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SYNTHESIS OF DIASTEREOISOMERS OF DIMETHYL 4-ARYLAMINO-N-PHTHALOYL-L-GLUTAMATES

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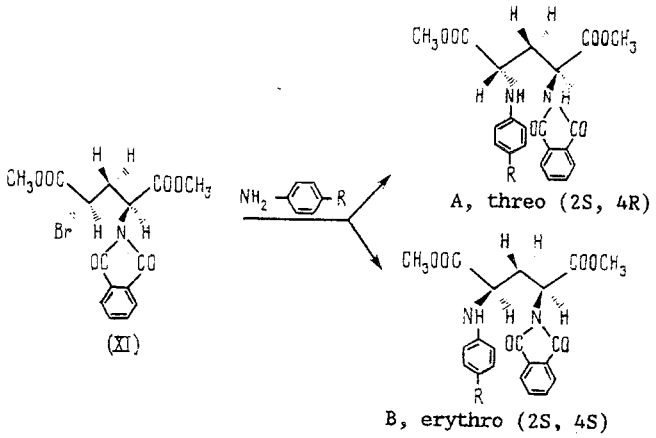
UDC 542.91:541.63:547.466.6

Reaction of p-substituted arylamines with dimethyl (2S,4RS)-4-bromo-N-phthaloylglutamate followed by separation of the stereoisomers has given the pure dimethyl (2S)-4-arylamino-N-phthaloylglutamates. Nucleophilic replacement of the halogen in dimethyl (2S,4RS)-4-bromo-N-phthaloylglutmate is diastereoselective, giving the threo-isomer preferentially.

Some glutamic acid derivatives have been found to posses antitumor [1] and radioprotectant properties [2]. The spatial structure of these compounds plays an important part in their activity.

The object of the present study was to obtain the dimethyl (2S)-4-arylamino-N-phthaloylglutamates (I)-(X) with a variety of substituents in the para position of the benzene ring.

These compounds were obtained by heating dimethyl (2S,4RS)-4-bromo- N-phthaloylglutamate (XI) [3] with an excess of the arylamine in acetonitrile or alcohol (Table 1).



2S, 4S (threo): R = CH_3O (I), OH (III), CH_3 (IV), H (VI), $NHCOCH_3$ (VII), I (VIII), Cl (IX), Br (X); 2S, 4R (erythro): R = CH_3O (II), CH_3 (V).

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Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 12, pp. 2781-2785, December, 1989. Original article submitted September 27, 1988.

0568-5230/89/3812-2545$12.50

TABLE 1. Reaction Conditions, Yields, and Properties of Dimethyl 4-Arylamino-N-phthaloyl-L-glutamates (R is the substituent in the p-position of the benzene ring)

R	Method 1				Method 2			
	reaction time, h	yield, %	amount of (2S, 4S)-isomer in the reaction mixture, (HPLC)	mp, °C	reaction time, h	yield, %	amount of (2S, 4S)-isomer in the reaction mixture, (HPLC)	mp, °C
CH_3O	11	63	76	131–145	10	60	72	137–146
OH	10	60		189–196	10 *	38		195–199
CH_3	8	61	78	149–157	10	64	77	157–160
H	11	68	78	173–184	10	73	79	183–188
$NHCOCH_3$	8	47	75	205–210	10	56	78	205–209
I	8	41	74	106–115	10	44	78	107–118
Cl	9	47	70	124–130	10	53	73	128–131
Br	8	39	74	116–126	10	40	75	125–131
Br	20	63	–	–	–	–	–	–

*Synthesis carried out under argon.

The use of (XI), which has the S-configuration at the α-carbon atom, reduced the task of separation of the stereoisomers to the separation of diastereoisomers, which was affected by recrystallization or chromatography.

As will be seen from Table 1, the rate of replacement depends on the nucleophilicity of the amine, which explains the low yields obtained when the reaction was carried out with haloarylamines. Good yields of (X) were obtained only when the reaction time was considerably increased.

