3-PHENYLAZO-4-METHYL-2,3-DIHYDRO-1,5-BENZODIAZEPIN-2-ONES

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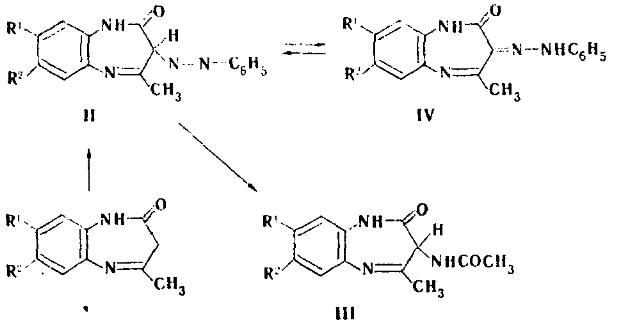
The corresponding azo derivatives, which exist primarily in the azo form, are formed in the reaction of 2,3-dihydro-1,5-benzodiazepin-2-ones with diazonium cations. The hydrazone form of these compounds is possible in solutions of acids.

Since substituents in the heterocyclic portion of 1,5-benzodiazepin-2-one molecules increase their tranquilizing and sedative activity [1], in the present research we accomplished the synthesis and studied the structure of 3-phenylazo derivatives of 4-methyl-2,3-dihydro-1,5-benzodiazepin-2-ones (II). Diazo coupling in hydrochloric acid was previously described [2] in the case of diazepinone (I), but no distinct evidence for the structure of IIa was presented.



I, II, III, IV a $R^1=R^2=H$; b $R^1=Cl$, $R^2=H$; c $R^1=H$, $R^2=NO_2$; d $R^1=Br$, $R^2=H$; e $R^1=R^2=CH_3$; f $R^1=CH_3$, $R^2=H$

In contrast to [2] we carried out diazo coupling in dimethylformamide (DMF) rather than in hydrochloric acid; this made it possible to considerably accelerate the reaction and to raise the yield to 80-90% (Table 1). The diazo coupling depends on the character of the substituents in the heterocyclic ring of the diazepinone. If there is a phenyl or p-methoxyphenyl group in the 4 position of I, this diazepinone does not react with the diazonium cation. Substituents in the aromatic ring of the azo component do not affect the rate and direction of the diazo coupling.

Azo compounds IIa-f are isolated in the form of the hydrochlorides, which are bright-red substances. The bases, which are formed when the hydrochlorides are heated with concentrated ammonium hydroxide, are most often yellow or orange substances.

In contrast to the PMR spectra of diazepinones Ia-f, the spectra of IIa-f do not contain signals of protons of CH_2 groups, and the signals of the CH_3 group are shifted to weak field (3.85 ppm). The absence of the signal of a methylidyne proton in the spectra of azo compounds IIa-f is evidently explained by the phenylhydrazone structure of the salt in trifluoroacetic acid. Such peculiarities in the PMR spectra have been previously noted [3] for azo derivatives of pyrrolo[1,2-a]benzimidazoles.

The IR spectra of IIa-f contain absorption bands at 1670-1690 cm^{-1} (amide group) and 1610 cm^{-1} (C=N), which are characteristic for 1,5-benzodiazepinones, and intense absorption bands of an azo group at 1540-1550 cm^{-1}. The absence of changes in the region of the stretching vibrations of N–H bonds as compared with the spectrum of the starting diazepinone constitutes evidence for the existence of the investigated diazo compounds primarily in the azo form.

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TABLE 1. 3-Phenylazo Derivatives of 4-Methyl-2,3-dihydro-1,5-benzodiazepin-2-ones (II)

Compound	mp, °C	UV spectra, λ_{max}, nm ($\sigma \cdot 10^{-3}$)	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
IIa	251	205 (31,5), 230 (27,4), 300 (5), 384 (40,8)	69,0	5,1	20,2	$C_{16}H_{14}N_4O$	69,1	5,0	20,1	84
IIb	272—273	210 (32,2), 235 (26,6), 295 (4,6), 380 (36,0)	61,4	4,2	17,8	$C_{16}H_{13}ClN_4O$	61,4	4,2	17,9	85
IIc	280—282	208 (22,4), 250 (15,5), 300 (12,8), 384 (27,0)	59,4	4,0	21,6	$C_{16}H_{13}N_5O_3$	59,4	4,0	21,7	55
IId	284	214 (32,0), 235 (27,0), 298 (5,8), 385 (35,2)	53,7	3,6	15,6	$C_{16}H_{13}BrN_4O$	53,8	3,6	15,7	88
IIe	271—272	210 (26,0), 235 (22,6), 300 (4,8), 385 (32,0)	70,5	5,9	18,2	$C_{18}H_{18}N_4O$	70,7	5,9	18,3	90
IIf	270—271	210 (2,8), 300 (4,2), 370 (15,0)	69,8	5,3	19,1	$C_{17}H_{16}N_4O$	69,9	5,5	19,2	80

The electronic spectra of IIa-f contain four absorption maxima at 208-210, 230-240, 310-320, and 380-410 nm. The latter band is absent in the spectra of the starting diazepinones and is due to the presence of an azo group in the conjugated chromophore.

