CONDENSATION OF N-(PIPERIDYLIDENE-4)ARYLAMINES WITH ACETYLENEDICARBOXYLIC ESTERS

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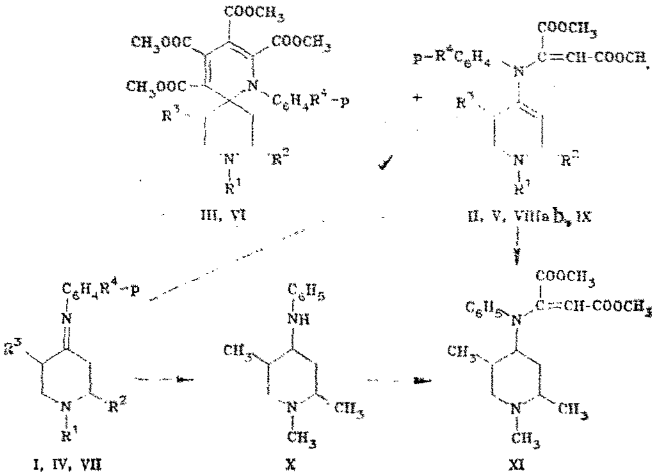
The substituted piperidines, N-(piperidin-3-en-4-yl)-N-(1,2-dimethoxycarbonyletheno)arylamine and 1-aryl-3,4,5,6-tetramethoxycarbonyl-1,2-dihydrospiro[cyclo-[pyridine-2,4'-piperidine], were synthesized by the condensation of acetylenedicarboxylic ester with an azomethine, obtained from a γ-piperidone. It was found that the amounts of 1:1 and 1:2 addition compounds obtained depends on the ratio of starting reagents. Compounds isomeric at the vinyl group were examined in the case of one of the 1:1 addition compounds. N-(1,2,5-trimethylpiperidin-4-yl)-N-(1,2-dimethoxycarbonyletheno)aniline was prepared by two methods.

The reaction of a N-(cyclohexylidene)arylamine with acetylenedicarboxylic ester (ADCE) proceeds with the addition of one molecule of ADCE to give a 1:1 addition compound, N-(cyclohexen-1-yl)-N-(1,2-dimethoxycarbonyletheno)arylamine, or by the addition of two molecules to give a 1:2 addition compound, 1-aryl-3,4,5,6-tetramethoxycarbonyl-1,2-dihydrospiro[cyclohexane-1', 2-pyridine] [1]. Two examples of analogous condensations of ADCE with azomethines obtained from γ-piperidones have been reported [2].

Since this reaction offers a promising method for obtaining new spiranes with two nitrogen-containing six-membered rings, we undertook to synthesize new compounds of this series and to examine their isomers. The starting azomethines, N-(1,2,5-trimethylpiperidylidene-4)-p-anisidine (I), N-(1-methylpiperidylidene-4)-p-toluidine (IV), and N-(1-benzyl-2,5-dimethylpiperidylidne-4)aniline (VII) were prepared as described in [3].



I—IV, IX $R^1=CH_3$, VII, VIIIa,b $R^1=CH_2C_6H_5$; I—III, VII—IX $R^2=R^3=CH_3$, IV—VI $R^2=R^3=H$; I—III $R^4=OCH_3$, IV—VI $R^4=CH_3$, VII—IX $R^4=H$

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Equimolar quantities of the azomethines I or IV and ADCE gave both 1:1 and 1:2 addition compounds: N-(1,2,5-trimethylpiperidin-3-en-4-yl)-N-(1,2-dimethoxycarbonyletheno)-p-anisidine (II) and 1',2',5'-trimethyl-1-p-anisyl-3,4,5,6-tetramethoxycarbonyl-1,2-dihydrospiro[pyridine-2,4'-piperidine](III), N-(1-methylpiperidin-3-en-4-yl)-N-(1,2-dimethoxycarbonyletheno)-p-toluidine (V), and 1'-methyl-1-p-tolyl-3,4,5,6-tetramethoxycarbonyl-1,2-dihydrospiro[pyridine-2,4'-piperidine](VI). In both cases the 1:1 addition compounds predominate (compounds II and V). However, using a 1:2 ratio of the starting reagents, azomethine and ADCE, gives an appreciable amount of the spiro compound (for example, in the synthesis of compound VI).

