The Reaction of Cycloalkanonhydrazones with Mercaptoacetic Acid. Synthesis of Novel *N*-Aminospirothiazolidinones

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Cycloalkanone hydrazones undergo condensation with mercaptoacetic acid to give predominantly the spirothiazolidinones. The structures of the products have been established on the basis of physico-chemical data. These compounds have shown promising antibacterial and antifungal activity.

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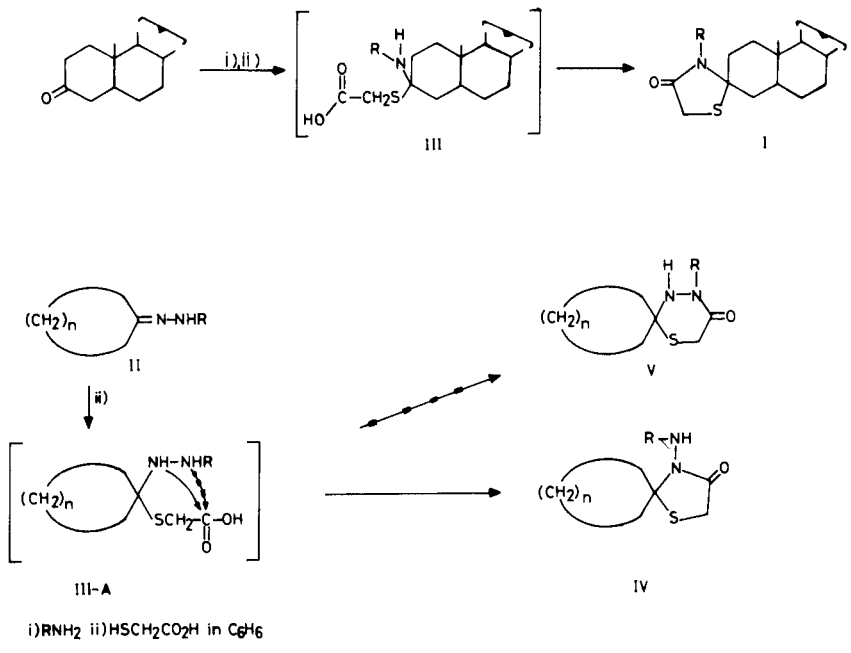
Reaction of cholestanone with different amines and mercaptoacetic acid has been reported by Paryzek *et al.* [1] to give the corresponding spirothiazolidines I. This cyclocondensation reaction of mercaptoalkanoic acids has been extended to several cycloalkanoneimines [2,3] and indole derivatives [4] because of the high versatility of the reaction and significant biological activities associated with the thiazolidine ring system. It has been suggested that the spiro compounds are formed *via* the intermediate acid III which then undergoes cyclocondensation of the carboxyl group with the imino-nitrogen. Cycloalkanone hydrazones II having a second nitrogen atom adjacent to the azomethine linkage offers an alternative site for cyclocondensation have received little attention. We have studied the reaction of cyclohexanone hydrazone (VI) with mercaptoacetic acid to investigate the two different reaction possibilities, *viz*, a) attack on the carboxyl group by the imino nitrogen atom forming a thiazolidine ring IV or b) attack by the second hydrazino nitrogen atom affording a thiadiazine ring system V.

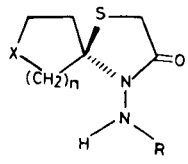
Results and Discussion.

Cyclohexanone phenyl hydrazone (VI) was reacted with mercaptoacetic acid by refluxing in benzene while removing the water formed in the reaction through azeotropic distillation. Removal of the solvent afforded a single product in 80% yield. The same product was obtained in excellent yield by refluxing cyclohexanone, phenylhydrazine and mercaptoacetic acid in benzene.

