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CONDENSATION OF N-ETHYLPIPERID-4-ONE WITH BENZALDEHYDE

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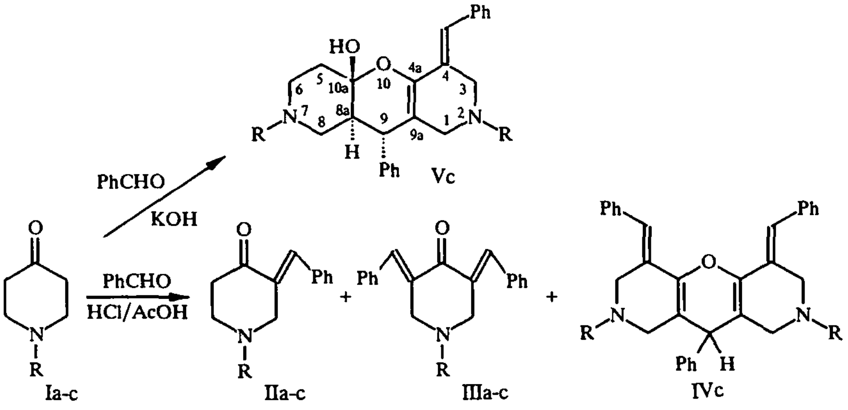
Reaction of N-ethylpiperid-4-one with benzaldehyde and KOH in 65% aqueous methanol gives 2,7-diethyl-10a-hydroxy-9-phenyl-4-(phenylmethylene)-2,7-diaza-10-oxa-1,2,3,4,5,6,7,8,8a,10a-decahydroanthracene. In the presence of HCl/EtOH, 3,5-bis(phenylmethylene)-1-ethylpiperid-4-one is formed. In the presence of HCl/AcOH, 2,7-diethyl-9-phenyl-4,5-bis(phenylmethylene)-2,7-diaza-10-oxa-1,2,3,4,5,6,7,8-octahydroanthracene is formed.

In the course of studying the ability of oximes of 2-arylmethylen-3-oxoquinuclidine to produce NO under mild oxidation [1, 2], we required monocyclic analogs of the bicyclic derivatives. The reaction of N-ethylpiperid-4-one (Ib), which is more accessible by comparison with N-ethylpiperid-3-one, with benzaldehyde seemed the optimal route to synthesize the initial ketones.

According to published data, when piperid-4-one [3, 4] and N-methylpiperid-4-one [3, 5, 6] react with aromatic aldehydes in EtOH or AcOH saturated with HCl, only the 3,5-bisbenzylidene derivatives (IIIa,b) are obtained. The reaction in an alkaline aqueous–alcoholic medium is not so clear. The N-methylpiperid-4-one forms the mixtures of mono- and bis-derivatives (IIb) and (IIIb), the ratio of which depends on the concentration of the alcohol [7, 8], as well as the tricyclic compound (Vb) [9]. Benzylidene derivatives of N-ethylpiperid-4-one were not described.



I–IV a R = H, b R = Me, c R = Et

As was expected on the basis of published analogies, the reaction of N-ethylpiperid-4-one with benzaldehyde in ethanol saturated with HCl only leads to the formation of the dibenzylidene derivative (IIIc). The substitution of ethanol by acetic acid gives the mixture of compound (IIIc) and the new tricycle (IVc), which is formally the condensation product of the compounds (IIc) and (IIIc). When the reaction was performed in an alkaline medium with the concentration of methanol and KOH guaranteeing a maximal yield of the monobenzylidene derivative (IIb) [7], only the dimer of (IIc) and the tricycle (Vc) were isolated.

The mass spectra of the compounds (IIIc)-(Vc) contain molecular ions. The IR spectra of the compounds (IVc) and (Vc) lack carbonyl absorption bands, and the spectrum of the tricycle (Vc) shows a band of the stretching vibrations of the OH

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group. The NMR spectra of compound (Vc) show the presence of one diastereomer, described by analogy with the structure determined for the corresponding N–Me-(p-bromophenyl) derivative [9]. The symmetrical structure of the tricycle (IVc) follows from the presence of a sole singlet of the two benzylidene groups in its PMR spectrum, and from the ^{13}C NMR spectrum.

