8-CH_3); 2,01 (s, 6-CH_3); 2,07 (d, J_{gem}=11,0, 7a-H); 2,31 (d.d, $J_{4a,4e}$=14,0, $J_{4a,5a}$=10,5, 4a-H); 2,83 (d.d, $J_{4e,5a}$=3,0, 5a-H); 2,99 (d.d, 4e-H); 3,26 (d, 7e-H); 7,24—7,37 (5H, m, H arom)	1720 (C=C), 1770 (C=O), 3535 (OH)	69,5	6,6	5,4	$C_{15}H_{17}NO_3$	69,5	6,6	5,4	40
V	103—104	1,64 (s, 4-CH_3); 2,01 and 2,23 (two d.t., Jgem=12,6 $J_{11,1}$=$J_{11,5}$= =2,6, N-CH_2); 2,71 (s, 2-CH_3); 2,93 (t, 5-H); 4,10 (t, 1-H); 5,59 (s, 3-H); 7,22 (d.d, $J_{9,10}$=7,2, $J_{8,10}$=0,6, 10-H); 7,36 (d.t, $J_{7,8}$=$J_{8,9}$=7,2, 8-H); 7,53 (d.t, $J_{7,9}$=0,6, 9-H); 8,16 (d.d 7-H)	1650 (C=C), 1675 (C=O)	78,7	7,1	6,7	$C_{14}H_{15}NO$	78,8	7,1	6,6	76
VI	101—102	1,81 (d, $J_{1\,CH_3,3}$ =1,0, 4-CH_3); 1,85—1,99 (m N—CH_2); 2,45—2,57 (m, 5-H); 2,59 (s, 2-CH_3); 3,91 (t, $J_{1,N-CH_2}$=2,6, 1-H); 4,99 (d. $J_{5,6}$=5,0, 6-H); 5,63 (q., 3-H); 6,99—7,35 and 7,61—7,73 (4H, m, H_{arom})	1660 (C=C), 3590 (OH), 3620 (OH)	78,4	7,9	6,4	$C_{14}H_{17}NO$	78,1	8,0	6,5	100
VII	158—159	1,27 (d. $J_{4\text{-}CH_3,4}$ =6,5, 4-CH_3); 1,51 and 2,44 (two d.t, Jgem=13,0, $J_{11,1}$=$J_{11,5}$=2,6, N—CH_2); 1,83 (d.d, Jgem=12,0. $J_{3a,4e}$=4,3, 3a-H); 1,96—2,00 (m 5-H); 2,06 (s, 2-CH_3); 2,12 (d, 3e-H); 2,28 (m, 4e-H); 3,56 (t, 1-H); 4,89 (d, $J_{5,6}$=6,3, 6-H); 6,89 (d.d, $J_{9,10}$=7,2, $J_{8,10}$=0,6, 10-H); 7,18 (d.t, $J_{7,8}$=$J_{8,9}$=7,2, 8-H); 7,29 (d.t, $J_{7,9}$=0,6, 9-H); 7,62 (d.d, 7-H)	3620 (OH)	77,5	8,9	6,3	$C_{14}H_{19}NO$	77,4	8,8	6,5	94

sodium hydroxide solution, and extracted with benzene. The extract was dried over Na_2SO_4 and passed through a thin layer of silica gel grade L40/100. After removal of part of the benzene, the residue was crystallized from a 2:1 mixture of benzene and hexane. The yield of (V) from (IV) was 89%, and from (III), 76%.

<u>1,2,5,6-Tetrahydro-6-endo-hydroxy-2-endo-(4-dimethyl-1,5-methano-2-benzazocin-3-ene (VI).</u> A. To a suspension of 0.46 g (12 mmoles) of lithium aluminum hydride in 100 ml of ether was added dropwise 2.66 g (36 mmoles) of tert-butanol, the mixture kept for 30 min, 2.13 g (10 mmoles) of the 2-benzazocine (V) added, and the mixture stirred for 1 h 30 min. The mixture was then treated dropwise with 10 ml of water, and the solid filtered off, washed with ether, and the combined ether solutions dried over Na_2SO_4. Evaporation of the ether gave 1.65 g (77%) of (VI).

B. To a solution of 1.70 g (8 mmoles) of the ketone (V) in 50 ml of ether was added 0.3 g (8 mmoles) of lithium aluminum hydride, followed after 15 min by the dropwise addition of 5 ml of water. Subsequent workup was as described above. Yield, 100%.

<u>1,2,3,4,5,6-Hexahydro-6-endo-hydroxy-2-endo-4-exo-dimethyl-1,5-methano-2-benzazocine (VII).</u> A. To a solution of 1.72 g (8 mmoles) of the enamine (VI) in 50 ml of ethanol was added 0.47 g (13 mmoles) of sodium borohydride, and the mixture boiled for 15 min. After cooling, it was acidified with acetic acid, evaporated, 10 ml of water added, basified with solid sodium carbonate, and extracted with ether. After removal of the ether, the residue was crystallized from a 3:1 mixture of benzene and hexane.

B. To a solution of 0.49 g (2.3 mmoles) of the ketone (V) in 30 ml of ethanol was added 0.28 g (7.8 mmoles) of sodium borohydride, and the mixture boiled for 15 min. After cooling, the mixture was worked up as in the preceding preparation, to give 0.4 g (80%) of (VII).

LITERATURE CITED

1. R. R. Bard and M. J. Strauss, J. Org. Chem., <u>41</u>, 2421 (1976).
2. V. F. Bystrov, Usp. Khimii, <u>41</u>, 512 (1972).
3. C. J. W. Brooks, G. Eglinton, and D. S. Magrill, J. Chem. Soc., 308 (1961).
4. M. Tichi, Advances in Organic Chemistry [Russian translation], Vol. 5, Mir, Moscow (1968), 117.
5. N. S. Zefirov, Usp. Khimii, <u>44</u>, 413 (1975).
6. L. S. Stanishevskii, I. G. Tishchenko, and A. Ya. Guzikov, Zh. Org. Khim., <u>7</u>, 2612 (1971).