VILSMEIER REACTION WITH 4-PHENYL-2,3-DIHYDRO-1H-1,5-BENZODIAZEPIN-2-ONE

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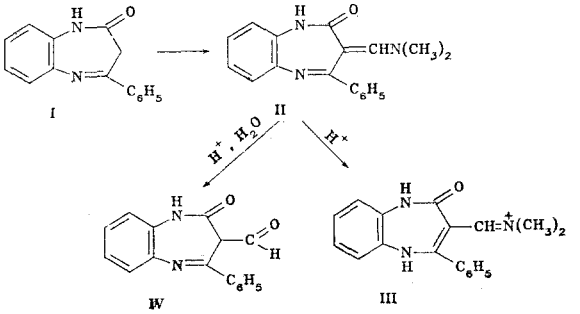
4-Phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one reacts with the Vilsmeier reagent to give a 3-dimethylaminomethylidene derivative, the hydrolysis of which leads to 3-formyl-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepinone.

It has been previously shown that the formylation of heterocyclic compounds with the Vilsmeier reagent leads to the formation of formyl [1], chloroformyl [2], or dimethylaminoalkylidene [3] derivatives. The reaction of 4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (I) with N-methylpyrrolidone and phosphorus oxychloride, which leads to 3-(N-methyl-2-pyrrolidinylidene)-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one, has been described [4]. In order to extend the range of application of seven-membered heterocyclic systems that are of interest as tranquilizers [5, 6], we decided to study the reaction of diazepinone I with phosphorus oxychloride and dimethylformamide (DMF).

Under the conditions of the Vilsmeier reaction benzodiazepinone I is converted to 3-dimethylaminomethylidene-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (II), the yield of which is doubled when the amount of the formylating agent is increased from 2 moles to 4 moles.



The IR spectra of II contain absorption bands at 1660 (C=O) and 3107-3173 cm^{-1} (NH). The introduction of a dimethylaminomethylidene group — a new chromophore system — gives rise to an increase in the intensity of a third maximum at 296 nm in the UV spectra of II and the appearance of an absorption band at 370 nm. Signals of protons of two NH groups at 8.75 and 9.48 ppm are observed in the PMR spectrum of a solution of II in trifluoroacetic acid. This provides a basis for the assumption that salt III is formed in an acidic medium as a consequence of protonation at the nitrogen atom in the 5 position; two signals of protons of methyl groups appear at 2.62 and 2.98 ppm. A similar phenomenon was previously observed for dimethylaminoformylideneazaindoles [7], as well as for enamines with electron-donor substituents [8]. The signal of the CH proton is found in the aromatic-proton region.

The PMR spectra of solutions in chloroform and dimethyl sulfoxide (DMSO) contain a broad signal of methyl protons at 2.5 ppm, and a signal of protons of a second NH group is absent in the low-field region; this is in agreement with the assumption expressed above.

The hydrolysis of II in acetic acid leads to the formation of a mixture of 3-formyl-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (IV) and 4-phenylbenzodiazepinone (I), which can be separated by recrystallization.

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The IR spectrum of 3-formylbenzodiazepinone IV contains bands of NH stretching vibrations at 3064-3212 cm^{-1} and two unresolved bands at 1640-1685 cm^{-1} (C=O). Bands of CONH stretching vibrations are observed at 1668 cm^{-1} in the spectrum of the starting benzodiazepinone.

The UV spectrum of IV contains absorption maxima at 206 and 270 nm and an inflection at 390 nm. Signals of protons of methyl groups are absent in the PMR spectra (CF_3COOH) of this compound, but signals of the protons of a formyl group (10.20 ppm) and of an NH group (8.75 ppm) are observed. A broad signal of the protons of a formyl group and an NH group at 9.31-9.35 ppm, the intensity of which is halved upon deuteration,* is observed in the PMR spectrum of a solution of this compound in DMSO.

The mass spectrum of IV contains a rather intense molecular-ion peak with m/z 264. The base ion peak in the mass spectrum corresponds to splitting out of $C_3H_2O_2$ groups; this is characteristic for compounds of this class [9]. The spectrum also shows a fragmentation pathway with loss of a molecule of CO, which is characteristic for aldehydes.

3-Formyl-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one phenylhydrazone was obtained from II.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra of solutions in ethanol were recorded with a Specord UV-Vis spectrophotometer. The PMR spectra of solutions in trifluoroacetic acid, chloroform, or DMSO were obtained with a Varian-60 spectrometer with hexamethyldisiloxane as the internal standard. The mass spectrum was recorded with an MKh-1303 spectrometer with direct introduction of the sample into the ion source at an ionizing voltage of 50 eV, an emission current of 150 mA, and an ionization-chamber temperature of 150°C. The course of the reaction and the individuality of the substances were monitored by means of thin-layer chromatography (TLC) on Silufol UV-254 plates in chloroform–alcohol (10:1).