Spectral data confirmed the presence of the dimethoxycarbonylvinyl group and the Δ^3-piperidine system in compounds II and V. The NMR spectra showed signals at 5.71 ppm (s, 1H) due to the vinyl proton, and at 4.93 ppm (m, 1H) and 5.25 ppm (m, 1H) due to the proton at position 3 of the piperidine ring. Protons of the ester group gave rise to signals at 3.76 ppm (s, 3H) and 3.7 ppm (s, 3H), 3.72 ppm (s, 3H) and 3.31 ppm (s, 3H), and δ_{OCH_3}(compound II) at 3.35 ppm. In the infrared spectrum the unsaturated bonds absorb at 1460 and 1510-1610 (compound II), 1390, 1445, 1520, and 1590-1610 cm^{-1} (compound V), and the ester group absorbs at 1710-1740 (C=O) and at 1040, 1175-1290 (C-O)(compound II), 1705-1730 (C=O) and 1140-1275 cm^{-1} (C-O) (compound V).

Thin-layer chromatography data showed that compounds II and V were present in two isomeric forms, which differed considerably in chromatographic mobility. The two isomers of N-(1-benzyl-2,5-dimethylpiperidin-3-en-4-yl)-N-(1,2-dimethoxycarbonyletheno)aniline (VIII) — the trans isomer VIIIa (an oily material) and the cis isomer VIIIb (crystals mp, 126-128°C) — were isolated by chromatography. The configuration of these isomers was determined from the position of the vinyl proton signal in the NMR spectrum (5.92 ppm for VIIIa and 4.89 ppm for VIIIb); these were compared with data in [1]. The proton at position 3 of the piperidine ring in these isomers gave rise to signals at 5.10 (m, 1H) and 5.47 ppm (d, 1H) respectively.

The presence of the four methoxycarbonyl groups in the spiro compounds formed by the condensation of ADCE with azomethines was confirmed by measuring the total intensity for these groups for 1',2',5'-trimethyl-1-p-tolyl-3,4,5,6-tetramethoxycarbonyl-1,2-dihydrospiro-[pyridine-2,4'-piperidine] [2]. Burzhen's method and Ramsey's formula [4] were employed for the calculations. The area under the absorption curve was calculated using Simpson's formula. Peak absorptions were within 20-80%; peak intensities were expressed in practical units $(moles/liter \cdot cm^2)^{-1}$. The diester 1-morpholino-2,3-dimethoxycarbonylcycloctadiene-1,3 was used as a standard. The intensity of both diester C=O bands at 1697 and 1720 cm^{-1} was $A = 5.1 \times 10^4$ for each band; the total intensity consequently is 10.2×10^4. Intensities for analogous bands in the infrared spectrum of the above spirane were: for the band ν_{CO} 1745 cm^{-1}, $A = 12.1 \times 10^4$ and for ν_{CO} 1706 cm^{-1}, $A = 10.28 \times 10^4$. The sum $\Sigma A = 22.38 \times 10^4$, i.e., it is approximately twice for the standard diester, thus confirming the presence of four methoxycarbonyl groups in the 1:2 addition compounds.

The double bond of the piperidine ring of N-(1,2,5-trimethyl piperidin-3-en-4-yl)-N-(1,2-dimethoxycarbonyletheno)aniline (IX) [2] was selectively reduced with sodium borohydride to give a mixtures of isomers of N-(1,2,5-trimethylpiperidin-4-yl)-N-(1,2-dimethoxycarbonyletheno)aniline (XI). One of the isomers of this tertiary amine was obtained by the condensation of ADCE with the δ-isomer of 1,2,5-trimethyl-4-phenylaminopiperidine (X) [5].

EXPERIMENTAL

Infrared spectra were recorded on Specord IR-75 and UR-20 instruments using KBr, NaCl, and LiF prisms; samples were prepared as KBr pellets or thin films between KBr plates. NMR spectra were measured on a Tesla BS-487c (60 MHz), solvent — $CDCl_3$, internal standard — TMS. Mass-spectra were taken on MX-1303 and LKB-900 instruments using an ionization potential of 70 eV. Column and thin-layer chromatography were carried out on aluminum oxide activity II.

N-(1,2,5-Trimethylpiperidylidene-4)-p-anisidine (I), N-(1-methylpiperidylidene-4)-p-toluidine (IV), and N-(1-benzyl-2,5-dimethylpiperidylidene-4)aniline (VII) were obtained in yields of 50, 45, and 46% respectively. Physical data were as follows: Azomethine I, bp 162-165° (3 mm), n_D^{22} 1.5510. IR spectrum (film): 1690 cm^{-1} (C=N). Picrate mp 165-167°. ›- (from alcohol). Found: N 14.5%. $C_{15}H_{22}N_2O \cdot C_6H_3N_3O_7$. Calculated: N 14.7%. Azomethine ıte, IV, bp 129-131° (1.5 mm), n_D^{21} 1.5519. IR spectrum (film): 1663 cm^{-1} (C=N₀. Picrate, mp 171° (decomp., from alcohol). Found: N 16.1%. $C_{13}H_{18}N_2 \cdot C_6H_3N_3O_7$. Calculated: N 16.4%. Azomethine VII, bp 182-186° (1.5 mm), n_D^{17} 1.5747. IR spectrum (film): 1680 cm^{-1} (C=N). Picrate, mp 145-145.5° (from alcohol). Found: N 13.6%. $C_{20}H_{24}N_2 \cdot C_6H_3N_3O_7$. Calculated: N 13.3%.