It was shown by TLC that the reaction mixture contained both diastereoisomers of the required products, the threo-isomers having the lower R_f values in the system hexane–toluene–acetone, and the erythro-isomers the higher values. The diastereoisomers A [compounds (I), (III), (IV), and (VI)-(X)] were isolated by repeated crystallization of the product obtained when the reaction was carried out in ethanol. The diastereoisomers B [compounds (II) and (V)] were obtained by separating the mixture by chromatography on silica gel followed by recrystallization. The product obtained by the reaction of (XI) with p-aminophenol could not be resolved by chromatography and the purity of (III) was shown by methylation to give the pure (according to HPLC) diastereoisomer (I).

Assignment of the configuration of the diastereoisomers was made from the PMR spectra, since it is known that the differences in the chemical shifts of the methylene protons in compounds with the threo-configuration should be less than in the erythro-diastereoisomers. The PMR spectra of the diastereoisomers A [compounds (I), (III), (IV), and (VI)-(X)], showed the same picture in the region of absorption of the protons of the CH_2 group, namely a multiplet of signal breadth ~0.25 ppm (Table 2). In the case of diastereoisomers B [compounds (II) and (V)], the signal for the methylene protons was shifted to lower field and became broader (0.4-0.6 ppm). It has previously been shown by X-ray crystallography that compounds (I) and (VII) are the threo-(2S,4S)-diastereoisomers [4]. This is in accordance with the PMR spectral findings. Hence, diastereoisomers A have the 2S,4S(threo)-configuration and the compounds B, the 2S,4R(erythro)-configuration.

It was found that greater amounts of the threo- than the erythro-diastereoisomers were formed in the reaction. It was shown by HPLC that irrespective of the type of substituent in the arylamine, the ratio of threo- to erythro-diastereoisomers in a sample obtained directly from the reaction mixture was ~3:1 (Table 1). It should be noted that under the conditions described above for the reaction of (XI) with aromatic amines, no stereoisomers with the R-configuration at the α-carbon atom were found. This was confirmed by the fact that when the pure threo- or erythro-stereoisomers were subjected to prolonged heating in acetonitrile or ethanol with the addition of the corresponding amine and its hydrobromide, HPLC showed that no product diastereoisomeric with the starting material was present, such as would have been formed on racemization.

Hence, the nucleophilic replacement of the halogen in (XI) is diastereoselective, possibly as a result of the presence of the bulky phthaloyl group and its influence on the nu-

TABLE 2. PMR Spectra of (I)-(X)

Compound	Assignment* (δ, ppm)							
	C_6H_4R-*p*	$C_6H_4N(CO)_2CH$	*p*-RC_6H_4NHCH	1-CH_2O	5-CH_2O	CH_3R**	CH_2	
							assignment	signal width
(I)	6.62 m (4H)	5.28 m (1H)	3.90 m (3H)	3.70 s (3H)	3.60 s (3H)	3.67 s (3H)	2.69 m (2H)	0.22
(II)	6.64 m (4H)	5.20 m (1H)	3.98 m (1H)	3.70 s (3H)	3.49 s (3H)	3.69 s (3H)	2.73 m (2H)	0.62
(III)	6.58 m (4H)	5.36 m (1H)	4.02 m (1H)	3.73 s (3H)	3.58 s (3H)	–	2.72 m (2H)	0.24
(IV)	6.87 d (2H) 6.47 d (2H)	5.23 m (1H)	4.01 m (1H)	3.70 s (3H)	3.60 s (3H)	2.14 s (3H)	2.73 m (2H)	
(V)	6.94 d (2H) 6.52 d (2H)	5.18 m (1H)	4.21 m (1H)	3.70 s (3H)	3.48 s (3H)	2.18 s (3H)	2.81 m (2H)	0.40
(VI)	6.85 m (5H)	5.23 m (1H)	4.05 m (1H)	3.73 s (3H)	3.66 s (3H)	–	2.75 m (2H)	0.15
(VII)	7.20 d (2H) 6.46 d (2H)	5.20 m (1H)	3.96 m (1H)	3.68 s (3H)	3.50 s (3H)	1.90 s (3H)	2.61 m (2H)	0.25
(VIII)	7.30 d (2H) 6.46 d (2H)	5.15 m (1H)	3.98 m (1H)	3.73 s (3H)	3.68 s (3H)	–	2.74 m (2H)	0.14
(IX)	7.05 d (2H) 6.48 d (2H)	5.20 m (1H)	4.00 m (1H)	3.73 s (3H)	3.67 s (3H)	–	2.74 m (2H)	0.12
(X)	7.14 d (2H) 6.43 d (2H)	5.19 m (1H)	4.00 m (1H)	3.73 s (3H)	3.68 s (3H)	–	2.74 m (2H)	0.15

*Signals for the protons of the phthaloyl group at 7.78-7.91 ppm (m, 4H).