3-Dimethylaminoformylidene-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (II). A 20-ml (0.260 mole) sample of DMF was added dropwise at 0-5°C to 8 ml (0.088 mole) of phosphorus oxychloride, after which the mixture was stirred at 5-10°C for 15 min. A solution of 4.4 g (0.018 mole) of I in 80 ml of THF was then added in the course of 1 h, and the mixture was stirred for 20 min and allowed to stand overnight. The solution was poured into ice water, and the aqueous mixture was neutralized to pH 7-8 with a saturated solution of sodium carbonate. The precipitate was separated to give 2.84 g (52%) of a product with mp 218-220°C. UV spectrum, λ_{max} (log ε): 205 (4.54), 296 (4.15), 252 (4.36), and 370 nm (3.85). IR spectrum: 3107-3179 (NH) and 1660 cm^{-1} (C=O). PMR spectrum (CF_3COOH): 2.62 (3H, s, N–CH_3), 2.98 (3H, s, N–CH_3), 8.75 (1H, s, NH), 9.48 (1H, s, NH), and 6.6-7.6 ppm (10H, m, Ar and CH=). Found: C 74.6; H 5.7; N 14.3%. $C_{18}H_{17}N_3O$. Calculated: C 74.2; H 5.8; N 14.4%.

3-Formyl-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (IV). A 1.6-g (0.005 mole) sample of II was dissolved by heating in 50 ml of alcohol, the solution was poured into a solution of 25 ml of dilute acetic acid (2:1), and the mixture was allowed to stand for 8-9 h. It was then neutralized with sodium carbonate to give 1.0 g of a mixture of starting diazepinone I and formyl derivative IV. The yield of I, with mp 205°C, was 0.75 g (58%). No melting-point depression was observed for a mixture of this product with the substance obtained by the method in [10]. PMR spectrum (CF_3COOH): 4.20 (2H, s, CH_2), 9.75 (1H, s, NH), and 7.25-8.025 ppm (9H, m, Ar). The yield of IV, with mp 209-211°C, was 0.15 g (10.2%). UV spectrum, λ_{max} (log ε): 206 (4.46) and 270 nm (4.29). IR spectrum: 3064-3212 (NH) and 1640-1685 cm^{-1} (C=O). PMR spectrum (CF_3COOH): 6.78-7.68 (10H, m, Ar and CH=), 8.75 (1H, s, NH), and 10.20 ppm (1H, s, CHO). Mass spectrum, m/z (%): 265 (12.5), 264 (60.9), 263 (9.4), 236 (19.5), 218 (6.3), 207 (6.6), 206 (7.0), 205 (6.6), 196 (7.8), 195 (53.0), 194 (100), 193 (25.8), 192 (4.7). Found: N 10.2%. $C_{16}N_{12}N_2O_2$. Calculated: N 10.6%.

Phenylhydrazone IV. A 1.6-g (5.5 mmole) sample of 3-dimethylaminoformylidene derivative III was dissolved by heating in 50 ml of alcohol, the resulting hot solution was added to a solution of 0.8 g (7 mmole) of phenylhydrazine in 10 ml of glacial acetic acid and 5 ml

*Our spectral data do not make it possible to draw accurate conclusions regarding the tautomerism and protonation of IV.

of water, and the mixture was allowed to stand overnight. The precipitated phenylhydrazone was separated to give 1.4 g (72%) of a product with mp 203-205°C and R_f 0.605. IR spectrum: 3027-3419 (NH) and 1682 cm^{-1} (C=O). Found: C 74.8; H 5.1; N 15.8%. $C_{22}H_{18}N_4O$. Calculated: C 74.6; H 5.1; N 15.8%.

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SYNTHESIS AND SOME CHEMICAL TRANSFORMATIONS OF 4'-ARYL-4-HYDROXY-4-METHYL-4,5,4',5'-TETRAHYDRO- AND 4,5-DIHYDRO-3,3'-DIPYRAZOLYLS

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The reaction of 3-epoxypropionyl-2-pyrazolines and 3(5)-epoxypropionylpyrazoles with hydrazine hydrate leads to 4,5,4',5'-tetrahydro- and -4,5-dihydro-3,3'-dipyrazolyls, on the basis of which 4',5'-dihydro-3,3'-dipyrazolyls and 3,3'-dipyrazolyls were subsequently obtained.

Depending on the structure of the substrate, the reaction of α,β-epoxy ketones with hydrazine hydrate may lead to hydroxypyrazolines, pyrazoles, or allyl alcohols [1, 2]. The application of this reaction in series of previously synthesized epoxypropionylpyrazolines and epoxypropionylpyrazoles [3] opens up a route to dipyrazolinyls, pyrazolinylpyrazoles, and dipyrazolyls.

In fact, when epoxypropionylpyrazolines Ia-c are refluxed with hydrazine hydrate in methanol, they are converted to 4'-aryl-4-hydroxy-4-methyl-4,5,4',5'-tetrahydro-3,3'-dipyrazolyls (II-IV), the structure of which was confirmed by chemical transformations and spectral methods. Thus the IR spectra of dipyrazolinyls II-IV (KBr) do not contain the absorption of a carbonyl group that is characteristic for the starting ketones, and the presence of hydroxy absorption at 3310 cm^{-1} indicates opening of the epoxide ring. Starting vibrations of the NH bonds of pyrazoline rings are observed at 3250 and 3340 cm^{-1}. The position of the band of stretching vibrations of an OH group at 3510 cm^{-1} (CCl_4, 10^{-3} mole/liter) indicates intramolecular bonding of the hydroxy group; this is possible in the case of an s-trans orientation of the pyrazoline rings. A characteristic feature of the PMR spectra of II-IV is the presence in them of an ABC spin system of the protons of a pyrazoline ring and an AB spin system of the protons of a hydroxypyrazoline ring (Table 1). The signals of the vicinal transoid protons (H_A and H_C) of the aryl-substituted pyrazoline ring are two quartets with J_{AC} = 4.0 Hz; the spin–spin coupling constants (SSCC) of the geminal pro-

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