SYNTHESIS OF 1H-2,3,4,5-TETRAHYDRO-1,5-BENZODIAZEPIN-2-ONES BY REDUCTIVE CYCLIZATION OF 3-(o-NITROPHENYLAMINO)PROPIONIC ACIDS

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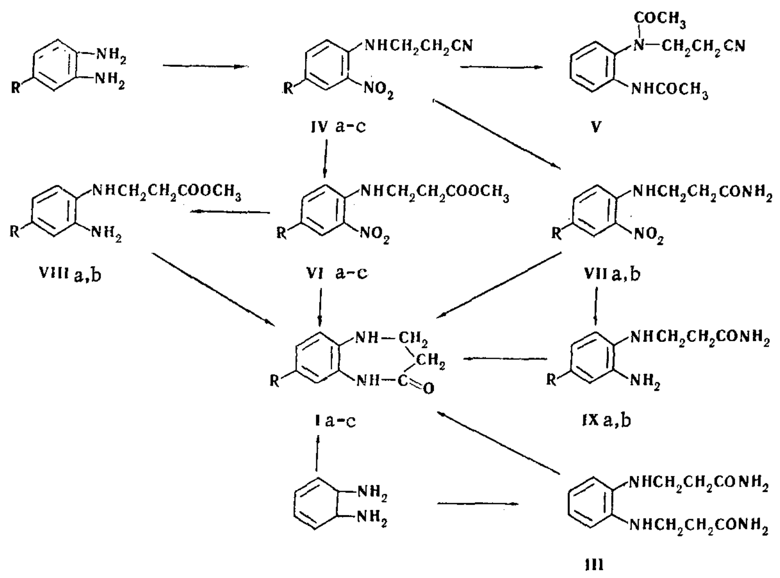
A new synthesis of 1H-2,3,4,5-tetrahydro-1,5-benzodiazepin-2-ones (I) by the reductive cyclization of o-nitro derivatives of N-phenyl-β-alanine is described. It is more convenient to use the amide of acrylic acid rather than acrylic acid itself, its nitrile, or ester for the synthesis of I from the appropriate o-phenylenediamines.

The synthesis of 1H-2,3,4,5-tetrahydro-1,5-benzodiazepin-2-ones (I) by the condensation of o-phenylenediamine or its derivatives with α,β-unsaturated or β-halo acids has been repeatedly described [1-3]. The simplest I (Ia) is obtained by the condensation of o-phenylenediamine with acrylic acid [1]. Our experiments have shown that this method is not always satisfactorily reproduced because of the facile oxidizability of the starting amine and polymerization of the acrylic acid, which must be introduced into the reaction in the freshly distilled state. In some experiments, compound I was formed as an uncrystallizable mass that was difficult to purify. Replacement of the acid by its ester did not improve and even lowered the yields, while the use of acrylamide made it possible to obtain Ia in a reproducible yield of up to 60%.



I, IV, VI–IX a R=H; b R=NO$_2$; c R=CH$_3$O

Acrylamide was also successfully used to synthesize 1H-2,3,4,5-tetrahydro-7,8-dimethyl-1,5-benzodiazepin-2-one (II) from 4,5-dimethyl-o-phenylenediamine:

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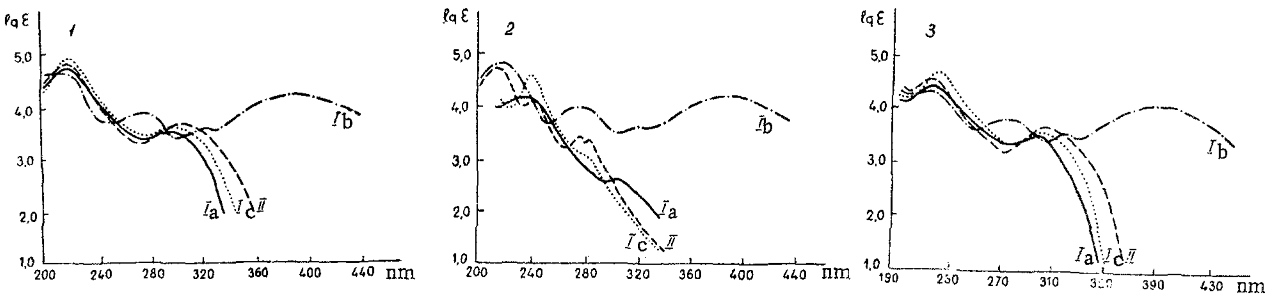
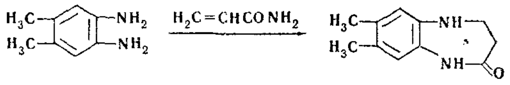


