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RESEARCHES ON 2, 1, 3-THIA- AND SELENADIAZOLE

XL. Di(β-chloroethyl)-amino Derivatives*

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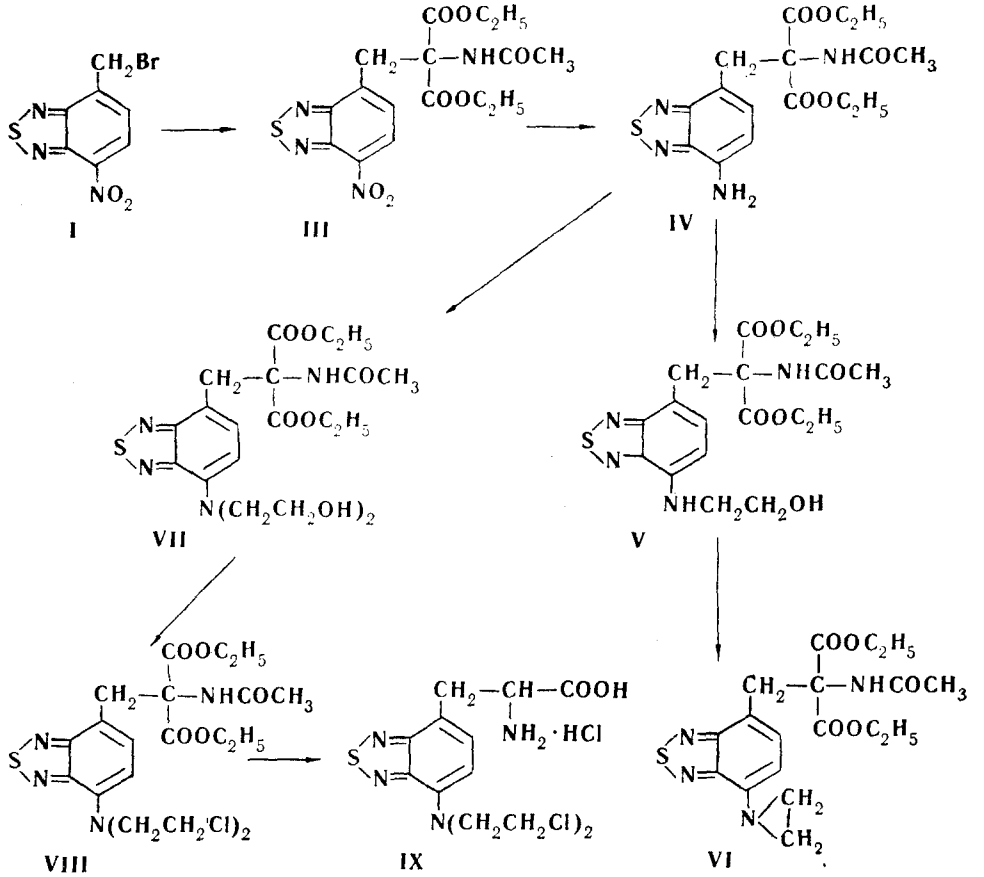
4-(β,β-Dicarboethoxy-β-acetylamino) ethyl-7-aminobenzo-2,1,3-thiadiazole (IV) and ethylene oxide form mainly the 7-(β-hydroxyethyl) amino derivative (V); the 7-di (β-hydroxyethyl) amino derivative VII was isolated in low yield. Action of $POCl_3$ on compound VII gave the 7-di (β-chloroethyl) amino derivative VIII, which was converted into 4-(β-amino-β-carboxy)-ethyl-7-di (β-chloroethyl) aminobenzo-2,1,3-thiadiazole (IX). 5-(β, β-dicarboethoxy-β-acetylamino) ethyl-4-nitrobenzo-2,1,3-thiadiazole (XI) was converted to 5-(β-carboxy-β-amino) ethyl-4-nitrobenzo-2,1,3-thiadiazole hydrochloride (XII), from which was prepared, by known routes, and in satisfactory yield, 5-(β-carboxy-β-amino) ethyl-4-di (β-chloroethyl)-aminobenzo-2,1,3-thiadiazole hydrochloride (XVII).

