Synthesis of 4-Amino-3-phenyl-2,3-dihydro-1,5-benzothiazepines and 3-Phenyl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)ones

J. B. Carr

The Biological Sciences Research Center, Shell Development Company, Modesto, California 95352

Received February 8, 1971

The bifunctional character of α,β-unsaturated carbonyl or nitrile compounds lends itself to the preparation of various heterocyclic ring systems by a Michael addition followed by cyclization. Krapcho and co-workers (1) have demonstrated the utility of such bifunctionality by the preparation of 2-methyl-3-phenyl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)one from 2-phenylcrotonic acid and 2-aminothiophenol. This paper deals with the similar utilization of atroponitriles (**1**) and atropic acids (**2**) for the synthesis of 4-amino-3-phenyl-2,3-dihydro-1,5-benzothiazepines (**6**) and 3-phenyl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)ones (**7**), respectively.

The Michael addition of a 2-aminothiophenol (**3**) to an atroponitrile (2) (**1**) (Scheme I) proceeded exothermically to give a β-(2-aminophenylthio)hydratroponitrile (**4**) (Table I). The acid catalyzed ring closure of **4** proceeded in refluxing ethanol to afford **6** (Table II). The chloro substituted 2-aminothiophenols were prepared by the procedure of Farrington and Warburton (3). Similarly, **3** reacted with an atropic acid (4) (**2**) (Scheme I) to afford a β-(2-aminophenylthio)hydratropic acid (**5**) (Table III). Cyclization of **5** with dicyclohexylcarbodiimide occured readily to give **7** (Table IV).

EXPERIMENTAL

Melting points are uncorrected and were taken on a Thomas-Hoover capillary apparatus. Structural determinations and purity were based on microanalyses and IR spectra. Since no unusual spectral features were observed for these compounds, no absorption peaks are listed. The preparative methods described herein are representative of the procedures used to obtain each class of compounds.

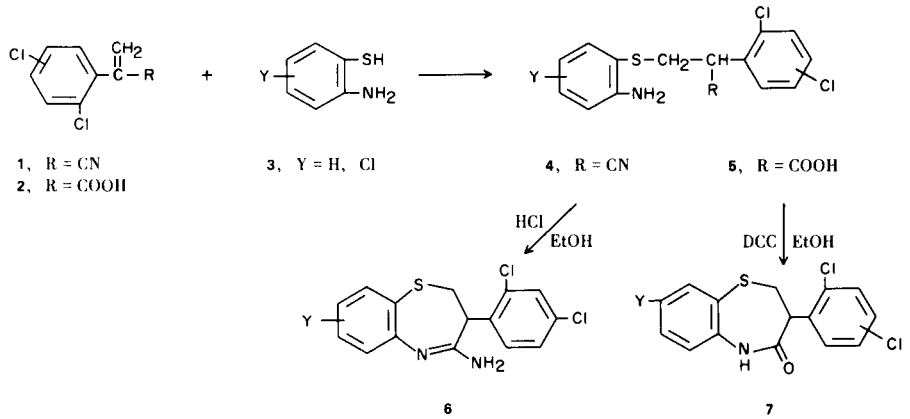
β-(2-Amino-4-chlorophenylthio)-2,4-dichlorohydratroponitrile (**4b**).

An ethanol solution of 5.5 g. (0.034 mole) of 4-chloro-2-aminothiophenol (3) and 6.8 g. (0.034 mole) of 2,4-dichloroatroponitrile (2) was refluxed for 1.5 hours, the solvent was stripped and the residual liquid was crystallized from an ether-hexane mixture to give 6.5 g. (53%) of a white compound (**4b**).

4-Amino-7-chloro-3-(2,4-dichlorophenyl)-2,3-dihydro-1,5-benzothiazepine (**6b**).

A solution of 5.8 g. (0.016 mole) of **4b** in 150 ml. of ethanol, containing 10 g. of hydrogen chloride gas, was refluxed for 24 hours. The reaction mixture was poured into a 5% sodium hydroxide solution and this solution was extracted with methylene chloride. The methylene chloride extracts were washed with water, dried with magnesium sulfate and stripped. The crude product was recrystallized from methylene chloride to give 4.0 g. (69%) of a white compound (**6b**).