Fig. 1. UV spectra of Ia-c and II: 1) at pH 7.0; 2) at pH 1.05; 3) at pH 12.4.



The chemical shifts of the protons of the methyl groups in the PMR spectrum of II, recorded in trichloroacetic acid, are practically the same (a six-hydrogen singlet at 2.23 ppm), two aromatic protons are displayed as distinct singlets at 7.08 and 7.3 ppm, while the four protons of two methylene groups give two triplets at 2.3 and 4.17 ppm. A similar spectrum was described for benzodiazepinone Ia [4].

The condensation proceeds on heating the components in the presence of a small amount of hydrochloric acid. If the reaction is carried out in acetic acid containing alcohol, the major reaction product proves to be a substance that corresponds to the product of the addition of two molecules of acrylamide. In the case of o-phenylenediamine, it has the $C_{12}H_{18}N_4O_2$ composition and is converted to Ia by refluxing with hydrochloric acid and hypothetically has the N,N'-bis(carbamidoethyl)-o-phenylenediamine (III) structure. If, however, acetone is used as the solvent, the latter reacts with o-phenylenediamine to give 2,4,4-trimethyl-3,4-dihydro-1,5-benzodiazepine [5].

In order to avoid some difficulties associated with the synthesis and the facile oxidizability of the diamines of the aromatic series, we used the method of reductive cyclization of o-nitro compounds that is used in the synthesis of many nitrogen heterocycles [6,7] but has not been reported for benzodiazepines. In fact, the readily accessible and stable o-nitroanilines were converted to esters or amides of 3-(o-nitrophenylamino)propionic acid and were then converted to benzodiazepinones I by reduction and subsequent hydrolysis.

The reduction of the nitro groups of 3-(o-nitrophenylamino)propionitrile does not cause any complications. Diacetyl derivative V can be isolated after acetylation of the reaction mass. However, the subsequent hydrolysis of the nitrile group requires very severe conditions, and we could not find preparatively convenient conditions for the cyclization. Characteristic absorption bands at 2290 (CN), 3250-3310 (NH), and 1665 cm^{-1} (C = O) are visible in the IR spectrum of V. The PMR spectrum has a singlet at 2.8 ($2CH_3$), a triplet at 2.0 (CH_2CN), a triplet at 3.3-3.4 ppm (CH_2N), and a multiplet from four aromatic protons at 6.9-7.17 ppm; this confirms the V structure.

Nitriles IV were obtained by the cyanoethylation of nitroanilines in the presence of a Rodionov catalyst. The appropriate nitriles were subjected to alcoholysis to synthesize esters VI. Correspondingly, partial hydrolysis of nitriles IV leads to amides VII.

The reduction of the nitro group in VI and VII proceeds satisfactorily both with hydrogen over Raney nickel and with zinc in hydrochloric acid to give, respectively, amines VIII or IX. Heating of VIIIa or IXa with sulfuric acid leads to cyclization to benzodiazepinone Ia. Benzodiazepinone Ib was similarly obtained from amino compounds VIIIb or IXb. Benzodiazepinones I can be obtained directly from nitro compounds VI or VII in sufficiently good yields by reduction in acid media.