It was previously [1] shown, that 4- and 5-aminobenzo-2,1,3-thiadiazoles react with ethylene oxide under the conditions described in the literature, for aromatic compounds, to give 4- and 5-(β-hydroxyethyl)-aminobenzo-2,1,3-thiadiazoles. Introduction of a methyl group ortho or para to the amino group promotes formation of di (β-hydroxyethyl) amino derivatives.

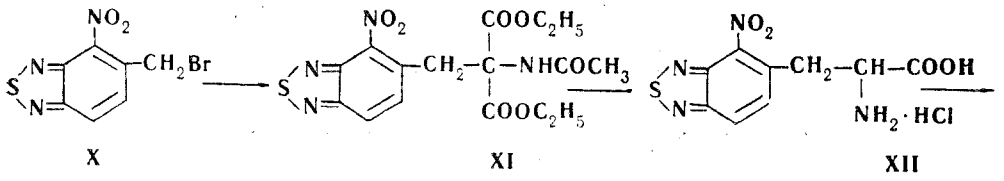


The present paper presents results relating to the ethylene oxide alkylation of amines which are benzo-2,1,3-thiadiazole derivatives, with an ortho or para methyl group, with one hydrogen atom replaced by an acetylaminomalonic ester group, or by a methyl phthalylaminoacetate one.

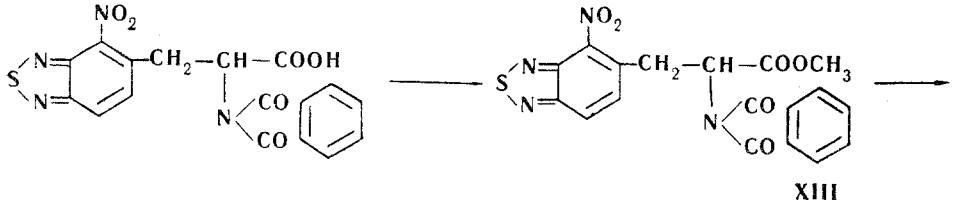
Treatment of 4-bromomethyl-7-nitrobenzo-2,1,3-thiadiazole (I) with acetylaminomalonic ester (II) in the presence of sodium ethoxide gives 4-(β,β-dicarboethoxy-β-acetylamino) ethyl-7-nitrobenzo-2,1,3-thiadiazole (III), reduced to the corresponding amine (IV). The latter reacts with ethylene oxide under the conditions given in the

* For Part XXXIX see [8].

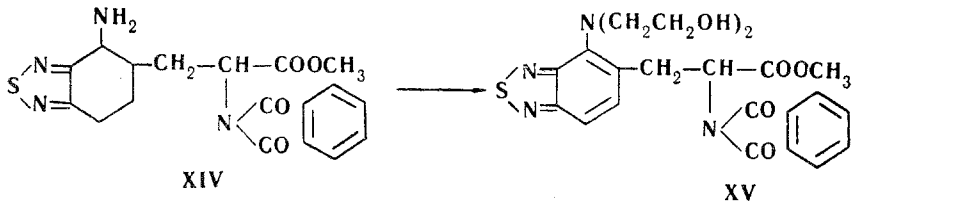
literature for such reactions [2-4], to give mainly the 7-(β-hydroxyethyl)-amino derivative V, treatment of which with phosphorus oxychloride gives what is assumed to be the ethylenimine derivative VI.* Another product of the reaction of amine IV with ethylene oxide is the 7-di(β-hydroxyethyl) amino derivative VII, which reacts with phosphorus oxychloride to give the 7-di(β-chloroethyl) amino derivative VIII. When the latter is submitted to acid hydrolysis, it simultaneously undergoes decarboxylation and conversion to 4-(β-amino-β-carboxy) ethyl-7-di-(β-chloroethyl) aminobenzo-2,1,3-thiadiazole (IX). It should be mentioned that the yield of compound VII is low, so that it cannot always be isolated.