**CH_3 group in substituent R.

cleophilic replacement, for example by the formation of an intermediate carbocation which is stabilized by interaction with the oxygen of the phthaloyl group, as in [5].

EXPERIMENTAL

Dimethyl (2S,4RS)-4-bromo-N-phthaloylglutamate (XI) was obtained as in [3].

PMR spectra were obtained on a Tesla BS-567A, operating frequency 100 MHz, solvents $CDCl_3$, $(CD_3)_2CO$, and $(CD_3)_2SO$. IR spectra were recorded on a Specord 75IR instrument in vaseline grease and UV spectra, on a Specord UV-VIS instrument in ethanol. $[\alpha]_D$ values were measured with an EPO A1 polarimeter and HPLC was carried out on a Millikhrom chromatograph, sorbent Silasorb-600, columns 62 × 4 mm, detection at 220 nm, solvent system hexane–isopropanol (40:1), rate of elution 0.20 ml/min. The separation coefficient was 1.13-1.70. TLC was carried out with Silufol UV-254 plates, in the systems (a): hexane–toluene–acetone (5:4:3), (b) hexane–toluene–acetone (5:4:8). Column chromatography was carried out with Chemapol L40/100μ silica gel.

The mixed diastereoisomers of the dimethyl (2S)-4-arylamino-N-phthaloylglutamates were obtained by two methods.

Method 1. A solution of 10 g (0.026 mole) of (XI) and the arylamine (0.078 mole) was boiled in 100 ml of dry acetonitrile for 8-11 h, then cooled, filtered from amine hydrobromide, evaporated, and 10-15 ml of ethanol added. The mixture was heated to boiling, cooled, and the crystalline product filtered off (mixed diastereoisomers of the (2S) dimethyl ester). The reaction times, yields, and some properties of the mixtures obtained are given in Table 1.

Method 2. A mixture of 10 g (0.026 mole) of (XI) and the arylamine (0.078 mole) was boiled in 100 ml of ethanol for 10 h, concentrated to 20-25 ml, cooled, and the solid which separated was filtered off (Table 1).

Dimethyl (2S,4S)-4-(p-methoxyphenylamino)-N-phthaloylglutamate (I). The mixture of diastereoisomers (6 g) obtained by method 1 from (XI) and p-methoxyaniline was twice recrystallized from ethanol, to give 4.4 g (77%) of deep yellow (I). The product was chromatographically homogeneous (HPLC: t_R 7.9 min), mp 150-152°C, $[\alpha]_D^{20}$ −50.7°(C1, $CHCl_3$), R_f 0.27 in system (a). Found: C, 62.09; H, 5.20; N, 6.80%. $C_{22}H_{22}N_2O$. Calculated: C, 61.97; H, 5.16; N, 6.57%. IR spectrum (ν, cm^{-1}): 3370(NH), 1770, 1740 (phthaloyl C=O), 1720, 1705 (ester C=O). UV spectrum (λ_{max}, nm): 205 (p-methoxyphenylamino group), 220, 300 (phthaloyl group.

Dimethyl (2S,4R)-4-(p-methoxyphenylamino)-N-phthaloylglutamate (II). The mixture of diastereoisomers remaining after evaporation of the filtrate obtained in the isolation of (I) (2.0 g) was resolved by column chromatography on silica gel in system (a). The fraction enriched in the erythro-isomer was recrystallized three times from ethanol, to give 0.56 g of (II) as pale yellow needles. The product was chromatographically homogeneous (HPLC: t_R 6.7 min), mp 141-145°C, $[\alpha]_D^{20}$ −65.4° (C1, $CHCl_3$), R_f 0.28 in system (a). Found: C, 62.27; H, 5.16; N, 6.92%. $C_{22}H_{22}N_2O_7$. Calculated: C, 61.97; H, 5.16; N, 6.57%. IR spectrum (ν, cm^{-1}): 3350 (NH), 1750 (phthaloyl C=O), 1720, 1700 (ester C=O). UV spectrum (λ_{max}, nm): 205 (p-methoxyphenylamino group), 220, 300 (phthaloyl group).

