The Cyclodesulfurization of Thio-Compounds. Part XVII. Synthesis of some Novel 2-Substituted Amino-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones by Cyclodesulfurization of Thiosemicarbazides with Dicyclohexylcarbodiimide (DCCD)

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Received April 5, 1979

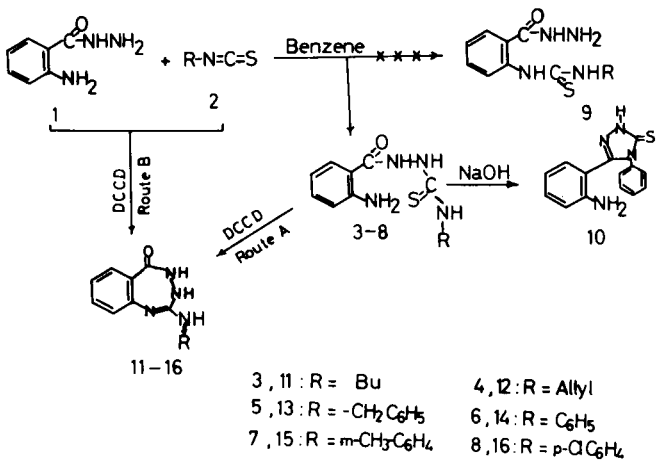
A simple method for the synthesis of a novel series of 2-substituted amino-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones (11-16) has been established through two routes. The first involving the cyclodesulfurization of the thiosemicarbazides (3-8) with DCCD and the second reacting mixtures of the acid hydrazide **1** with a variety of the isothiocyanates **2** and DCCD. The structure of the cyclized products was confirmed by nmr and mass spectra.

J. Heterocyclic Chem., **16**, 1435 (1979).

In the previous studies in this series, we have synthesized a variety of heterocyclic compounds, including isoquinoline (1), β-carboline (2), benzimidazole (3), and phenanthridine (4) derivatives through a newly established method involving the cyclodesulfurization of thioamides and *N,N'*-disubstituted thioureas with mercuric chloride (5). The studies have also been concerned with checking the efficacy of many desulfurizing agents in conducting the ring closure of thio-compounds. In this respect, we discovered that in those thio-compounds whose cyclization progresses through a carbodiimide intermediate (6,7), for example *N,N'*-disubstituted thioureas, the ring closure could be effected by mercuric oxide (8), mercuric acetate (8), alkyl iodides (9,10), dialkyl sulfates (11), or with DCCD (12).

The results obtained from the reactions with DCCD (12) encouraged the utilization of this reagent in the cyclodesulfurization of several 1-(*o*-aminobenzoyl)-4-substituted-3-thiosemicarbazides (**3-8**) into the corresponding 2-substituted amino-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones (**11-16**), route A, Scheme 1. Moreover, we were interested in applying the one-step method, recently established for the synthesis of azoles (12), to the synthesis of the same triazepinones by reacting mixtures of 1-(*o*-aminobenzoyl)hydrazine (**1**) and the isothiocyanate derivatives **2** with DCCD, route B, Scheme 1. The results of the study, as reported here, revealed the benefit of the applied cyclodesulfurization routes and established an efficient method for the synthesis of such new series of benzotriazepinone derivatives. Interest in the synthesis of the designated benzotriazepinones accompanies the recent trend of preparing a variety of benzotriazopinone derivatives (13-17) as central nervous system agents. The

Scheme 1



thiosemicarbazides **3-8** were prepared, in accordance with established methods (18-19), by treating 1-(*o*-aminobenzoyl)hydrazine (**1**) with the appropriate alkyl, aryl, or aralkylisothiocyanate (**2**) in refluxing ethanol. The products were identified by elemental analysis (Table 1), infrared and nmr spectra (Experimental). A further confirmation of the formation of the thiosemicarbazides **3-8**, rather than the corresponding thiourea **9** (20), was reached by cyclizing compound **6** with sodium hydroxide and comparing the melting point of the triazole derivative **10** produced with the reported one (19). The cyclodesulfurization of the thiosemicarbazides **3-8** was achieved by refluxing with 1.5 molar equivalents of DCCD in benzene. The separation of the cyclized products was dependent on the nature of the group attached to the exocyclic nitrogen atom. The products **14-16**, containing aryl