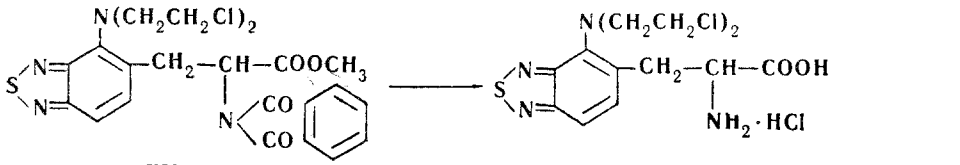
X XI XII



XIII



XIV XV



XVI XVII

Reaction of compound II with 5-bromomethyl-4-nitrobenzo-2,1,3-thiadiazole X in the presence of sodium ethoxide gives 5-(β,β-dicarboethoxy-β-acetylamino) ethyl-4-nitrobenzo-2,1,3-thiadiazole (XI), converted on heating with 20% hydrochloric acid to 5-(β-carboxy-β-amino) ethyl-4-nitrobenzo-2,1,3-thiadiazole hydrochloride (XII). The amino group of the latter was phthalated, and the resultant phthalide methylated at the carboxyl group to give an ester amide XIII, reduced to amine XIV. Treatment of the latter with ethylene oxide gave a 58% yield of di(β-hydroxyethyl)-amino derivative** XV, converted by phosphorus oxychloride or thionyl chloride to di(β-chloroethyl) amino derivative XVI. Acid hydrolysis of the latter gives 5-(β-amino-β-carboxy) ethyl-4-di(β-chloroethyl)-aminobenzo-2,1,3-thiadiazole hydrochloride XVII.

Experimental

Starting materials. 4-Bromomethyl-7-nitrobenzo-2,1,3-thiadiazole (I) and 5-bromomethyl-4-nitrobenzo-2,1,3-thiadiazole (X) were obtained by the method of [5].

* Compounds V and VI are at present being studied.

** This is analogous to a previously [1] mentioned phenomenon. 4-Methylamino- or 5-methyl-4-aminobenzo-2,1,3-thiadiazole are comparatively smoothly alkylated to ethylene oxide; under the same conditions, the isomeric 4-methyl-7-aminobenzo-2,1,3-thiadiazole cannot be converted to a di(β-hydroxyethyl) amino derivative.

4-(β,β-Dicarboethoxy-β-acetylamino) ethyl-7-nitrobenzo-2,1,3-thiadiazole (III). 5.5 g (0.025 mole) acetylaminomalonic ester (II) was added to a solution of 0.58 g (0.025 g at) Na in 30 ml dry EtOH at 45°-50° C, the mixture stirred for 1 hr at room temperature, then with stirring 6.9 g (0.025 mole) I in 60 ml dry benzene added, after which stirring was continued for 3 hr, at room temperature. The precipitate formed was filtered off, washed first with benzene, then with water, and the solvent was distilled off under reduced pressure from the benzene filtrate. 9.5 g (91%) of material was obtained; after recrystallizing from EtOH it formed white plates, mp 205° C. Found: N 14.05, 13.78; S 8.27, 8.22%. Calculated for $C_{16}H_{18}N_4O_7S$: N 13.60; S 7.80%.

Compounds Prepared

Compound No.	Mp, °C (crystallization solvent)	Formula	Found, %		Calculated, %		Yield, %
			N or Cl	S	N or Cl	S	
XI	163—164 (EtOH)	$C_{16}H_{18}N_4O_7S$	13.62 13.89	8.22 8.11	13.60	7.80	75
XV	141—142 (EtOH-H_2O)	$C_{22}H_{22}N_4O_6S$	14.81 14.73	8.40 8.49	15.10	8.90	58
XVI	98—100 (EtOH)	$C_{22}H_{20}Cl_2N_4O_4S$	Cl 17.61 17.59		17.20		51

4-(β,β-Dicarboethoxy-β-acetylamino) ethyl-7-aminobenzo-2,1,3-thiadiazole (IV). A mixture of 4.5 g (0.011 mole) compound III, 120 ml EtOH, 40 ml water, 3.6 g glacial AcOH, and 7 g Fe filings was heated for 2 hr on a boiling water bath with vigorous stirring, the products filtered hot, and the filtrate evaporated under reduced pressure. Yield 3.5 g (85%) material, which had mp 164.5°-165° C after recrystallizing from 20% EtOH. Found: N 14.53, 14.42; S 8.05, 8.17%. Calculated for $C_{16}H_{20}N_4O_5S$: N 14.82; S 8.47%.

