SYNTHESIS AND CYCLIZATION OF N-(2-HYDROXYPHENYL)- AND N-(2-BENZYLOXYPHENYL)-β-ALANINES

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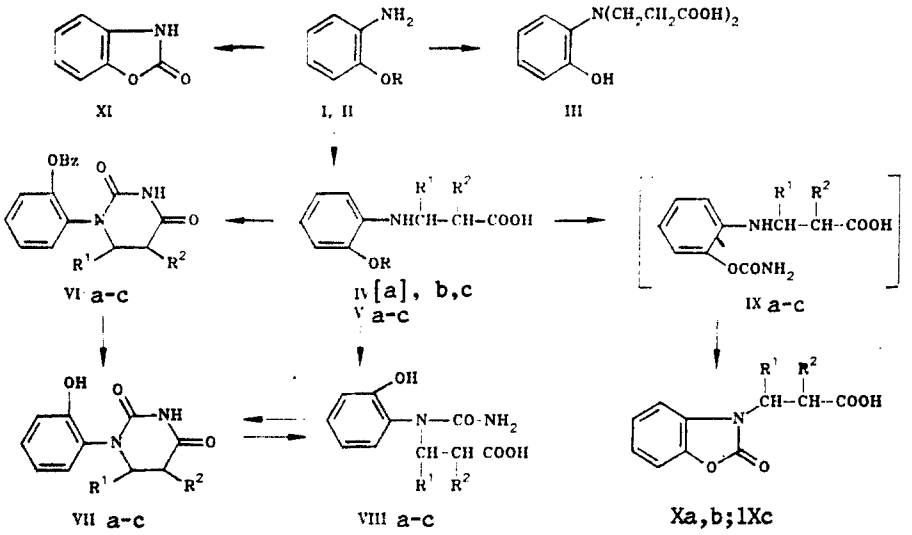
UDC 547.854'787'466.07

N-Substituted β-alanines have been synthesized by treating o-aminophenol or o-benzyloxyaniline with acrylic, methacrylic, or crotonic acids. Their cyclization to 2-benzoxazolinones and dihydro-2,4(1H,3H)-pyrimidinediones has been studied.

We have shown [1] that, in contrast to N-aryl-β-alanines (which react with urea in acid media to form 1-aryldihydro-2,4(1H,3H)-pyrimidinediones [2]), N-(2-hydroxyphenyl)-β-alanine and its methyl homolog react under these conditions to give 3-(3-benzoxazolonyl)propanoic acid or its methyl homolog. There is a connected interest in synthesizing 1-(2-hydroxyphenyl)dihydro-2,4(1H,3H)-pyrimidinediones by cyclization of 1-(2-hydroxyphenyl)-β-alanines (or their preparation by other means) and to examine the process by which they are formed.



I, IV R=H; II, V R=Bz; IV—X a $R^1=R^2=H$, b $R^1=H$, $R^2=CH_3$, c $R^1=CH_3$, $R^2=H$

N-(2-RO-Phenyl)-β-alanines and their methyl homologs IVa-c and Va-c were obtained by reaction of amines I or II with acrylic, methacrylic, or crotonic acids. Reaction of o-aminophenol I with acrylic acid takes place even at room temperature and is always accompanied by formation of N-(2-hydroxyphenyl)-N-(2-carboxyethyl)-β-alanine (III), which can be obtained in high yields when using an excess of acrylic acid. Condensation of N-(2-hydroxyphenyl)-β-methyl-β-alanine (IVc) with urea forms both 3-(3-benzoxazolonyl)-3-methylpropanoic acid (Xc) and a significant amount of the benzoxazolinone XI.

Treatment of N-(2-hydroxyphenyl)-β-alanine hydrochloride and its homolog IV with urea in acetic acid forms a mixture of benzoxazolinones and dihydropyrimidinediones in amounts determined from their PMR spectra.

Under these conditions N-(2-hydroxyphenyl)-β-alanine hydrochloride (IVa) forms a mixture of VIIa and Xa in the ratio 1:3 and N-(2-hydroxyphenyl)-α-methyl-β-alanine hydrochloride (IVb) a mixture of VIIb and Xb in the ratio 5:6 but β-alanine hydrochloride (IVc) gives the benzoxazolinone XI also. In this case VIIc, Xc, and XI are formed in approximately equal amounts. The separation of the dihydropyrimidinediones and benzoxazolinones does not present a problem because of their different solubility in organic solvents. Compounds VIIa-c have lower solubilities in ethanol, toluene, and dioxane than Xa-c which permits their isolation by fractional crystallization.