0022-152X/79/071435-04$02.25

Table I

Synthesized 1-(*o*-Aminobenzoyl)-4-substituted-3-thiosemicarbazides

Compound No.	Yield (%)	M.p. (°C)	Molecular formula	Elemental Analysis (%) Calcd./Found C	H	N	S	Cl
3	79	198	$C_{12}H_{18}N_4OS$			21.04		
						21.20		
4	77	130-131	$C_{11}H_{14}N_4OS$	52.78	5.64	22.38	12.81	
				52.80	5.70	22.20	12.30	
5	75	200	$C_{15}H_{16}N_4OS$	59.97	5.38	18.66	10.68	
				60.10	5.70	18.20	10.70	
6	84	167-168(a)						
7	80	162	$C_{15}H_{16}N_4OS$	59.97	5.37	18.66	10.68	
				60.10	5.50	18.20	10.50	
8	90	203	$C_{14}H_{13}ClN_4OS$			17.47	10.00	11.0
						17.20	9.70	11.6

(a) Reported (19), m.p. 167-168°.

Table II

Synthesized 2-Substituted Amino-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones

Compound No.	Cryst solvent	Yield (%) Route A	Yield (%) Route B	M.p. (°C)	Molecular formula	Elemental Analysis (%) Calcd./found C	H	N	Cl
11	Ethanol	69	65	220 (a)	$C_{18}H_{19}N_7O_8$	46.86	4.12	21.25	
						47.30	4.20	21.00	
12	Benzene/ light petroleum	72	67	115	$C_{11}H_{12}N_4O$	61.10	5.60	25.91	
						60.90	6.00	25.50	
13	Benzene	75	69	168	$C_{15}H_{14}N_4O$	67.65	5.31	21.05	
						67.40	5.60	20.60	
14	Acetone	82	79	263	$C_{14}H_{12}N_4O$	66.65	4.80	22.21	
						66.90	5.10	21.80	
15	Benzene	80	76	212	$C_{15}H_{14}N_4O$	67.65	5.31	21.05	
						67.70	5.20	21.00	
16	Acetone	85	82	277	$C_{14}H_{11}ClN_4O$	58.65	3.87	19.54	12.37
						59.10	3.80	19.50	12.80

(a) Separated as the picrate salt.

moieties, easily separated when the reaction mixtures were cooled to room temperature. In the case of butyl **11**, allyl **12** and benzyl **13** derivatives, the separation required shaking the mixtures with excess aqueous hydrochloric acid, neutralization of the acid solutions with aqueous sodium carbonate and extraction with chloroform. The allyl **12** and the benzyl **13** derivatives were separated as solid free bases on removal of the solvent while the butyl **11** derivative was obtained as an oil and converted into its picrate salt for identification. In respect to the preparation of the same triazepinones (**11-16**) in a one-step reaction (route B, Scheme 1) the mixture of the acid hydrazide **1** and equimolar amounts of alkyl, aryl, or aralkylisothiocyanate **2** were heated briefly in benzene, then treated with 1.5 molar equivalent of DCCD and refluxed until completion of cyclization. The reaction mixtures were separated as specified above giving the cyclized products in almost the same yields as those given by route A. Their structure was confirmed by mixed melting point determination, elemental analysis, ir, uv, nmr, and mass spectra (Table 2).