4-(β,β-Dicarboethoxy-β-acetylamino) ethyl-7-(β-hydroxyethyl) aminobenzo-2,1,3-thiadiazole (V). A mixture of 0.5 g (1.3 mmole) amine IV, 20 ml 25% AcOH, and 5 ml ethylene oxide was kept at room temperature for 48 hr, excess ethylene oxide distilled off, and the residue neutralized with saturated $NaHCO_3$ solution. The red tarry material which separated was dissolved in $CHCl_3$, and run through an Al_2O_3 column, to give three layers: lowest—yellow middle—dark orange, top—yellow (insignificant). After cutting the column and extracting each section, with EtOH, an orange tarry mass was obtained from the top layer. It was not possible to isolate any individual compound from this layer. The lowest layer gave the amine IV mp 165°-166° C, the middle one a reddish product mp 131° C (ex AcOEt-petrol ether), giving a depressed mixed mp with the di-(β-hydroxyethyl) amino derivative VII. Found: N 13.44, 13.71; S 7.45, 7.81%. Calculated for $C_{18}H_{24}N_4O_6S$: N 13.20; S 7.54%.

4-(β,β-Dicarboethoxy-β-ethylamino) ethyl-7-ethyleniminobenzo-2,1,3-thiadiazole (VI).* 3 g (7 mmole) compound V was added in portions to 15 ml $POCl_3$, the mixture heated for 2 hr at 50° C, after which the products were stirred into a mixture of ice and water. The precipitate formed was filtered off, made alkaline with $NaHCO_3$, and extracted with $CHCl_3$. Yield 0.4 g material, mp 73°—74° C (ex benzene-petrol ether). Found: N 14.31, 14.20%. Calculated for $C_{18}H_{22}N_4O_5S$: N 13.85%.

4-(β,β-Dicarboethoxy-β-acetylamino) ethyl-7-di(β-hydroxyethyl) aminobenzo-2,1,3-thiadiazole (VII). 6 ml freshly-distilled ethylene oxide was added to a suspension of 3.5 g (9.2 mmole) IV in 25 ml 25% AcOH at 10° C, and the mixture left for 100 hr at room temperature. After filtering, excess ethylene oxide was distilled off under reduced pressure, and the residue carefully made alkaline with saturated $NaHCL_3$ solution. The precipitate formed (2.7 g) mp 78° C, was repeatedly recrystallized from water, to give yellow plates mp 134° C. Found: N 11.80, 11.82; S 7.34, 6.98%. Calculated for $C_{20}H_{28}N_4O_7S$: N 12.00; S 6.90%. When the experiment was repeated, compound V was obtained, and it proved impossible to isolate the compound mp 134° C.

4-(β,β-Dicarboethoxy-β-acetylamino) ethyl-7-di(β-chloroethyl) aminobenzo-2,1,3-thiadiazole (VIII). 2 g

*The IR spectrum of compound VI (fluorinated freon oil, IKS-14, NaCl prism) has bands at 860 and 1220 cm^{-1}, corresponding to ethylenimine ring absorption [6]. However, these data cannot be interpreted uniquely since the molecule in question contains groups (ester, amide) absorbing in an adjacent region [7]. The spectra obtained do not, however, contradict the present assumption.

(4.3 mmole) compound VII was added in portions to 10 g (65 mmole) $POCl_3$, and the resultant solution kept at 50°–60° C for 2 hr. Then the products were poured into water, and the whole extracted with $CHCl_3$, to give 0.8 g (37%) material, which on recrystallization from aqueous EtOH gave brownish needles mp 61°–62° C. Found: Cl 14.10, 14.38; S 6.78, 6.54%. Calculated for $C_{20}H_{26}Cl_2N_4O_5S$: Cl 14.00; S 6.30%.