The IR spectra of benzodiazepinones I and II in the region of the NH valence vibrations each have two bands at 3300-3430 cm^{-1} (nonassociated bond) and at 3200-3250 cm^{-1} (associated by a hydrogen bond). The first of these in unsubstituted I lies at 3380 cm^{-1}, and, under the influence of a methoxyl group, is shifted to 3300 cm^{-1} and appears at 3430 cm^{-1} upon introduction of a nitro group into the molecule; this is typical for aromatic amines. The effect of substituents on the frequency of amide I is somewhat less clear (absorption at 1655-1665 cm^{-1}) since these substituents are in the meta position relative to the amide group. The same thing can be said about the frequency of the NH vibrations at 3190-3200 cm^{-1}, which is related to the amide grouping.

The effect of a nitro group is clearly exerted on the location of the out-of-plane deformation vibration bands ($C_{ar}-H$) at 800-910 cm^{-1}. Of the two bands that characterize 1,2,4-substituted benzene compounds (805 and 845 cm^{-1} for V), the second band is shifted to 910 cm^{-1} in compound Ib.

The UV spectrum (Fig. 1) of Ia in a neutral medium is identical to the spectrum of Ic and has two absorption maxima at 221 and 302 nm, while the spectrum of Ib is characterized by absorption maxima at 217, 279, 327, 392, and 559 nm. In acid media (pH 1.05) the carbonyl maximum of Ia undergoes a bathochromic shift, while the long-wave band that characterizes absorption of the benzene chromophore does not change. In Ic, which contains an electron−donor group, there is a hypsochromic shift, and a new absorption maximum appears; this is apparently associated with the inductive effect of the methoxy group. The spectrum does not change substantially for compound Ib. An amine of such low basicity apparently is not protonated under these conditions. In alkaline media (pH 12.4) a spectrum close to that obtained in neutral medium is observed for all of the compounds, i.e., tetrahydrobenzodiazepinones, in contrast to dihydrobenzodiazepines [8], do not undergo tautomeric transformations.

EXPERIMENTAL

The purity of the substances was monitored by chromatography in a thin, loose layer of aluminum oxide. The IR spectra of mineral oil and hexafluorobutadiene mulls were recorded with an IKS-22 spectrophotometer. The UV spectra were recorded with an SF-4A spectrophotometer. The PMR spectra in trifluoroacetic acid were recorded with an RS-60 spectrometer.

1H-2,3,4,5-Tetrahydro-1,5-benzodiazepin-2-one (Ia).* A. A mixture of 3.24 g (0.03 mole) of o-phenylenediamine, 3.19 g (0.045 mole) of acrylamide, and 5 ml of dilute hydrochloric acid was refluxed for 3 h, neutralized with ammonia, and extracted with benzene or carbon tetrachloride to give 2.93 g (60%) of a product with mp 140-141° (from benzene) [1].

B. A 2.24 g (0.01 mole) sample of N-(o-nitrophenyl)-β-alanine methyl ester (VIa) was hydrogenated at room temperature and normal pressure in the presence of Raney nickel. The catalyst was removed, and the solution was refluxed with 20 ml of dilute hydrochloric acid for 6 g to give 0.68 g (46%) of a product with mp 141-142°.

C. Zinc dust (4 g) was added gradually with stirring to a mixture of 2.24 g (0.01 mole) of ester VIa, 30 ml of methanol, and 15 ml of concentrated hydrochloric acid. The solution acquired a light-yellow color. The solution was neutralized with sodium bicarbonate solution to pH 7-8, the precipitate was filtered, and the filtrate was evaporated to dryness. The residue was extracted with benzene in a Soxhlet apparatus to give 0.7 g (48%) of a product with mp 141-142°.

If 2.09 g (0.01 mole) of o-nitroanilinopropionamide (VIIa) is similarly reduced, 0.7 g (43%) of Ia is obtained.

D. A mixture of 0.3 g (0.0016 mole) of the amide of N-(o-aminophenyl)-β-alanine (IXa), 4 ml of water, and 2 ml of concentrated hydrochloric acid was refluxed for 2 h. The solution was neutralized with ammonia to pH 7 and extracted with carbon tetrachloride. The solvent was removed, and the residue of Ia was recrystallized from benzene to give 0.15 g (60%) of a product with mp 139.5-140°. The hydrochloride had mp 191-192°. The picrate had mp 186-187° (from alcohol). Found %: N 17.6, 18.0. $C_9H_{10}N_2O \cdot C_6H_3N_3O_7$. Calculated %: N 17.9. The nitroso derivative had mp 187-188° (from alcohol). Found %: N 21.8, 21.6. $C_9H_9N_3O_2$. Calculated %: N 22.0.

