SYNTHESIS AND REACTIONS OF β-DIETHYLAMINOETHYL β-AMINOETHOXYDIPHENYLACETATE

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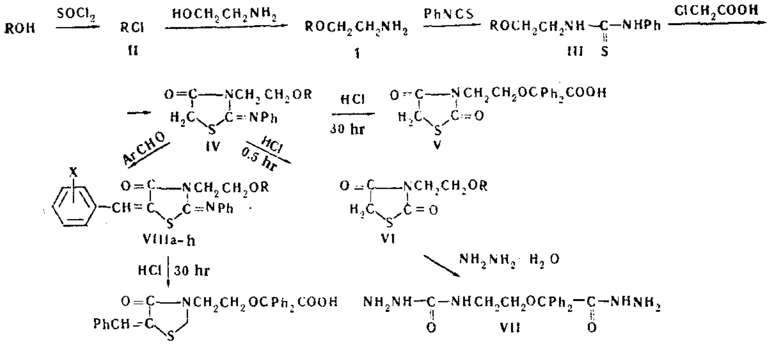
The reaction of β-diethylaminoethyl chlorodiphenylacetate with ethanolamine has given β-diethylaminoethyl β-aminoethoxydiphenylacetate, the reaction of which with phenyl isothiocyanate followed by condensation with monochloroacetic acid has led to a derivative of a disubstituted thiazolidin-4-one, whose structure has been shown by hydroolytic cleavage. A number of arylidene derivatives of thiazolidin-4-one has been obtained. Their UV spectra agree with their structures.

Aminoalkyl esters of arylaliphatic acids, of which the most common are the β-dialkylaminoethyl esters, are known as physiologically active medicinal substances [1]. The dialkylaminoethyl esters of derivatives of diphenylacetic acid occupy a special position [2–6], being known as neuroplegic, sedative, and local anaesthetic agents.

In view of what has been said above, we set ourselves the aim of synthesizing β-diethylaminoethyl β-aminoethoxydiphenylacetate (I) and a number of its derivatives. Starting from the medicinal agent amizil [benactyzine], we obtained its chloro analog [7] (II), whose reaction with excess β-ethanolamine led to I. Ethanolamine can react with II at both the hydroxy and the amino group, but the reactions given below show that the molecule of the substance formed contained a free amino group.



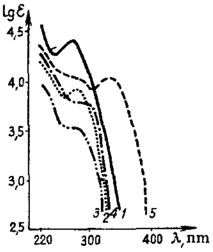
$R = Ph_2CCOOCH_2CH_2N(C_2H_5)_2$

a X = H; b X = p-NO₂; c X = m-NO₂; d X = p-Cl; e X = p-Br; f X = p-N(CH₃)₂; g X = p-OCH₃; h X = 3,4 (OCH₃)₂

Heating I with an equimolecular amount of phenyl isothiocyanate gave the thiourea III, whose condensation with monochloroacetic acid [8] led to the disubstituted thiazolidin-4-one IV. Since the thiourea III is not symmetrical, and in its condensation with monochloroacetic acid the formation of two isomers differing by the position of the phenyl group is possible, prolonged acid hydrolysis (30 hr) was carried out, which led to 3-{β-[carboxy-(diphenyl)methoxy] ethyl}thiazolidine-2,4-dione (V), according to which IV is 3-(β-alkoxyethyl)-2-phenyliminothiazolidin-4-one. Brief acid hydrolysis under milder conditions gave 3-(β-alkoxyethyl)thiazolidine-2,4-dione (VI), which also confirms the structure of IV. When substance VI was heated with hydrazine hydrate, an interesting cleavage of the ring of the heterocycle at the 1—2 and 3—4 bonds took place with the simultaneous hydrazinolysis of the ester group in the side chain, as a result of which the dihydrazine of β-carboxyaminoethoxydiphenylacetic acid (VII) was formed. The reaction of IV with various aromatic aldehydes in acetic acid gave the corresponding 5-arylidenethiazolidin-4-ones (VIIIa-h).