1-(2-Hydroxyphenyl)dihydro-2,4(1H,3H)pyrimidinediones (VIIa-c) can be synthesized from 1-(2-benzyloxyphenyl)dihydro-2,4(1H,3H)-pyrimidinediones (VIa-c) by acid fission of the ether bond or by hydrochloric acid cyclization of N-(2-

Kaunas Polytechnic Institute, Kaunas. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 527-531, April, 1991. Original article submitted July 21, 1989; revision submitted May 28, 1990.

0009-3122/91/2704-0420$12.50

TABLE 1. Parameters for Compounds III-VIII, X, and XI

Compound	Empirical formula	mp, °C*	PMR Spectrum, δ, ppm (solvent)	Yield, % (method of synthesis)
III	$C_{12}H_{15}NO_5$	170...172	2,18...2,60 (4H, m, α-$(CH_2)_2$); 3,21...3,99 (4H, m, β-$(CH_2)_2$); 6,55...7,17 (4H, m, ArH) (TFA)	89 A 76 B
IVb	$C_{10}H_{13}NO_3$	183...184	0,96 (3H, d, CH_3); 2,55...3,73 (3H, m, CH_2+—CH); 6,56...7,20 (4H, m, ArH); 8,03...9,01 (2H, br s $+NH_2$) (TFA)	51
IVc	$C_{10}H_{13}NO_3$	209 (dec.)	1,03 (3H, d, CH_3); 2,59 (2H, d, CH_2); 3,46...4,06 (1H, m, CH); 6,43...7,16 (4H, m, ArH); 7,68...8,80 (2H, br s., $+NH_2$) (TFA)	88
Va	$C_{16}H_{17}NO_3$	87...88	2,55 (2H, t, α-CH_2); 3,40 (2H, t, β-CH_2); 5,03 (2H, s, OCH_2); 6,25...7,64 (9H, m, ArH) (acetone-d6)	56
Vb	$C_{17}H_{19}NO_3$	61...62	1,11 (3H, d, CH_3); 2,50...2,93 (1H, m, CH); 3,29 (2H, t, N—CH_2); 5,03 (2H, s, O—CH_2); 6,08...7,53 (9H, m, ArH) (acetone-d6)	39
Vc	$C_{17}H_{19}NO_3$	92...93	1,20 (3H, d, CH_3); 2,13...2,79 (2H, m, α-CH_2); 3,70...4,16 (1H, m, CH); 5,08 (2H, s, OCH_2); 6,25...7,65 (9H, m, ArH) (acetone-d6)	57
VIa	$C_{17}H_{16}N_2O_3$	154...155	2,47 (2H, t, 5-CH_2); 3,42 (2H, t, 6-CH_2); 4,70 (2H, s, OCH_2); 6,46...7,40 (9H, m, ArH) (TFA)	58
VIb	$C_{18}H_{18}N_2O_3$	185...186	0,81 (3H, d, CH_3); 2,25...2,77 (1H, m, CH); 2,97...3,70 (2H, m, N—CH_2); 4,71 (2H, s, OCH_2); 6,50...7,50 (9H, m, ArH); 9,05 (1H, s, NH) (TFA)	43
VIc	$C_{18}H_{18}N_2O_3$	145...147	1,05 (3H, d CH_3); 2,40and 2,78 (2H, q and br s, CH_2-5[e] and 5[a]); 3,87 (1H, q, CH), 5,15 (2H, s, OCH_2); 6,5...7,2 (9H, m, ArH); 11,50 (1H, s, NH) (DMSO-d6, at 360 MHz)	35
VIIa	$C_{10}H_{10}N_2O_3$	220...222	2,66 (2H, t, 5-CH_2); 3,56 (2H, t, 6-CH_2); 6,47...7,1 (4H, m, ArH); 9,06 (1H, s, NH) (TFA)	70 A 100 B
VIIb	$C_{11}H_{12}N_2O_3$	222...223	1,08 (3H, d, CH_3); 2,59...2,97 (1H, m, CH); 3,07...3,65 (2H, m, CH); 6,56...7,3 (4H, m, ArH); 9,48 (1H, s, NH); 10,13 (1H, s, OH) (DMSO-d6)	75 A 100 B
VIIc	$C_{11}H_{12}N_2O_3$	235...236	0,91 (3H, d, CH_3); 2,11...3,02 (2H, m, CH_2); 3,52...4,01 (1H, m, CH); 6,55...7,2 (4H, m, ArH); 10,68 (1H, s, NH); 11,46 (1H, s, OH) (DMSO-d6)	68 A 100 B
VIIIa	$C_{10}H_{12}N_2O_4$	209 (dec.)	2,45 (2H, t, α-CH_2); 3,55...4,20 (2H, m, β-CH_2); 6,5...7,2 (4H, m, ArH) (TFA)	32
VIIIb	$C_{11}H_{14}N_2O_4$	191 (dec.)	0,88 (3H, d, CH_3); 2,25...2,78 (1H, m, CH); 3,20...4,17 (2H, m, CH_2); 6,48...7,20 (4H, m, ArH) (TFA)	55
VIIIc	$C_{11}H_{12}N_2O_4$	183 (dec.)	0,92 (3H, d, CH_3); 1,97...2,75 (2H, m, CH_2); 4,31...5,25 (1H, m, CH); 6,50...7,44 (4H, m, ArH) (TFA)	73
Xa	$C_{10}H_9NO_4$	122,5...123 (125 [4])	2,59 (2H, t, α-CH_2); 3,90 (2H, t, β-CH_2); 6,88...7,45 (4H, m, ArH) (DMSO-d6)	55
Xb	$C_{11}H_{11}NO_4$	135...137	0,88 (3H, d, CH_3); 2,52...3,03 (1H, m, CH); 3,45...4,08 (2H, m, CH_2); 6,87...7,53 (4H, m, ArH) (DMSO-d6)	66
Xc	$C_{11}H_{11}NO_4$	150...151	1,31 (3H, d, CH_3); 2,49...3,12 (2H, m, CH_2); 4,28...4,82 (1H, m, CH); 6,83...7,41 (4H, m, ArH) (DMSO-d6)	38
XI	$C_7H_5NO_2$	137 (138 [5])		75