The nmr spectra of the cyclized triazepinones showed two protons attached to the ring nitrogen (N-3) and the exocyclic nitrogen as a singlet between 6.0 and 6.7 ppm (Table 3). This was split into two singlets in compounds **14** and **16**. The proton attached to N-4 in compounds **14** and **16** appeared as a singlet in the high field region between 9.6 and 10.05 ppm. In the benzyl derivative **13**, it appeared as a doublet around 8 ppm. The mass spectra of compounds **13**, **14** and **16** gave the parent ion as the base peak. A common fragmentation pathway for all the compounds was found to proceed through the loss of m/e 58, corresponding to CO-NH-NH-, from the parent ion and production of the ion A (Path A, Scheme 2). In compounds **14** and **16**, elimination of R-NH occurred and

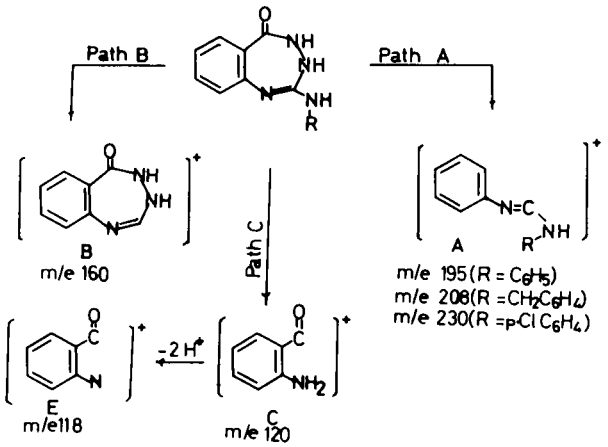
Table III

Nmr and Mass Spectra of Representative Benzotriazepinones

Compound No.	Nmr (Deuteriochloroform-DMSO-d_6)	Mass Spectra (70 eV) m/e (relative intensity)
13	4.51 (d, 2H, J = 3.5 Hz, CH_2), 6.30 (s, 2H, -N=C(-NH)-NH), 7.98 (d, 1H, J = 3 Hz, CO-NH)	266 (M^+, 100), 210 (2.3), 208 (4.5), 194 (3.4), 175 (2.3), 149 (1.7), 148 (2.8), 147 (3.4), 133 (10.2), 130 (7.5), 120 (64.6), 118 (19), 105 (11.5), 104 (30.7), 92 (26), 91 (89), 78 (10), 77 (11), 65 (26), 63 (7), 52 (6), 51 (10), 39 (11).
14	6.69 (s, split, 2H, -N=C(NH)-NH), 10.05 (s, 1H, -CO-NH),	252 (M^+, 100), 195 (11), 160 (10), 134 (2.5), 133 (3), 126 (4), 120 (23), 119 (8), 118 (56), 105 (4), 104 (18), 93 (18), 92 (18), 91 (8), 78 (8), 77 (18), 65 (13), 51 (8), 39 (6).
15	2.38 (s, 3H, CH_3), 6.0 (s, 2H, -N=C(-NH)-NH), 9.6 (s, 1H, CO-NH).	
16	6.68 (s, split, 2H, -N=C(NH)-NH), 10.05 (s, 1H, -CONH).	288 and 286 (M+2 and M^+, 35 and 100), 231 (3), 230 (8), 161 (3), 160 (19), 146 (3), 144 (7), 133 (5), 127 (6), 126 (5), 120 (22), 119 (10), 118 (89), 105 (4), 104 (11), 92 (11), 91 (8), 78 (3), 77 (5), 75 (5), 65 (11), 51 (5), 39 (4)

the ion B m/e 160 resulted (Path B). This fragmentation pattern did not appear in the spectrum of the benzyl derivative **13**. The ion C at m/e 120 was intense in compound **13** but much weaker in compounds **14** and **16**. The reverse was observed in the intensities of the ion E at m/e 118; it was much weaker in **13** than in compounds **14** and **16**.

Scheme 2



EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The nmr spectra were measured in the specified deuterated solvents, then treated with deuterium oxide to detect the exchangeable protons. The spectroscopic data were obtained on the instruments listed: ir (Beckmann 4210), uv (Beckmann 24), nmr (Perkin-Elmer R 32), and mass spectra (AEI. MS-50). Microanalysis was performed by the Microanalytical Unit, Faculty of Science, University of Cairo. Light petroleum used in this study has a b.p. of 40-60°.

Synthesis of 1-(*o*-Aminobenzoyl)-4-substituted-3-thiosemicarbazides (**3-8**), General Procedure.

