Amidoxime of 4-Piperidinofurazan-3-carboxylic Acid (IIc). A solution of 1.27 g (6 mmoles) Z or E oxime II and 1.12 g (20 mmoles) KOH in 5 ml ethylene glycol was heated at 120-140°C for 7 h. The reaction mixture was cooled, diluted with 8 ml of water, and neutralized with hydrochloric acid. The residue was filtered off and recrystallized from water to yield 0.95 g of product.

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SYNTHESIS OF PYRIDO[1,2-c][1,3]BENZOXAZINES BASED ON 1-BENZYL-3-HYDROXY-3-METHYL-6-(2-BENZYLOXYPHENYL)-4-PIPERIDONES

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The stereomeric 1-benzyl-3-hydroxy-3-methyl-6e-(2-benzyloxyphenyl)-4-piperidones on debenzylation and subsequent reaction with formaldehyde are converted into cis- and trans-1,3,4-10b-tetrahydro-3-hydroxy-3-methyl-2-oxopyrido-[1,2-c][1,3]benzoxazines.

Arising out of the growing interest in recent years in the chemistry of cannabinoids (certain derivatives of 9H-dibenzo[b,d]pyrans, isolated from *Cannabis sativa Linn.* and possessing high biological activity [1]), published work has appeared on the synthesis of their heterocyclic analogs, in particular pyrido[1,2-c][1,3]benzoxazines [2, 3].

We have developed a new approach to the synthesis of these compounds based on the stereoisomeric piperidones III and IV and involving catalytic debenzylation over palladium and subsequent treatment with formaldehyde, it being possible thus to prepare benzoxazines V and VI without isolating the intermediate NH-piperidones. The piperidones III and IV are prepared by the known route [4] of crotonic condensation of the epoxy ketone I with 2-benzyloxybenzaldehyde and further reaction of the cinnamoyloxirane II with benzylamine.

The composition and structure of the compounds synthesized were confirmed by elemental analysis, and their IR, PMR, and ^{13}C NMR spectra. Thus, the configuration of the piperidones III and IV follows from the values of the chemical shifts of the methyl groups in the PMR spectra (Table 1) [4]. In the IR spectrum of compound V, the so-called Bohlmann bands [5] are observed in the 2700-2850 cm^{-1} region, these being associated with trans-hydrogen bonding. The absence of these bands from the IR spectrum of compound VI is evidence of cis-hydrogen bonding (see scheme below).

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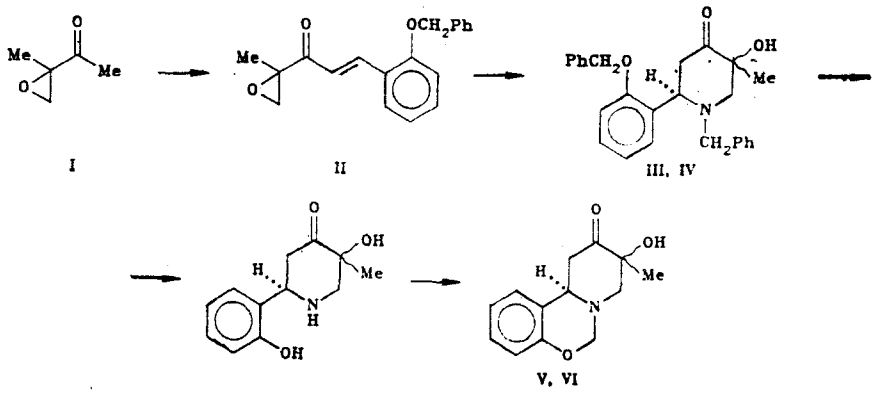
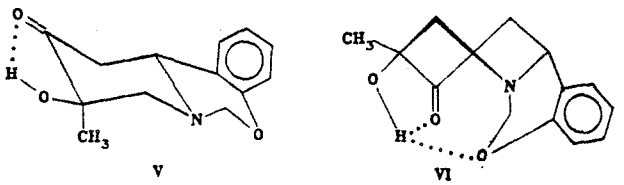
TABLE 1. Characteristics of Compounds Prepared