*Compounds III and IVc were crystallized from dioxane, IVb, VIa-c, VIIc, Xa, c, and XI from ethanol, Va-c from hexane, VIIa, b from acetic acid, VIIIa-c from water, and Xb from benzene.

hydroxyphenyl)-N-carbamoyl-β-alanines VIIIa-c, separated during alkaline hydrolysis of VIIa-c. The dihydropyrimidinediones VIa-c were prepared from N-(2-benzyloxyphenyl)-β-alanine (Va) and homologs Vb, c with urea by heating them in glacial acetic acid with subsequent cyclization of the formed ureido acid using concentrated HCl. It was found that cyclization proceeds very readily and is complete after 5-10 min refluxing of the reaction mixture. Continued heating of the mixture leads to fission of the ether bond and formation of 1-(2-hydroxyphenyl)dihydro-2,4(1H,3H)-pyrimidinediones VIIa-c.

Refluxing VIIIa-c in concentrated HCl causes quantitative cyclization to the pyrimidinediones VIIa-c. When the same compounds are heated in glacial acetic acid traces of VIIa-c are found by chromatography even after 30 min. Thus, formation of the benzoxazoline ring occurs not via the ureido acids VIIIa-c but, apparently, through the urethanes IXa-c which are cyclized to 2-benzoxazolinones by separation of ammonia. Condensation of IVc with urea is accompanied by breakdown of the intermediate IXc during its cyclization to form Xc and XI in approximately equal amounts. 2-Benzoxazolinone (XI) was also obtained by us in 75% yield by refluxing o-aminophenol I and urea in acetic acid.

In their PMR spectra assignment of proton signals for the dihydropyrimidinedione or the benzoxazolinones is not a problem because of the difference in the proton shifts for the N—CH_2 and N—CH—CH_3 groups in the cyclic and acyclic situations. Thus the triplet proton signals for the N—CH_2 in Xa are shifted by 0.34 ppm to low field when compared to the analogous signals of VIIa. In the PMR spectrum of Xc the doublet methyl proton signal is shifted by 0.40 ppm when compared with the same group in VIIc.