Benzilic acid contains no high-intensity absorption maxima (ε < 1000), since the individual chromophores (COOH and C_6H_5) or groups (OH) in its molecule are not conjugated. This situation also applies to the esters of benzilic, chlorodiphenylacetic, and β-aminoethoxydiphenylacetic acids.

The thiourea III, like phenylthiourea, has a characteristic absorption maximum at 269 nm (figure), which is due to the presence in the molecule of the thioamide chromophore $-NH-\underset{|}{C}{=}S$. In the pseudothiohydantoin derivative IV, the main chromophore is the isothioamide grouping. Because of this there is a marked hypsochromic effect and a small bathochromic shift of the absorption maximum, which is due to the capacity of this chromophore for polarization: $C_6H_5-\overset{-}{N}-\underset{|}{C}=\overset{+}{S}-$. The acid hydrolysis of IV leads to the destruction of the isothioamide chromophore, as a result of which the absorption maximum of the thiazolidinediones V and VI are almost imperceptible and the spectral curves have characteristic inflections in the 273 nm region.



Absorption spectra:
1) III; 2) IV; 3) V;
4) VI; 5) IX.

The introduction of arylidine groups into position 5 of the thiazolidin-4-one derivatives leads to an extension of the conjugation chain, as a result of which a K-band with a characteristic maximum in the 328–262-nm region appears in the UV absorption spectra. At the same time, the maxima in the 270–280-nm region disappear completely or are converted into inflections, since the arylidine groups actively counteract the polarization of the isothioamide chromophore of substance IV. An exception is the 5-p-dimethylaminobenzylidene derivative (VIIIf), the absorption maximum of which is shifted bathochromically to 413 nm because of the presence of the powerful electron-donating substituent.

EXPERIMENTAL

β-Diethylaminoethyl β-aminoethoxydiphenylacetate (I). A mixture of 46.8 g (0.1 mole) of II and 50 ml of anhydrous ethanolamine was heated at 110–115° C for 4 hr. After cooling, the resulting homogeneous oily mass was poured into water. After solidification, the product was filtered off and crystallized from dilute propanol. This gave 28 g of a white substance readily soluble in ethanol, acetone, and chloroform, sparingly soluble in ether and benzene; and insoluble in water.

β-Diethylaminoethyl diphenyl(β-phenylthioureidoethoxy)acetate (III). A mixture of 18.5 g (0.05 mole) of I and 5.95 ml (0.05 mole) of phenyl isothiocyanate was heated in a boiling water bath for 2–3 hr. The resulting mass was dissolved in 100 ml of methanol and the solution was poured into 500 ml of water. After crystallization from 50% CH_3COOH, 19 g of a light yellow product soluble in alcohols and acetone, and insoluble in ether, benzene, and water was obtained.

3-{β-[β-Diethylaminoethoxycarbonyl(diphenyl)methoxy]ethyl}thiazolidin-4-one (IV). A mixture of 50 ml of glacial acetic acid, 10.1 g (0.02 mole) of III, 3.76 g (0.04 mole) of monochloroacetic acid, and 4 g of anhydrous sodium acetate was boiled for 5 hr and cooled, the NaCl that had deposited was filtered off, and the filtrate was evaporated. The residue was crystallized from dilute propanol and dried in air.

3-{β-[Carboxy(diphenyl)methoxy]ethyl}thiazolidine-2,4-dione (V). Concentrated HCl, 10 ml, and 2.7 g (0.005 mole) of IV were added to 10 ml of CH_3COOH, and the mixture was boiled for 30 hr. The organic mass that deposited was separated off after cooling, washed with water, and triturated with ether. This gave 0.66 g of a cream-colored powder which was crystallized from a mixture of CCl_4 and C_3H_7OH (1 : 1).

3-{β-[β-diethylaminoethoxycarbonyl(diphenyl)methoxy]ethyl}thiazolidine-2,4-dione (VI). A mixture of 10 ml of ethanol and 10 ml of conc HCl was boiled for 1 hr with 5.4 g (0.01 mole) of IV. After cooling, the mass that had deposited was separated off, washed with water, and crystallized from a mixture of CCl_4 and C_3H_7OH (1 : 1). Compound VI was obtained in the form of a white powder.