7,8-Dimethyl-1H-2,3,4,5-tetrahydro-1,5-benzodiazepin-2-one (II). This was obtained in 56% yield from 4,5-dimethyl-o-phenylenediamine and acrylamide and had mp 176-176.5° (from benzene). Found %: C 69.2; 69.3; H 7.7, 7.6; N 14.4, 14.4. $C_{11}H_{14}N_2O$. Calculated %: C 69.5; H 7.4; N 14.7.

8-Methoxy-1H-2,3,4,5-tetrahydro-1,5-benzodiazepin-2-one (Ic). Zinc dust [12 g (0.18 g-atom)] was added gradually in the course of 30 min to 7.62 g (0.03 mole) of ester VIc in 90 ml of methanol and 54 ml of

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*According to the IUPAC rules, these compounds should be called benzo[b]-1,4-diazepine derivatives. However, we will retain the name 1,5-benzodiazepines, adopted in [9, 10] for these systems.

TABLE 1. Esters and Amides of 3-Arylaminopropionic Acids

Compound	mp	Empirical formula	Found %			Calc. %		
			C	H	N	C	H	N
VIb	99—100[a]	$C_{10}H_{11}N_3O_6$	44,5	4,2	15,6	44,6	4,1	15,6
VIIa	135,5—136[a]	$C_9H_{11}N_3O_3$	52,1	5,5	20,1	51,7	5,3	20,1
VIIb	141,5—142, 5[a]	$C_9H_{10}N_4O_5$	42,1	3,8	22,4	42,5	3,9	22,0
VIc	86—87[b]	$C_{11}H_{14}N_2O_5$	51,5	5,4	11,1	52,0	5,5	11,0
VIIIb	132—133[c]	$C_{10}H_{13}N_3O_4$	50,4	5,6	18,0	50,2	5,4	17,6
IXa	91—92[b]	$C_9H_{13}N_3O$	60,4	7,6	28,9	60,3	7,3	23,5
IXb	202,5—203[d]	$C_9H_{12}N_4O_3$	—	—	25,0	—	—	25,1

[a] From water.

[b] From benzene.

[c] From ether.

[d] From ethanol.

concentrated sulfuric acid. The reaction mixture was refluxed for 5 h (until the color of the solution changed from cherry-red to light-yellow). The solution was neutralized with sodium carbonate to pH 7-8, and the precipitate was filtered. The filtrate was evaporated, and diazepinone Ic was extracted with benzene to give 2.94 g (51%) of a product with mp 146.5-147° (from benzene). Found %: C 62.7, 63.0; H 6.5, 6.7; N 14.9, 15.0. $C_{10}H_{12}N_2O_2$. Calculated %: C 62.5; H 6.2; N 14.6. The picrate had mp 173-174°. Found %: N 16.7, 17.0. $C_{10}H_{12}N_2O_2 \cdot C_6H_3N_3O_7$. Calculated %: N 16.6.

8-Nitro-1H-2,3,4,5-tetrahydro-1,5-benzodiazepin-2-one (Ib). A. A mixture of 1 g (0.0045 mole) of amide IXb, 7 ml of distilled water, and 1 ml concentrated sulfuric acid was heated on a water bath for 4-5 h and neutralized with ammonia to pH 7. The resulting precipitate was filtered to give 0.73 g (79%) of a product with mp 274.5-275° (from ethanol). Found %: C 52.7; H 4.6; N 20.3, 20.6. $C_9H_9N_3O_3$. Calculated %: C 53.1; H 4.4; N 20.3. In the PMR spectrum of Ib, the four protons of the two methylene groups give two triplets at 2.9 and 4.3 ppm, and a singlet at 8.16 ppm corresponds to the aromatic protons.