EXPERIMENTAL

PMR spectra were recorded on Tesla BS-487 (80 MHz) and Bruker WM-360 spectrometers using HMDS internal standard. The reaction course and compound purities were monitored by TLC on Silufol UV-254 in ether—hexane or acetone—hexane in various ratios. Visualization was by UV light or iodine vapor.

Parameters for the compounds are given in Table 1. Elemental analytical data for C, H, and N were in agreement with those calculated.

N-(2-Hydroxyphenyl)-N-(2-carboxyethyl)-β-alanine (III). A. A mixture of aminophenol I (10.9 g, 0.1 mole), acrylic acid (18 g, 0.25 mole), and water (50 ml) was refluxed for 4 h, cooled, and the precipitated III filtered and washed with water.

B. A mixture of I (10.9 g, 0.1 mole) and acrylic acid (21.6 g, 0.3 mole) was left at 20°C for 14 h and the precipitate filtered off and washed with water.

N-(2-Hydroxyphenyl)-α-methyl-β-alanine (IVb). I (10.9 g, 0.1 mole), methacrylic acid (12.9 g, 0.15 mole), hydroquinone (0.5 g), and toluene (50 ml) were refluxed for 8 h, cooled, and the precipitate filtered and washed with toluene and ether.

N-(2-Hydroxyphenyl)-β-methyl-β-alanine (IVc). I (10.9 g, 0.1 mole), crotonic acid (12.9 g, 0.15 mole), and water (150 ml) were refluxed for 6 h, cooled, and the precipitated IVc filtered off.

N-(2-Benzyloxyphenyl)-β-alanine (Va). Aniline II (19.9 g, 0.1 mole), acrylic acid (7.2 g, 0.1 mole), hydroquinone (0.1 g), and toluene (100 ml) were refluxed for 3 h, cooled, and a solution of sodium hydroxide (5%, 100 ml) and toluene or ether (4 × 50 ml) were added to extract amine from the residue. The alkaline solution was acidified with acetic acid to pH 6, and the separated oily product washed three times with water. Upon standing at 4°C the product crystallized to give Va which was filtered off, washed with water, and dried.

N-(2-Benzyloxyphenyl)-α-methyl-β-alanine (Vb). II (19.9 g, 0.1 mole), methacrylic acid (12.9 g, 0.15 mole), hydroquinone (0.1 g), and toluene (50 ml) were refluxed for 8 h, the mixture cooled, and a solution of sodium hydroxide (5%, 150 ml) added to give Vb, which was isolated similarly to Va.

N-(2-Benzyloxyphenyl)-β-methyl-β-alanine (Vc). II (19.9 g, 0.1 mole), crotonic acid (12.9 g, 0.15 mole), and toluene (50 ml) were refluxed for 6 h, the mixture cooled, and sodium hydroxide (5%, 150 ml) was added to give Vc, which was isolated similarly to Va.

1-(2-Benzyloxyphenyl)-dihydro-2,4(1H,3H)-pyrimidinediones (VIa-c). The corresponding β-alanine V (0.05 mole), urea (6 g, 0.1 mole), and acetic acid (30 ml) were refluxed for 12 h and concentrated HCl (15 ml) added. The mixture was refluxed for a further 5 min, diluted with water (1:4) and crystals of VI filtered off, washed with water, and dried.

1-(2-Hydroxyphenyl)dihydro-2,4-(1H,3H)-pyrimidinediones (VIIa-c). A. The corresponding dihydro-2,4-pyrimidinediones VIa-c (0.025 mole) in a mixture of acetic acid (15 ml) and hydrochloric acid (5 ml) was refluxed for 6 h, the liquid fraction distilled in vacuo, and the residue heated in ethanol (10 ml) to dissolve it. Cooling and filtration gave VII.

B. The alanine VIIIa-c (0.025 mole) and concentrated HCl (5 ml) were refluxed for 20 min, the liquid fraction distilled in vacuo, and the residue treated with water and filtered.

N-(2-Hydroxyphenyl)-N-carbamoyl-β-alanine (VIIIa). A mixture of VIIa (2.06 g, 0.01 mole), sodium hydroxide (2 g), and water (5 ml) was heated to reflux and allowed to stand at 20°C for 20 min and then acidified with acetic acid to pH 6. The liquid fraction was distilled in vacuo, and the residue dissolved in hot ethanol (5 ml). Crystals were formed after 12-h standing at 4°C and were filtered off and crystallized from water (2 ml), filtered, and washed with ethanol (50%, 2 ml).