The introduction of substituents in the aromatic ring of the azo component gives rise to a hypsochromic effect of the absorption bands, which is most pronounced when there is a methyl group in the 8 position (IIe, f). The long-wave absorption maxima at 380 nm in the spectra of IIa-f in acetic acid undergoes a 60 nm bathochromic shift, which is evidently associated with the tautomeric conversion of azo IIa to hydrazone form IVa (see Fig. 1). This phenomenon has also been previously observed [4].

The electronic spectra of IIa-f in alcohol solutions of hydrochloric acid (0.001-0.0007 N) at 380-490 nm contain two absorption maxima at 395 and 440 nm. The presence of these two absorption maxima and the isobestic point confirm azohydrazone tautomerism of the compounds obtained [5]. Alcohol solutions of hydrochloric acid (0.0005 N) do not give rise to tautomeric transformations (See Fig. 1).

The reductive acylation of diazo compounds IIa, e with zinc in acetic acid in the presence of acetic anhydride leads to 3-acetyl derivatives (IIIa, e). The IR spectra of IIIa, e contain absorption bands characteristic for benzodiazepinones: 1660 (amide groups, broad band), 1600 (C═N), and 3300 cm^{-1} (N—H). In addition, an intense amide II absorption band appears at ~1510 cm^{-1}, and the absorption at 1540-1550 cm^{-1} that is characteristic for azo derivatives IIa-f is absent.

In addition to the multiplet of aromatic protons at 7.20-8.00 ppm, signals of protons of two nonequivalent methyl groups at 1.66 and 1.80 ppm and a singlet of a methylidyne proton at 4.08 ppm are observed in the PMR spectrum of IIIa.

Thus the corresponding azo derivatives, which exist primarily in the azo form, are formed in the reaction of 1,5-benzodiazepin-2-ones with diazonium cations. The hydrazone form of these compounds is possible in solutions of hydrochloric and acetic acids.

EXPERIMENTAL

The electronic spectra of IIa-f were obtained with a Specord spectrophotometer. The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in trifluoroacetic acid were obtained with a Tesla spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard. The course of the reactions and the purity of the products were monitored by thin-layer chromatography (TLC) on activity II aluminum oxide and on Silufol UV-254 plates.

4-Methyl-3-phenylazo-2,3-dihydro-1H-1,5-benzodiazepin-2-ones (IIa-f). A) A solution of 0.01 mole of diazepinone Ia-f in 15 ml of hydrochloric acid was added slowly with stirring to a solution of 0.01 mole of benzenediazonium chloride, and the mixture was allowed to stand at room temperature for 10-12 h. The resulting crystals were then separated. The yield was 10-15%.

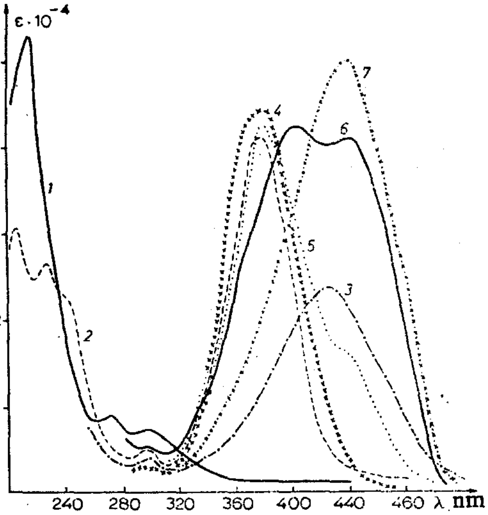

Fig. 1. Electronic spectra of 3-phenylazo-4-methyl-2,3-dihydro-1H-1,5-benzodiazepinones: 1) I; 2-7) IIa; 1, 2) in ethanol; 3) in acetic acid; 4-7) in alcohol solutions of hydrochloric acid: 0.0005, 0.0007, 0.001, and 0.45 N, respectively.

B) A prepared solution of the diazonium salt was added with stirring to 0.01 mole of benzodiazepinone Ia-f in 20 ml of DMF, during which the mixture turned dark-red, and slight warming was observed. The mixture was allowed to stand at room temperature for 3-4 h, and the resulting precipitate was removed by suction filtration and washed with water and alcohol.

The corresponding hydrochlorides, which were obtained by method B, were heated in 25% ammonium hydroxide until the color of the mixtures changed. The mixture was then cooled, and the precipitate was separated and recrystallized from ethanol (Table 1).

4-Methyl-3-acetamido-2,3-dihydro-1H-1,5-benzodiazepin-2-one (IIIa). A 10-g (0.15 g-atom) sample of zinc dust was added in small portions to a heated (to 60°C) mixture of 6.28 g (0.02 mole) of the hydrochloride of IIa, 80 ml of glacial acetic acid, 4 ml (0.04 mole) of acetic anhydride, and 2 g (0.025 mole) of fused sodium acetate, and the mixture was refluxed for 2 h. It was then cooled and poured into 200 ml of water, and the aqueous mixture was neutralized to pH 7-8. The resulting precipitate was separated, and the filtrate was extracted three times with chloroform. The solvent was removed by distillation, and the residue was washed successively with ether–alcohol and ether and recrystallized from toluene to give 2.7 g (58.3%) of a product with mp 182°C. Found: N 18.2%. $C_{12}H_{13}N_3O_2$. Calculated: N 18.2%.

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