Dimethyl (2S,4S)-4-(p-hydroxyphenylamino)-N-phthaloylglutamate (III). The product (6.43 g) obtained from (XI) and p-aminophenol by method 1 was recrystallized three times from ethanol to give 4.63 g (72%) of (III), mp 200-202°C, $[\alpha]_D^{20}$ −129.9° (C1, DMF), R_f 0.41 in system (b). Found: C, 61.28; H, 4.83; N, 6.93%. $C_{21}H_{20}N_2O_7$. Calculated: C, 61.17; H, 4.86; N, 6.80%. IR spectrum (ν, cm^{-1}): 3335 (NH), 1760, 1720 (phthaloyl C=O), 1705 (ester C=O). UV spectrum (λ_{max}, nm): 203, 250 (p-hydroxyphenylamino group), 220, 300 (phthaloyl group).

Methylation of (III). To a solution of 0.5 g (1.2 mmoles) of (III) and 0.11 ml (1.2 mmoles) of dimethyl sulfate in 5 ml of DMF was added dropwise 0.5 ml of 10% NaOH solution (1.2 mmoles). The mixture was kept for 1 h at 40°C, poured into 50 ml of water and extracted with chloroform. After drying over Mg_2SO_4, the solution was analyzed by TLC and HPLC, showing it to contain (I) only (HPLC: t_R 7.9 min).

Dimethyl (2S,4S)-4-(p-methylphenylamino)-N-phthaloylglutamate (IV). The product (6.0 g) obtained by method 1 or 2 from (XI) and p-toluidine was twice recrystallized from ethanol to give 4.74 g (79%) of (IV) as a colorless, crystalline solid. The product was chromatographically homogeneous (HPLC: t_R 4.6 min), mp 161-163.5°C, $[\alpha]_D^{20}$ −52.0° (C1, $CHCl_3$), R_f 0.32 in system (a). Found: C, 64.52; H, 5.48; N, 7.09%. $C_{22}H_{22}N_2O_6$. Calculated: C, 64.39; H, 5.40; N, 6.83%. IR spectrum (ν, cm^{-1}): 3390, 3370 (NH), 1780, 1750 (phthaloyl C=O), 1710 (ester C=O). UV spectrum (λ_{max}, nm): 206 (p-methylphenylamino group), 220, 297 (phthaloyl group).

Dimethyl (2S,4S)-4-(p-methylphenylamino)-N-phthaloylglutamate (V). The mixed diastereoisomers (1.0 g) obtained on evaporating the filtrate remaining after isolation of the threo-isomer (IV) was separated by column chromatography on silica gel in system (a). The fraction enriched in the erythro-isomer was collected. Repeated recrystallization from ethanol gave 0.11 g of colorless crystals of (V). The product was chromatographically homogeneous (HPLC: t_R 4.0 min), mp 99-102°C, $[\alpha]_D^{20}$ −74.6° (C1, $CHCl_3$), R_f 0.36 in system (a). Found: C, 64.24; H, 5.47; N, 6.49%. $C_{22}H_{22}N_2O_6$. Calculated: C, 64.39; H, 5.40; N, 6.83%. IR spectrum (ν, cm^{-1}): 3350 (NH), 1770, 1735 (phthaloyl C=O), 1710 (ester C=O). UV spectrum (λ_{max}, nm): 206 (p-methylphenylamino group), 220, 297 (phthaloyl group).

Dimethyl (2S,4R)-4-phenylamino-N-phthaloylglutamate (VI). The mixed stereoisomers (6.0 g) obtained by method 2 from (XI) and aniline was twice recrystallized from ethanol to give 4.38 g (73% of light-yellow crystals of (VI). The product was chromatographically homogeneous (HPLC: t_R 5.3 min), mp 190.5-192°C, $[\alpha]_D^{20}$ −44.2° (C1, $CHCl_3$), R_f 0.30 in system (a). Found: C, 63.96; H, 5.32; N, 7.27%. $C_{21}H_{20}N_2O_6$. Calculated: C, 63.64; H, 5.05; N, 7.07%. IR spectrum (ν, cm^{-1}): 3370, 3315 (NH), 1770, 1750 (phthaloyl C=O), 1710 (ester C=O). UV spectrum (λ_{max}, nm): 207 (phenylamino group), 220, 296 (phthaloyl group).