B. Under similar conditions, 0.76 g (89%) of Ib was obtained from 1 g of ester VIIIb.

N,N'-Diacetyl-N-(2-cyanoethyl)-o-phenylenediamine (V). A 3.82 g (0.02 mole) sample of nitrile IVa in 50 ml of absolute ethanol was hydrogenated in the presence of 1 g of Raney nickel with vigorous shaking. The catalyst was separated, and 10 ml of acetic anhydride was added to the darkened solution. The mixture was refluxed for 6 h, the solvent was removed, and crushed ice was added to the residue to precipitate 1.34 g (27%) of V with mp 153.5-154.5° (from benzene). Found %: C 63.2, 63.5; H 6.0, 6.1; N 16.8, 16.6. $C_{13}H_{15}N_3O_2$. Calculated %: C 63.7; H 6.1; N 17.1.

N,N'-Bis(2-carbamidoethyl)-o-phenylenediamine (III). A mixture of 5.4 g (0.05 mole) of o-phenylenediamine, 3.55 g (0.05 mole) of acrylamide, 8 ml of glacial acetic acid, and 20 ml of absolute alcohol was held at 40° for 2 h and allowed to stand overnight. The reaction mixture was then neutralized to pH 7 with ammonia to give 7.5 g (83%) of III with mp 170-171° (from alcohol). Found %: C 57.9, 57.9; H 7.5, 7.4; N 22.8. $C_{12}H_{18}N_4O_2$. Calculated %: C 57.6; H 7.2; N 22.4.

Nitrile of N-(2-Nitro-4-methoxyphenyl)-β-alanine (IVc). A Rodionov catalyst (5 ml) was added with stirring to 16.8 g (0.1 mole) of 2-nitro-4-methoxyaniline, 40 ml of dioxane, and 20 ml of acrylonitrile. The mixture was allowed to stand overnight. The nitrile crystallized to give 15.8 g (72%) of orange-red needles with mp 99.5-100° (from alcohol). Found %: C 54.3, 54.5; H 5.2, 4.8; N 19.3, 19.5. $C_{10}H_{11}N_3O_3$. Calculated %: C 54.3; H 5.0; N 19.0.

Amide of N-(o-Aminophenyl)-β-alanine (IXa). A 2.09 g (0.01 mole) sample of amide VIIa in 30 ml of absolute alcohol was hydrogenated in the presence of 2 g of Raney nickel at room temperature and normal pressure. The catalyst was removed by filtration, and the solvent was evaporated to give 1.52 g (85%) of amide IXa as a colorless substance with mp 91-92° (from benzene) that was quite soluble in water, alcohols, acetone, and dioxane, and soluble on heating in benzene, chloroform, and dichloroethane. IR spectrum: 4480, 3380, 3300, 1615, and 750 cm^{-1}. The diacetyl derivative had mp 186-188° (from benzene). Found %: N 16.3, 16.1. $C_{13}H_{17}N_3O_3$. Calculated %: N 16.0.

Compounds VIIIb and IXb (see Table 1) were similarly obtained in 92 and 94% yield, respectively.

Esters VIb and VIc were synthesized by the alcoholysis of nitriles IV and were obtained in yields of 78 and 79%, respectively (see Table 1).

Amide of N-(2,4-Dinitrophenyl)-β-alanine (VIIb). A total of 0.85 ml of 6 N sodium hydroxide was added dropwise to 2.5 g (0.01 mole) of nitrile IVb, 10 ml of 12% hydrogen peroxide, and 12.5 ml of ethanol, and the mixture was heated for 3 h on a water bath and cooled to precipitate 1.83 g (72%) of amide VIIb with mp 141.5-142.5° (from water).

If amide VIIb is obtained through the acid chloride, the yield is 95% (based on acid); correspondingly, amide VIIa is formed in 95% yield (see Table 1). IR spectrum: 3500 (N−H), 1690 (C=O), 1630 (C−N), and 1510 and 1365 cm^{-1} (NO_2).

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