Compound	Empirical formula	Mp, °C	IR spectrum, cm^{-1}	PMR spectrum, δ, ppm (J, Hz)	Yield, %
II	$C_{19}H_{18}O_3$	69...70	1680	1,38 (s, CH_3); 2,63 (s, OCH_2); 5,00 (s, OCH_2Ph); 6,81 and 7,84 (two d, J_{gem}=16,0, CH=CH); 6,54...7,53 (9H, m, Ar)	92
III	$C_{26}H_{27}NO_3$	92...93	1720, 3510	1,44 (s, CH_3); 2,08 and 3,02 (two d, J_{gem}=11,5; 2-H); 2,52 (d.d, J_{5e5a}=14,0; J_{5e6a}=3,5; 5-H_e); 2,82 and 3,78 (two d, J_{gem}=13,5, NCH_2Ph); 2,88 (d.d, J_{5a6a}=11,0; 5-H_a); 3,68 (s, OH); 4,11 (d.d; 6-H_a); 5,05 (s, OCH_2Ph); 6,82...7,69 (10H, m, Ar)	83
IV	$C_{26}H_{27}NO_3$	136...137	1730, 3485	1,10 (s, CH_3); 2,18 and 2,90 (two d, J_{gem}=12,5; 2-H); 2,51 (d.d, J_{5e5a}=14,5, J_{5e6a}=4,5, 5-H_e); 3,06 and 3,71 (two d, J_{gem}=13,3, NCH_2Ph); 3,17 (d.d, J_{5a6a}=10,0, 5-H_a); 3,95 (s, OH); 4,15 (d.d. 6-H_a); 5,08 (s, OCH_2Ph); 6,89...7,55 (10H, m, Ar)	61
V	$C_{13}H_{15}NO_3$	91...92	1715, 2760, 2775, 2825, 3505	1,49 (s, CH_3); 2,52 (d, J_{gem}=11,2, 4-H_α); 2,72 (d.d, $J_{1\alpha1\beta}$=14,0, $J_{1\beta10b\alpha}$=10,7; 1-H_β); 3,05 (d.d, $J_{1\alpha10b\alpha}$=4,0, 1-H_α); 3,15 (d, 4-H_β); 3,83 (s, OH); 3,93 (d.d, 10b-H_α); 4,47 and 4,76 (two d, J_{gem}=7,8; 5-CH_2); 6,86...7,05 (4H, m, Ar)	70
VI	$C_{13}H_{15}NO_3$	168...169	1720, 3510	1,55 (s, CH_3); 2,92 (d, J_{gem}=11,6; 4-H_α); 3,03 (d, 4-H_β); 3,03 (d.d, $J_{1\alpha1\beta}$=14,4; $J_{1\beta10b\alpha}$=3,6; 1-H_β); 3,13 (d.d, $J_{1\alpha10b\alpha}$=6,4; 1-H_α); 3,69 (s, OH); 4,69 (d.d, 10b-H_α); 4,82 and 5,02 (two d, J_{gem}=9,5; 5-CH_2); 6,75...7,16 (4H, m, Ar)	60



III, V 3α-OH; IV, VI β-OH

Spin–spin coupling between the protons of the piperidine ring and the 5-CH_2 group [6, 7] in compounds V and VI, together with the existence of clearcut dipole–dipole interactions, studied by the nuclear Overhauser effect, between the 3-CH_3 and 1-H, 4-H (for VI, with 4-H_2), provide evidence in support of the trans form for V and a distorted cis form for VI



In the ^{13}C NMR spectra (Table 2) of compounds III and IV, an upfield displacement of the $C_{(4)}$ and 3-CH_3 is observed. This is characteristic for 3-hydroxy-4-piperidones in the case of axial orientation of the hydroxyl group, and is connected with a change in the configuration of the carbinol center and the character of the intramolecular hydrogen bond. In pyrido[1,2-c][1,3]benzoxazines V and VI there is no noticeable difference in the chemical shifts of the analogous $C_{(2)}$ and 3-CH_3 atoms. This is in good agreement with the proposed structure of compounds V and VI and with an identical type of intramolecular hydrogen bond therein, i.e., between the proton of the hydroxyl group and the unshared pair of the carbonyl oxygen atom. In compound VI one should note the upfield displacement of the majority of the signals of the carbon atoms of the pyrido[1,2-c][1,3]oxazine fragment; however, such a displacement is more noticeable in the case of axial orientation of the phenyl substituent in the piperidone ring [8, 9].