N-(2-Hydroxyphenyl)-N-carbamoyl-β-alanine (VIIIb, c). A mixture of the corresponding dihydro-2,4-pyrimidinedione VIIb, c (0.01 mole), sodium hydroxide (2 g), and water (5 ml) was heated to reflux and allowed to stand at 20°C for 20 min. The product was filtered and the filtrate acidified with acetic acid to pH 6. The precipitated VIIIb or VIIIc separated on standing and were filtered and washed with ethanol (50%, 3 ml).

3-(3-Benzoxazolonyl)propanoic Acid (Xa). I (54.5 g, 0.5 mole), acrylic acid (36 g, 0.5 mole), water (50 ml), and acetic acid (100 ml) were refluxed for 3 h. Urea (45 g, 0.75 mole) was added and the product refluxed for 4-5 h. The mixture was diluted with water (1:3), concentrated HCl added to pH 1, and $Na_2S_2O_4$ added (0.5-1.0 g) until a change in color to green or yellow-green occurred. Xa crystallized on cooling and was washed with water to neutrality and dried.

3-(3-Benzoxazolonyl)-2-methylpropanoic Acid (Xb). Alanine IVb (7.8 g, 0.04 mole), urea (3.6 g, 0.06 mole), and acetic acid (20 ml) were refluxed for 5 h, diluted with water (1:3) and concentrated HCl (to pH 1) and $Na_2S_2O_4$ (≃0.2 g) were added until the color changed to yellow-green. Cooling gave a precipitate of Xb which was filtered off, washed with water to neutrality, and dried.

3-(3-Benzoxazolonyl)-3-methylpropanoic Acid (Xc) and 2-Benzoxazolinone (XI). Alanine IVc (7.8 g, 0.04 mole), urea (3.6 g, 0.06 mole), and acetic acid (20 ml) were refluxed for 5 h. Separation as for Xb gave a mixture of Xc and XI (6.7 g) which PMR spectral data showed to be in the ratio ≃1:1.

Mixture of VIIa and Xa. I (10.9 g, 0.1 mole), acetic acid (30 ml), water (10 ml), and acrylic acid (7.9 g, 0.11 mole) were refluxed for 2 h with stirring and concentrated HCl (15 ml) was added. The liquid fraction was evaporated using a rotary evaporator. When exactly 0.1 mole of concentrated HCl was added, the distillation of the liquid fraction was not needed. Urea (9 g, 0.15 mole) and acetic acid (40 ml) were added, refluxing continued for a further 6 h, and concentrated HCl added to pH 1. After refluxing for a further 20 min the mixture was diluted with water (1:4), $Na_2S_2O_4$ (0.1 g) was added, and the product left at 20°C for 24 h. The precipitate of VIIa and Xa was washed with water to neutrality to give a mixture of VIIa and Xa (10.8 g) (ratio 1:3 by PMR spectroscopy).

Mixture of VIIb and Xb. IVb (9.8 g, 0.05 mole), urea (4.5 g, 0.075 mole), acetic acid (20 ml), and the amount of HCl corresponding to 0.05 mole were refluxed for 6 h. Concentrated HCl was added to pH 1 and refluxing continued for a further 20 min. The mixture was diluted with water (1:4), $Na_2S_2O_4$ (0.1 g) added, and the product left for 24 h at 20°C. The precipitated VIIb and Xb were filtered off and washed with water to give VIIb and Xb (7.6 g) in the ratio 6:5 (PMR spectroscopy).

Mixture of VIIc, Xc, and XI. IVc (9.8 g, 0.05 mole), urea (4.5 g, 0.075 mole), acetic acid (20 ml), and the calculated amount of concentrated HCl (0.05 mole) were refluxed for 6 h. Concentrated HCl was added to pH 1 and refluxed for a further 20 min. The liquid fraction was distilled in vacuo and the residue treated with water (50 ml). Crystals of VIIc, Xc, and XI were filtered off and washed with water to give a mixture (8.2 g) in the ratio ≃1:1:1 (PMR spectroscopy).

2-Benzoxazolinone (XI). I (10.9 g, 0.1 mole), urea (12 g, 0.2 mole), and acetic acid (30 ml) were refluxed for 12 h. Concentrated HCl (30 ml) was added and the product was diluted with water (1:4). The precipitate was filtered off, washed with water, and dried.

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