SCHEME I



1, R = CN
2, R = COOH

3, Y = H, Cl

4, R = CN

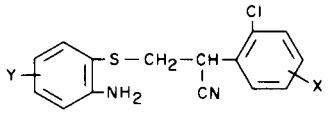
5, R = COOH

6

7

TABLE I

β-(2-Aminophenylthio)hydratroponitriles

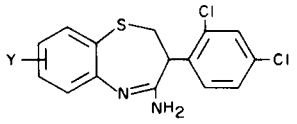


No.	X	Y	M.p., °C	Yield, %	Formula	Element	Analyses, % Calcd.	Found
4a	4-Cl	H	159-163	36	$C_{15}H_{13}Cl_3N_2S$ (a)	N	7.8	7.7
						Cl	29.6	29.4
						Cl^-	9.9	10.2
4b	4-Cl	4-Cl	114-116	53	$C_{15}H_{11}Cl_3N_2S$	N	7.9	7.8
						Cl	29.9	29.7
						S	9.0	9.0
4c	4-Cl	5-Cl	89-93	62	$C_{15}H_{11}Cl_3N_2S$	N	7.9	7.6
						Cl	29.9	30.1
						S	9.0	8.9
4d	5-Cl	H	164.5-166	72	$C_{15}H_{13}Cl_3N_2S$ (a)	N	7.8	7.7
						Cl	29.6	29.5
						Cl^-	9.9	9.6

(a) Isolated as the hydrochloride salt.

TABLE II

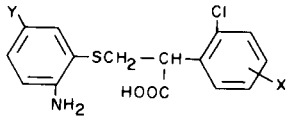
4-Amino-2,3-dihydro-3-phenyl-1,5-benzothiazepines



No.	Y	M.p., °C	Yield, %	Formula	Element	Analyses, % Calcd.	Found
6a	H	184-187	45	$C_{15}H_{12}Cl_2N_2S$	N	8.7	8.5
					Cl	21.9	21.6
					S	9.9	10.0
6b	7-Cl	195-198	69	$C_{15}H_{11}Cl_3N_2S$	N	7.9	7.6
					Cl	29.8	29.4
6c	8-Cl	182-185	53	$C_{15}H_{11}Cl_3N_2S$	N	7.9	7.6
					Cl	29.8	29.8

TABLE III

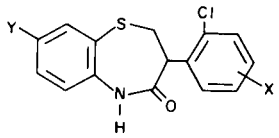
β-(2-Aminophenylthio)hydratropic Acids



No.	X	Y	M.p., °C	Yield, %	Formula	Element	Analyses, % Calcd.	Found
5a	4-Cl	H	127-130	85	$C_{15}H_{13}Cl_2NO_2S$	N	4.1	4.3
						Cl	20.8	20.6
5b	5-Cl	H	122-125	90	$C_{15}H_{13}Cl_2NO_2S$	N	4.1	4.1
						Cl	20.1	20.2
5c	4-Cl	5-Cl	151-153	31	$C_{15}H_{12}Cl_3NO_2S$	N	3.7	3.8
						Cl	28.3	28.5

TABLE IV

2,3-Dihydro-3-phenyl-1,5-benzothiazepin-4(5*H*)-ones



No.	X	Y	M.p., °C	Yield, %	Formula	Element	Analyses, % Calcd.	Found
7a	4-Cl	H	253-256	81	$C_{15}H_{11}Cl_2NOS$	N	4.3	4.3
						Cl	21.9	21.5
						S	9.9	9.7
7b	5-Cl	H	238-242	80	$C_{15}H_{11}Cl_2NOS$	N	4.3	4.3
						Cl	21.9	21.5
7c	4-Cl	8-Cl	242-244	55	$C_{15}H_{10}Cl_3NOS$	N	3.9	3.7
						Cl	29.7	29.6

β-(2-Aminophenylthio)-2,4-dichlorohydratropic Acid (**5a**).

A solution of 17.0 g. (0.078 mole) of 2,4-dichloroatropic acid (4) and 9.8 g. (0.078 mole) of 2-aminothiophenol in 200 ml. of ethanol was refluxed for 2 hours, the solvent was stripped and the residue was crystallized from a methylene chloride-hexane mixture to give 22.7 g. (85%) of a yellow compound (**5a**).

3-(2,4-Dichlorophenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)one (**7a**).

To an absolute ethanol solution of 8.2 g. (0.024 mole) of **5a** was added with ice bath cooling 4.95 g. (0.024 mole) of dicyclohexylcarbodiimide. An immediate white precipitate began to form. The reaction was exothermic and required occasional cooling. The reaction was allowed to stand at ambient temperature overnight. Filtration of the precipitate gave 10.3 g. of white crystals, m.p. 210-244°. Repeated extractions of the crystals with hot ethanol dissolved the more soluble dicyclohexylurea to give 6.3 g. (81%) of a white compound (**7a**).

Acknowledgment.

The author gratefully acknowledges the contributions of Mr. R. L. Franz for the synthesis of many of the compounds reported herein and to Mr. G. E. Pollard and Mr. P. M. Saliman of this laboratory for providing spectroscopic and analytical data.

REFERENCES

(1) J. Krapcho, E. R. Spitzmiller and C. F. Turk, *J. Med. Chem.*, **6**, 544 (1963).

(2) J. G. Kuderna, U. S. Patent 3,513,186 (1970) (to Shell Oil Co.).

(3) K. J. Farrington and W. K. Warburton, *Aust. J. Chem.*, **8**, 545 (1955).

(4) J. G. Kuderna and R. D. Skiles, personal communication.