N-(1,2,5-Trimethylpiperidin-3-en-4-yl)-N-(1,2-dimethoxycarbonyletheno)-p-anisidine (II) and 1',2',5'-trimethyl-1-p-tolyl-3,4,5,6-tetramethoxycarbonyl-1,2-dihydrospiro[pyridine-2,4'-piperidine] (III). A solution of 4.2 g (17 mmole) of azomethine I and 2.66 g (17 mmole) of ADCE in 25 ml of dry methylene chloride was maintained at 1-3° for 24 h. The solvent was then distilled and the residue (6.8 g) chromatographed (h = 75 cm, d = 3 cm). Elution with ether gave 2.3 g (35%) of an orange oil which was a mixture of cis- and trans-isomers of compound II with R_f values of 0.60 and 0.65 (1:1 mixture of ethyl acetate and hexane). Found: N 6.9%; M^+ 388. $C_{21}H_{28}N_2O_5$. Calculated: N 7.2%; M 388. Oxalate, mp 159-162° (from alcohol). Found: N 6.0%. $C_{21}H_{28}N_2O_5 \cdot C_2H_2O_4$. Calculated: N 5.8%. Elution with ethyl acetate gave 1.38 g of an oil which crystallized from a 10:1 mixture of heptane and ethyl acetate to give 0.18 g (2.6%) of compound III, as a bright-orange amorphous powder with mp 86-88°, and R_f 0.33 (same system). IR spectrum (KBr): 2795 ($N-CH_3$), 1755 and 1710 (C=O), 1590 and 1520 (C=C), 1252 and 1165 cm^{-1} (C-O). Found: C 61.6; H 6.2; N 5.2%; M^+ 530. $C_{27}H_{34}N_2O_9$. Calculated: C 61.6; H 6.4; N 5.3%; M 530.

N-(1-Methylpiperidin-3-en-4-yl)-N-(1,2-dimethoxycarbonyletheno)-p-toluidine (V) and 1'-methyl-1-p-tolyl-3,4,5,6-tetramethoxycarbonyl-1,2-dihydrospiro[pyridine-2,4'-piperidine] (VI). A. The reaction was carried out with 1.64 g (8.1 mmole) of imine IV, 1.2 g (8.4 mmole) of ADCE, and 25 ml of methylene chloride. The reaction products were chromatographed (h = 52 cm, d = 3 cm). Elution with a 1:20 mixture of ethyl acetate and hexane gave 1.4 g (40%) of a mixture of isomers of compound V as a bright-orange oil with R_f values 0.5 and 0.52 (1:2 ethyl acetate and hexane). Found: N 7.6%; M^+ 344, $C_{19}N_{24}N_2O_4$. Calculated: N 8.1%; M 344. Diiodomethylate, mp 137-142° (from acetone). Found: N 4.7%. $C_{19}H_{24}N_2O_4 \cdot 2CH_2I$. Calculated: N 4.5%. Elution with ethyl acetate gave 0.2g (7%) of compound VI as a yellow amorphous powder with mp 102-106°C (from 4:1 heptane and ethyl acetate), and R_f 0.13 (same system). NMR spectrum: 7.20-6.95 (m, 4H, aromatic protons), 3.90-3.55 (12H, $4COOCH_3$), 3.43 (s, 3H, $p-CH_3$), 2.45 ($N-CH_3$), 2.60-2.18 ppm (m, 6H, CH_2-piperidine). IR spectrum (KBr): 1760 and 1710 (C=O), 1590 and 1520 (C=C), 1220-1270 and 1160 cm^{-1} (C-O). Found: N 5.6%; M^+ 486. $C_{25}H_{30}N_2O_8$. Calculated: N 5.8%; M 486.