Dihydrazide of β-carboxyaminoethoxy(diphenyl)acetic acid (VII). A solution of 4.7 g (0.01 mole) of VI in 15 ml of ethanol was boiled with 1.25 ml (0.025 mole) of hydrazine hydrate for 5 hr. The reaction mixture was evaporated and the resulting oil was triturated with ether. After crystallization from CCl_4–ethanol (1 : 1), a pale yellow product was obtained.

5-Benzylidene-3-{β-[β-diethylaminoethoxycarbonyl(diphenyl)methoxy]ethyl}-2-phenyliminothiazolidin-4-one (VIIIa). A mixture of 5.45 g (0.01 mole) of IV, 30 ml of glacial CH_3COOH, 1.2 g of anhydrous sodium acetate, and 1.6 g (0.015 mole) of benzaldehyde was boiled for 3 hr. The reaction mixture was filtered, the filtrate was evaporated, and the residue was washed with water, and then crystallized from dilute ethanol. This gave a bright-colored powder readily soluble in ethanol, acetone, and chloroform. Compounds VIIIb–h were obtained similarly.

5-Benzylidine-3-{β-[carboxy(diphenyl)methoxy]ethyl}thiazolidine-2,4-dione (IX) was obtained in a manner similar to V.

The analytical results and characteristics of the compounds obtained are given in the table.

Characteristics of Compounds I–IX

Compound	Mp, ° C	UV spectra		Empirical formula	Found, %		Calculated, %		Yield, %
		λ_{max}, nm	lg ε		N	S	N	S	
I	123—125	—	—	$C_{22}H_{30}N_2O_3$	7.6	—	7.2	—	76
III	107—109	269	4.40	$C_{29}H_{35}N_3O_3S_1$	8.0	6.5	8.3	6.3	76
IV	102—106	278	3.92	$C_{31}H_{35}N_3O_4S_1$	7.8	5.9	7.7	5.9	49
V	131—133	273	3.56	$C_{19}H_{17}N_1O_5S_1$	4.1	8.4	3.8	8.6	36
VI	112—113	273	3.84	$C_{25}H_{30}N_2O_5S_1$	6.1	6.7	6.0	6.8	37
VII	149—150	—	—	$C_{17}H_{21}N_5O_3$*	20.1	—	20.4	—	31
VIIIa	106—110	333	4,26	$C_{38}H_{39}N_3O_4S_1$	6.3	5.2	6.6	5.1	25
VIIIb	120—123	379	4.21	$C_{38}H_{38}N_4O_6S_1$	8.4	4.9	8.3	4.8	24
VIIIc	105—107	338	4.21	$C_{38}H_{38}N_4O_6S_1$	8.3	4.6	8.3	4.8	28
VIIId	125—128	328	4.12	$C_{38}H_{38}Cl_1N_3O_4$**	6.0	—	6.3	—	35
VIIIe	117—120	335	4.27	$C_{38}H_{38}B_1N_3O_4S_1$***	5.8	—	5.9	—	45
VIIIf	129—132	413	4.05	$C_{40}H_{44}N_4O_4S_1$	7.9	4.6	8.3	4.7	26
VIIIg	111—114	348	4.23	$C_{39}H_{41}N_3O_5S_1$	6.0	4.6	6.3	4.8	21
VIIIh	96—97	362	4.10	$C_{40}H_{43}N_3O_6S_1$	5.8	4.5	6.1	4.6	18
IX	208—209	333	4.09	$C_{26}H_{21}N_1O_5S_1$	3.2	7.1	3.0	7.0	57

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* Found, %: C 59,8; H 5,8 Calculated, %: C 59,5 ; H 6,2

** Found, %: C 67,9; H 6,0 Calculated, %: C 68,3 ; H 5,7

*** Found, %: C 64,1; H 5,1 Calculated, %: C 64,0 ; H 5,4

The UV spectra of 0.001–0.009-M alcoholic solutions were recorded on an SF-4 spectrophotometer.

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