It is difficult to present that the observed differences in the behavior of the N-methyl- and N-ethylpiperid-4-ones are associated with differences in their basicity or in steric hindrance caused by the N-alkyl group. The most reasonable hypothesis seems to be that the direction of the multistep condensation may be determined by the solubility of the intermediates and final products in the aqueous–alcoholic medium [7].

EXPERIMENTAL

The NMR spectra were taken on the Varian Unity Plus 400 instrument. The mass spectra were taken on the Finnigan MAT SSQ 710 instrument. The IR spectra were taken in mineral oil using the Perkin–Elmer 457 instrument. Melting temperature was determined in a sealed capillary. The TLC utilized Silufol UV-254 in the 10:1 system of chloroform–methanol, and development was performed in UV light and with Dragendorff's reagent.

Hydrochloride of 3,5-Bis(phenylmethylene)-1-ethylpiperid-4-one (IIIc·HCl). To 1.25 g (10 mmole) of N-ethylpiperid-4-one in 60 ml of dry ethanol saturated with HCl are added 2.47 g (20 mmole) of freshly distilled benzaldehyde. The resulting red solution is maintained for 2 weeks at 0-5°C prior to the distillation of 40 ml of ethanol from it. To the residue are added 80 ml of water. The yield of 2.7 g (79%) of yellow crystals of (IIIc) is obtained. The mp is 215-218°C (from 20% ethanol), and the R_f is 0.79. The ^1H NMR spectrum ($DMSO-D_6$) is as follows: 1.23 ppm (3H, t, NCH_2CH_3), 3.33 ppm (2H, q, NCH_2CH_3), 4.62 ppm (4H, m, 2-H + 6-H), 7.50-7.60 ppm (10H, m, Ph), 7.92 ppm (2H, s, =CHPh), and 11.83 ppm (1H, s, NH). Found, %: C 74.06, H 6.50, and N 3.96. $C_{21}H_{21}NO \cdot HCl$. Calculated, %: C 74.21, H 6.52, and N 4.11.

3,5-Bis(phenylmethylene)-1-ethylpiperid-4-one (IIIc) and 2,7-Diethyl-9-phenyl-4,5-bis(phenylmethylene)-2,7-diaza-10-oxa-1,2,3,4,5,6,7,8-octahydroanthracene (IVc). The solution of 4.9 g (39 mmole) of N-ethylpiperid-4-one and 8.2 g (78 mmole) of benzaldehyde in 10 ml of dry acetic acid saturated with HCl is maintained for 2 weeks at 20°C prior to its neutralization with potassium carbonate and the extraction with 3 × 50 ml portions of chloroform. The residue remaining after the distillation of the chloroform is triturated with ether, and the insoluble residue is crystallized from 100 ml of methanol. The yield of 1 g (9%) of (IIIc) is obtained; it has the mp 115-117°C. The evaporation of the mother liquor to 30 ml leads to the isolation of 1.2 g (12%) of compound (IVc). The mp is 136-142°C, and the R_f is 0.32. The IR spectrum is as follows: 1640 cm^{-1}, 1635 cm^{-1}, and 1595 cm^{-1} (C=C). The ^1H NMR spectrum ($CDCl_3$) is as follows: 0.94 ppm (6H, t, $NCH_2\underline{CH_3}$), 2.41 ppm (4H, q, $N\underline{CH_2}CH_3$), 2.76 and 3.04 ppm (4H, m, 1-H + 8-H),* 3.40 and 3.70 ppm (4H, m, 3-H + 6-H),* 3.83 ppm (1H, s, 9-H), 7.13 ppm (2H, s, $=\underline{CH}Ph$), and 7.20-7.40 ppm (15H, m, $=CH\underline{Ph}$ + Ph). The ^{13}C NMR spectrum ($CDCl_3$) is as follows: 12.2 ppm ($NCH_2\underline{CH_3}$), 50.7 ppm ($N\underline{CH_2}CH_3$), 52.5 ppm ($C_{(1)} + C_{(8)}$),* 53.0 ppm ($C_{(3)} + C_{(6)}$),* 110.0 ppm ($C_{(8a)} + C_{(9a)}$), 122.3 ppm ($=\underline{CH}Ph$), 128.4 ppm ($C_{(4)} + C_{(5)}$), 45.0 ppm ($C_{(9)}$), [Ph: 127.0 C_p, 128.2 C_o, 128.6 C_m, 142.5 C_x], [$=CH\underline{Ph}$: 126.6 C_p, 128.0 C_m, 129.1 C_o, 136.8 C_x], and 140.9 ppm ($C_{(4a)} + C_{(10a)}$). Found, %: C 82.01, H 7.05, and N 5.38. $C_{35}H_{36}N_2O \cdot 0.5H_2O$. Calculated, %: C 82.51, H 7.26, and N 5.50.