To the mixture of 1-(*o*-aminobenzoyl)hydrazine (**1**) (0.5 g., 0.003 mole) in benzene (2 ml.), the equivalent amount of the appropriate alkyl, aryl, or aralkylisothiocyanate (**2**) was added and the mixture heated under reflux for 0.5 to 1 hour. The mixture first became clear and then deposited the products as reflux proceeded. After cooling, the products were filtered and crystallized from ethanol. They were identified by ir, nmr and elemental analysis (Table 1); ir (Nujol): ν max 3480-3140 (NH), 1665-1635 (C=O) and in the regions 1535-1510, 1360-1330, 1200-1120 and 961-910 cm^{-1} (N=C=S I, II, III, and IV amide bands respectively) (19).

The nmr for representative compounds (deuteriochloroform-DMSO-d_6): δ (ppm) are listed below.

Compound 3.

6.26 (s, 2H, NH_2), 6.7 (s, 1H, Bu-NH), 8.68 (s, 2H, CO-NH-NH-CS).

Compound 5.

4.84 (d, 2H, J=3.5 Hz, CH_2), 6.25 (s, 2H, NH_2), 6.5 (s, 1H, CH_2NH), 8.13 (m, 1H, NH-CS), 9.16 (s, 1H, CO-NH).

Compound 7.

2.33 (s, 3H, CH_3), 6.5 (s, mixed with aromatic protons, 2H, NH_2), 9.31 (s, 1H, NH-Ar), 9.51 (s, 2H, CO-NHNH-CS).

Preparation of 2-Substituted Amino-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones (**11-16**); General Procedure.

Route A. Through the Cyclodesulfurization of the Thiosemicarbazides (**3-8**) with DCCD.

Dicyclohexylcarbodiimide (DCCD) (0.003 mole) was added to the suspension of the thiosemicarbazides 3-8 (0.002 mole) in benzene (25 ml.) and the mixture heated under reflux for 7 hours. After cooling, some of the cyclized products, namely 2-anilino- (**14**), 2-*m*-toluidino- (**15**), and 2-*p*-chloroanilino- (**16**) derivatives, deposited as solids. They were filtered, crystallized from the proper solvents (Table 2) and identified as free bases. In case of the butyl (**11**), allyl (**12**) and benzyl (**13**) derivatives, no solid separated on cooling the reaction mixtures. Therefore, the mixtures were shaken with 10% aqueous hydrochloric acid solution (4 X 10 ml.), the acidic solutions neutralized with 10% aqueous sodium carbonate solution and the products which separated extracted with chloroform (3 X 20 ml.). Removal of the solvent gave compounds **12** and **13** as solids while compound **11** was obtained as an oil and converted into its picrate salt for identification.

Route B. One Step Reaction using 1-(*o*-Aminobenzoyl)hydrazine (**1**), the Isothiocyanates (**2**) and DCCD.

The equivalent amount of the appropriate isothiocyanate derivatives (**2**) was added to the suspension of the acid hydrazide **1** (0.76 g., 0.005 mole) and the mixture heated under reflux for 30 minutes, DCCD (1.54 g., 0.75 mole) was added and reflux continued for 7 hours. The final reaction mixtures were concentrated to small volumes, left to cool to room temperature and treated as specified in route A. The yields and physical constants of the products **11-16** are collectively recorded in Table 2. Nmr and mass spectra of representative examples of the cyclized products are summarized in Table 3; ir (Nujol): ν/max 3460-3160 (NH), 1680-1650 (C=O), and 1610 cm^{-1} (C=N); uv (ethanol): λ max (log ϵ): 215-220 (4.25-4.29), 245-255 (4.08-4.23), 280 (3.8-4.3) and 285 nm (3.8-4.3). No shift was observed on addition of acids or alkalies.

Acknowledgement.

The authors wish to acknowledge with appreciation the measurement of the nmr spectra by Miss Y. Cabaret, Université de Paris-Sud, Orsay, France, and the mass spectra by Dr. B. C. Das, Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, France.

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