B. A solution of 2.3 g (10 mmole) of azomethine IV and 3.25 g (20 mmole) of ADCE in 25 ml of absolute ether was maintained at 1-3°C for 48 h. Filtration of the powdery precipitate gave 1.38 g (20%) of compound VI with mp 100-105°; admixture with a sample of A gave no melting point depression. The mother liquors were chromatographed to yield 0.7 g (13%) of compound V and 0.65 g (12g) of compound VI in a total yield of 32%.

trans- and cis-Isomers of N-(1-benzyl-2,5-dimethylpyridin-3-en-4-yl)-N-(1,2-dimethoxycarbonyletheno)aniline (VIIIa and b). The reaction was carried out under the same conditions as used previously with 0.85 g (3 mmole) of azomethine VII, 0.43 g (3 mmole) of ADCE, and 15 ml of methylene chloride. Elution of the mixture with a 1:20 ethyl acetate-hexane mixture yielded 0.41 g (31.5%) of the trans-isomer VIIIa, an orange oil with R_f 0.65 (1:4 ethyl acetate-hexane). NMR spectrum: 7.52-6.98 (m, 10H, aromatic protons), 5.92 (s, 1H, $-C{=}CH-COOCH_3$), 510 (m, 1H, Δ^3-H-piperidine), 3.73 and 3.32 (s, 3H, $COOCH_3$), 2.46 (AB, 2H, $N-CH_2-$), 1.25-0.86 ppm (m, 10H, $CH-$, CH_2-, CH_3-piperidine). IR spectrum (film): 1730 and 1715 (C=O), 1590 and 1490 (C=C), 1260, 1222 and 1180 cm^{-1} (C-O). Found: N 6.3%; M^+ 434. $C_{26}H_{30}N_2O_4$. Calculated: N 6.4%; M 434. Diiodomethylate, mp 139-142° (from acetone). Found: N 3.8%. $C_{26}H_{30}N_2O_4 \cdot 2CH_3I$. Calculated: N 3.9%. Elution with 1:10 ethyl acetate-hexane yielded 0.04 g (3.5%) of the cis-isomer VIIIb, as colorless crystals with mp 126-128° (from petroleum ether, bp 40-70°), R_f 0.50 (same solvent system). NMR spectrum: 7.23 (s, 10H, aromatic protons), 5.47 (d, 1H, Δ^3-H-piperidine), 4.83 (s, 1H, $-C{=}CH-COOCH_3$), 3.81 and 3.60 (s, 3H, $COOCH_3$), 2.38 (AB, 2H, $N-CH_2-$), 1.27-0.96 ppm (m, 10H, $CH-$, CH_2-, CH_3-piperidine). IR spectrum (KBr): 1750 and 1710 (C=O), 1585 and 1500 (C=C), 1280-1140 cm^{-1} (C-O). Found: N 6.2%; M^+ 434. $C_{26}H_{30}N_2O_4$. Calculated: N 6.4%; M 434.

N-(1,2,5-Trimethylpiperidin-4-yl)-N-(1,2-dimethoxycarbonyletheno)aniline (XI). A. To 4 g (105 mmole) of sodium borohydride in 15 ml of methanol with vigorous mixing was gradually added a solution of 1.3 g (4 mmole) of compound IX in 5 ml of methanol. This was refluxed for 5 h, 50 ml of water added, and heating was continued for 2 h. The solution was evaporated to 30 ml. The reaction products were extracted with ether and dried over magnesium sulfate to yield 0.8 (61.5%) of compound XI (mixture of isomers), as a powder with mp 55-65° (from heptane), and Rf values 0.71, 0.65, and 0.32 (ether). IR spectrum (KBr); 2800 ($N-CH_3$), 1760 and 1708 ($C{=}O$),1610, 1590 and 1512 ($C{=}C$),1170, 1085 and 1065 cm^{-1} ($C-O$). Found: N 7.7%; M^+ 360. $C_{20}H_{28}N_2O_4$. Calculated: N 7.8%; M 360.

B. Solutions of 0.25 g (1.15 mmole) of the δ-isomer of compound X in 10 ml of methylene chloride and 0.16 g (1.12 mmole) ADCE in 5 ml of methylene chloride were cooled to 0° and combined. The mixture was refluxed for 40 h, the solvent evaporated, and the residue (0.4 g) chromatographed (h = 70 cm, d = 2 cm, eluent 1:20 ethyl acetate—hexane) to yield 0.07 g of the starting compound X and 0.08 g (24% based on amine X) of compound XI, mp 89-93° (from heptane), with R_f 0.71 (ether). NMR spectrum: 7.26-7.05 (m, 5H, aromatic protons), 4.80 (s, 1H, $-C{=}CH-COOCH_3$),3.65 and 3.55 (s, 3H, $COOCH_3$), 2.20 (s, 3H, $N-CH_3$), 1.38-0.90 ppm (m, $CH-$, CH_2-, CH_3-piperidine). IR spectrum (KBr): 2790 ($N-CH_3$), 1763 and 1712 ($C{=}O$),1578 ($C{=}C$),1578 ($C{=}C$), 1222, 1155 and 1130 cm^{-1} ($C-O$). Found: N 7.5%; M^+ 360. $C_{20}H_{28}H_2O_4$. Calculated: N 7.8%; M 360.

C. When the reaction was carried out in methanol (refluxed 24 h), compound XI was obtained in 55% yield.

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