Dimethyl (2S,4S)-4-(p-acetamido)phenylamino-N-phthaloylglutamate (VII). The product (6.0 g) obtained by method 1 or 2 from p-aminoacetanilide and (XI) was recrystallized from ethanol to give 4.62 g (77%) of light yellow crystals of (VII). The product was chromatographically homogeneous (HPLC: t_R 4.8 min), mp 212-214°C, $[\alpha]_D^{20}$ −167° (C1, DMF_3), R_f 0.15 in system (b). Found: C, 63.36; H, 5.11; N, 9.38%. $C_{23}H_{23}N_3O_7$. Calculated: C, 63.14; H, 5.08; N, 9.27%. IR spectrum (ν, cm^{-1}): 3375, 3320 (NH), 1770, 1760 (phthaloyl C=O), 1720 (ester C=O), 1675 (amide C=O). UV spectrum (λ_{max}, nm): 203, 268 (p-acetamidophenylamino group), 220, 306 (phthaloyl group).

Dimethyl (2S,4S)-4-(p-iodophenylamino)-N-phthaloylglutamate (VIII). The mixed diastereoisomers (5.0 g) obtained from (XI) and p-iodoaniline by method 1 was twice recrystallized from ethanol to give 3.75 g (75%) of colorless crystals of (VIII). The product was chromatographically homogeneous (HPLC: t_R 5.6 min), mp 115-118°C, $[\alpha]_D^{20}$ −59.7° (C1, $CHCl_3$), R_f 0.31 in system (a). Found: C, 48.52; H, 4.04; I, 23.97; N, 5.70%. $C_{21}H_{10}IN_2O_6$. Calculated: C, 48.29; H, 3.67; I, 24.30; N, 5.36%. IR spectrum (ν, cm^{-1}): 3380 (NH), 1770, 1750 (phthaloyl C=O), 1720, 1705 (ester C=O). UV spectrum (λ_{max}, nm): 204, 256 (p-iodophenylamino group), 220, 295 (phthaloyl group).

Dimethyl (2S,4S)-4-(p-chlorophenylamino)-N-phthaloylglutamate (IX). The product (5.0 g) obtained from (XI) and p-chloroaniline by method 1 was twice recrystallized from ethanol to give 3.8 g (76%) of colorless crystals of (IX). The product was chromatographically homogeneous (HPLC: t_R 5.6 min), mp 131-134°C, $[\alpha]_D^{20}$ −58.5° (C1, $CHCl_3$), R_f 0.31 in system (a). Found: C, 58.42; H, 4.16; Cl 8.72; N, 6.30%. $C_{21}H_{19}ClN_2O_6$. Calculated: C, 58.54; H, 4.14; Cl, 8.25; N, 6.50%. IR spectrum (ν, cm^{-1}): 3390, 3350 (NH), 1780, 1750 (phthaloyl C=O), 1710 (ester C=O). UV spectrum (λ_{max}, nm): 205, 252 (p-chlorophenylamino group), 220, 295 (phthaloyl group).

Dimethyl (2S,4S)-4-(p-bromophenylamino)-N-phthaloylglutamate (X). The mixture of diastereoisomers (4.0 g) obtained from (XI) and p-bromoaniline by method 1 or 2 was twice recrystallized from ethanol to give 2.68 g (67%) of colorless crystals of (X). The product was chromatographically homogeneous (HPLC: t_R 5.8 min), mp 133-135°C, $[\alpha]_D^{20}$ −57.8° (C1, $CHCl_3$), R_f 0.32 in system (a). Found: C, 53.07; H, 4.12; Br 17.08; N, 5.89%. $C_{21}H_{19}BrN_2O_6$. Calculated: C, 53.05; H, 4.00; Br, 16.84; N, 5.89%. IR spectrum (ν, cm^{-1}): 3400, 3370 (NH), 1780, 1760 (phthaloyl C=O), 1710 (ester C=O). UV spectrum (λ_{max}, nm): 206, 252 (p-bromophenylamino group), 220, 297 (phthaloyl group).

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