4-(β-Amino-β-carboxy)ethyl-7-di(β-chloroethyl)aminobenzo-2,1,3-thiadiazole hydrochloride (IX). 1.2 g (2.4 mmole) VIII was boiled for 8 hr with 60 ml 20% HCl, the products filtered hot, and the filtrate vacuum-dried, to give 0.7 g material which after recrystallizing from dry EtOH formed pinkish crystals mp 161°–168° C (decomp). Found: Cl 27.60%. Calculated for $C_{13}H_{16}Cl_2N_4O_2S \cdot HCl$: Cl 27.30%.

5-(β-Carboxy-β-amino)ethyl-4-nitrobenzo-2,1,3-thiadiazole (XII) hydrochloride (XII). A mixture of 9 g (0.022 mole) XI and 200 ml 20% HCl was refluxed for 18 hr till the solid all dissolved. Then the solution was boiled with active charcoal, filtered hot, the filtrate evaporated to a viscous mass which was washed, first with EtOH and then with ether, 6 g material was obtained, which on recrystallizing from EtOH-ether gave yellow crystals mp 270° C, R_f 0.67. Found: N 18.45, 18.67; S 10.47, 10.14%. Calculated for $C_9H_8N_4O_4S \cdot HCl$: N 18.40; S 10.50%.

5-(β-Carbomethoxy-β-phthalimido)ethyl-4-nitrobenzo-2,1,3-thiadiazole (XIII). A mixture of 1.6 g (5.2 mmole) XII, 0.8 g (5.4 mmole) phthalic anhydride, and 16 ml dry pyridine was heated at 80° C for 2 hr, the pyridine distilled off, 2.5 ml Ac_2O added to the residue, the mixture held 1 hr at 80° C, then the products stirred into water. The 2 g brown powder which separated was dissolved in 20 ml dry MeOH, and the solution saturated with HCl gas at 60°C. On cooling, 2.2 g brown material separated, which was recrystallized from MeOH to give yellowish-brown plates mp 199°–200° C. Found: N 13.62, 13.83; S 7.57, 7.58%. Calculated for $C_{18}H_{12}N_4O_6S$: N 13.50; S 7.80%.

5-(β-Carbomethoxy-β-phthalimido)ethyl-4-aminobenzo-2,1,3-thiadiazole (XIV). 10 ml water, 1.5 g reduced Fe, and 2 ml AcOH were added to a hot solution of 3.5 g (8.5 mmole) XIII in 50 ml dioxane, the mixture heated for 1 hr 30 min on a water bath, and the products filtered hot. The filtrate was evaporated under reduced pressure, and the tarry residue triturated with water. Yield 2.3 g material, mp 161°–161.5° C (ex EtOH). Found: N 14.72, 14.84; S 8.82, 8.46%. Calculated for $C_{18}H_{14}N_4O_4S$: N 14.80; S 8.50%.

5-(β-Carboxy-β-amino)ethyl-4-di(β-chloroethyl)aminobenzo-2,1,3-thiadiazole (XVII). A mixture of 3.5 g (6.9 mmole) XVI and 80 ml 20% HCl was refluxed for 2 hr, cooled to 0° C, the phthalic acid which separated filtered off, and the filtrate vacuum-dried to give 0.8 g material mp 188° C (decomp, ex dry EtOH). R_f 0.73*. Found: Cl 27.83, 27.39; S 8.34, 8.59%. Calculated for $C_{13}H_{16}Cl_2N4O_2S \cdot HCl$: Cl 27.30; S 8.20%.

5-(β,β-Dicarboethoxy-β-acetylamino)ethyl-4-nitrobenzo-2,1,3-thiadiazole (XI), 5-(β-carbomethoxy-β-phthalimido)ethyl-4-di-(β-hydroxyethyl)aminobenzo-2,1,3-thiadiazole (XV), 5-(β-carbomethoxy-β-phthalimido)ethyl-4-di(β-chloroethyl)aminobenzo-2,1,3-thiadiazole (XVI), were prepared in the same way from, respectively, X, XIV, XV (see preparation of III, VII, VIII).

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*Compounds XII and XVII were chromatographed on slow-filtering paper (Leningrad paper factory), previously cleaned with a mixture of n-BuOH-iso-PrOH-HCl (2:1:1). The same mixture was used for developing. Separation time 10–12 hr, visualizer ninhydrin.