2,7-Diethyl-10a-hydroxy-9-phenyl-4-(phenylmethylene)-2,7-diaza-10-oxa-1,2,3,4,5,6,7,8,8a,10a-decahydroanthracene (Vc). The solution of 3.9 g (30 mmole) of N-ethylpiperid-4-one, 3.8 g (35 mmole) of benzaldehyde, and 0.9 g (16 mmole) of KOH in 135 ml of 65% aqueous methanol is maintained for 30 days at 20°C. The solvent is evaporated, and the residue is crystallized from 70 ml of 50% methanol. The yield of 2.2 g (34%) of the tricycle (Vc) is obtained; it has the mp 164-168°C and the R_f 0.27. The IR spectrum is as follows: 3400-3150 cm^{-1} (OH), 1640 cm^{-1}, 1635 cm^{-1}, and 1595 cm^{-1} (C=C). The ^1H NMR spectrum ($CDCl_3$) is as follows: 0.92 and 0.94 ppm (3H + 3H, t, $NCH_2\underline{CH_3}$), 1.97 ppm (1H, m, 5-H), 1.99 ppm (1H, t, 8-H), 2.04 ppm (1H, m, 5-H), 2.16 ppm (1H, m, 8a-H), 2.28 ppm (1H, m, 6-H), 2.30-2.40 ppm (4H, q, $N\underline{CH_2}CH_3$), 2.43 ppm (1H, q, 8-H), 2.47 ppm (1H, d, 1-H), 2.87 ppm (1H, m, 6-H), 3.08 ppm (1H, d, 3-H), 3.09 ppm (1H, d, 1-H), 3.20 ppm (1H, d, 9-H), 3.82 ppm (1H, d, 3-H), 6.93 ppm (1H, s, $=\underline{CH}Ph$), and 7.15-7.30 ppm (10H, m, $=CH\underline{Ph}$ + Ph). The ^{13}C NMR spectrum ($CDCl_3$) is as follows: 11.8 and 12.0 ppm ($NCH_2\underline{CH_3}$), 37.2 ppm $C_{(5)}$, 42.4 ppm $C_{(9)}$, 45.9 ppm $C_{(8a)}$, 49.3 ppm $C_{(6)}$, 51.2 and 51.6 ppm ($N\underline{CH_2}CH_3$), 52.8 ppm $C_{(3)}$, 53.4 ppm $C_{(8)}$, 53.9

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*The reverse assignment of the signals is possible.

ppm $C_{(1)}$, 95.1 ppm $C_{(10a)}$, 112.0 ppm $C_{(9a)}$, 121.3 ppm =CHPh, [126.4, 126.7, 128.0, 128.3, 128.5, 129.1 $C_{o,m,p}$ in =CH$\underline{Ph}$ + Ph], 130.1 ppm $C_{(4)}$, [137.1 and 141.6 C_x in =CH$\underline{Ph}$ + Ph], and 140.4 ppm $C_{(4a)}$. Found, %: C 77.80, H 8.00, and N 6.34. $C_{28}H_{34}N_2O_2$. Calculated, %: C 78.10, H 7.96, and N 6.51.

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