EXPERIMENTAL

Infrared spectra were run on a Specord IR-75 instrument in CCl_4. A Bruker WM-360 was used to obtain the NMR spectra in solution in $CDCl_3$. The experiments on the nuclear Overhauser effect were carried out by difference spectroscopy using HMDS as internal standard.

Results for elemental analysis corresponded to those calculated.

1,2-Epoxy-2-methyl-5-(2-benzyloxyphenyl)-4-pentene-3-one (II). To a solution of 0.48 mole of 2-benzyloxybenzaldehyde and 0.6 mole methylisopropylketone epoxide I in a mixture of 150 ml methanol and 50 ml dioxane was added at 12-15°C 40 ml 15% NaOH in methanol. The reaction mixture was held at this temperature for 40 min, diluted with 200 ml aqueous methanol and the product which separated was filtered off, washed with 50% aqueous methanol and with water, and dried in air.

1-Benzyl-3e-hydroxy-3a-methyl-6e-(2-benzyloxyphenyl)-4-piperidone (III). The epoxide II (0.08 mole) was dissolved in 100 ml dioxane and 0.14 mole benzylamine and 15 ml distilled water added. The reaction mixture was allowed to stand until TLC showed that the initial epoxide II had disappeared; it was then evaporated and the residue dissolved in 10% hydrochloric acid. The solution was left to stand for 10 h and filtered. The filtrate was neutralized and the product which separated extracted with benzene and the solution so obtained dried over Na_2SO_4, evaporated, and the residue recrystallized from a 2:1 mixture of isopropyl alcohol and hexane.

1-Benzyl-3a-hydroxy-3e-methyl-6e-(2-benzyloxyphenyl)-4-piperidone (IV). To a boiling solution of 0.17 mole oxirane II in 300 ml isopropyl alcohol, 0.3 mole benzylamine was added over a period of 1 h. The reaction mixture was cooled and treated as in the preceding experiment.

TABLE 2. ^{13}C NMR Spectra of Compounds III and IV

Compound	δ, ppm								
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	CH_3	NCH_2Ph	OCH_2Ph	Ar
III	63,49	75,48	211,20	44,61	61,87	24,50	57,32	70,19	112,52; 121,55; 127,31; 126,84; 128,50; 136,65; 138,60; 155,92
IV	62,04	73,76	208,50	43,81	61,33	19,07	57,12	70,26	112,55; 121,38; 127,15; 128,06; 128,76; 136,58; 137,86; 155,99

TABLE 3. ^{13}C NMR Spectra of Compounds V and VI

Compound	δ, ppm								
	$C_{(4)}$	$C_{(3)}$	$C_{(2)}$	$C_{(1)}$	$C_{(10b)}$	CH_3	$C_{(5)}$	—	Ar
V	60,69	75,35	209,95	41,99	59,61	24,29	82,19	—	116,87; 121,15; 122,23; 125,20; 128,40; 152,52
VI	58,45	74,34	209,27	38,62	57,62	23,59	83,40	—	116,60; 120,13; 120,88; 125,89; 129,10; 152,86

1,3,4,10b-Tetrahydro-3-hydroxy-3-methyl-2-oxopyrido[1,2-c][1,3]benzoxazines (V, VI). Dry HCl was passed into a solution of 0.05 mole piperidone III and IV in 100 ml methanol to give a pH of 3-4 and 200 mg $PdCl_2$ and 0.5 g activated carbon were added. The reaction mixture was vigorously stirred in an atmosphere of hydrogen until the latter was no longer absorbed. The catalyst was removed by filtration and the methanol by distillation under reduced pressure, and the residue dissolved in 20 ml water. To this was added 10 ml 28% formaldehyde solution and after 15 min the reaction mixture was neutralized with saturated aqueous $NaHCO_3$, extracted with ether, and the ether extract washed with water, dried over Na_2SO_4, and evaporated. The residue was recrystallized from 1:2 ether–hexane.

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