The structure of the product was established as 4-anilino-1-thia-4-azaspiro[4.5]decan-3-one (VII) on the basis of elemental analysis and spectral data and finally by an unambiguous independent synthesis of IX; ms: M^+ m/e 262. The ir spectrum (ν, potassium bromide) exhibited the carbonyl absorption at 1690 cm^{-1} suggesting it to be a spirothiazolidinone [3]. In the ^1H nmr spectrum (δ, deuteriochloroform) the 2-methylene signal appeared at 3.60 which is in agreement with the values reported for similar spirothiazolidines [3]. The cyclohexanone methylene envelope appeared between 1.40 and 2.20 while the aromatic

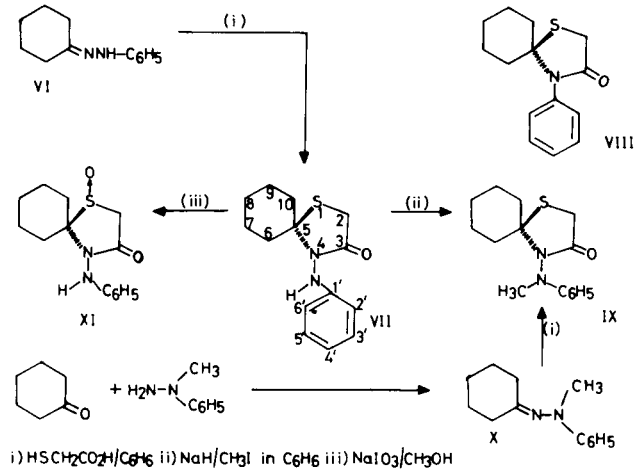


Table



Compound No.	R	n	X	Formula	Analysis % Carbon Calcd.	Carbon Found	Nitrogen Calcd.	Nitrogen Found	(ν) C=O	Mp °C	Yield %
1	Phenyl	2	CH_2	$C_{14}H_{18}N_2OS$	64.12	63.89	10.69	10.52	1690	171	80
2	2-Pyridyl	2	CH_2	$C_{13}H_{17}N_3OS$	59.31	59.02	15.97	15.65	1690	165	78
3	2-Quinolyl	2	CH_2	$C_{17}H_{19}N_3OS$	65.17	64.95	13.42	12.98	1685	192	75
4	Methyl	2	CH_2	$C_9H_{16}N_2OS$	54.00	53.64	14.00	13.85	1660	141	85
5	$SO_2C_6H_5$	2	CH_2	$C_{14}H_{18}N_3O_3S_2$	51.53	51.25	8.59	8.43	1690	204	80
6	Phenyl	1	CH_2	$C_{13}H_{16}N_2OS$	62.90	62.63	11.29	11.08	1690	157	80
7	2-Pyridyl	1	CH_2	$C_{12}H_{15}N_3OS$	57.83	57.54	16.87	16.69	1690	124	78
8	2-Quinolyl	1	CH_2	$C_{16}H_{17}N_3OS$	64.21	63.96	14.05	14.10	1690	low melting solid	75
9	Methyl	1	CH_2	$C_8H_{14}N_2OS$	51.61	51.37	15.05	14.85	1660	88	85
10	Phenyl	2	N-CH_3	$C_{14}H_{19}N_3OS$	60.65	60.58	15.16	14.79	1690	116	80
11	2-Pyridyl	2	N-CH_3	$C_{13}H_{18}N_4OS$	56.11	55.68	20.14	20.06	1690	148	78
12	2-Quinolyl	2	N-CH_3	$C_{17}H_{20}N_4OS$	62.19	61.59	17.07	16.85	1685	229	75

protons had the pattern of aniline appearing at 6.80-7.00 (3H) and 7.20-7.40 (2H). Conclusive proof was obtained from its ^{13}C nmr spectrum (δ, deuteriochloroform) which had the carbonyl carbon at 170.00, a low intenstiy signal at 73.47 attributable to the spiro carbon (C-5), the thiazolidine methylene carbon (C-2) at 28.93 alicyclic carbons C-6 and C-10 at 37.01, C-7 and C-9 at 24.43 and C-8 at 23.24. These values are in agreement with those of the 4-phenyl derivative VIII [5]. The aromatic ring carbon showed a pattern similar to that of the amino substituted phenyl moiety comprising a quarternary carbon signal at 146.99 assignable to C-1′, two signals at 129.06 and 113.72 due to C-3′ and C-5′ and C-2′ and C-6′, respectively, and the C-4′ signal at 121.31. It has been reported [6] that the amino substituent on the phenyl ring causes a significant deshielding effect on the substituted carbon (−18 ppm with respect to the benzene chemical shifts) while shielding the *ortho* and *para* carbons. If it were to be a thiadiazine system V the deshielding effect suffered by C-1′ would be much lower (−8 to 11 ppm). This was evidenced in the case of VIII where C-1′ appeared at 136.26.



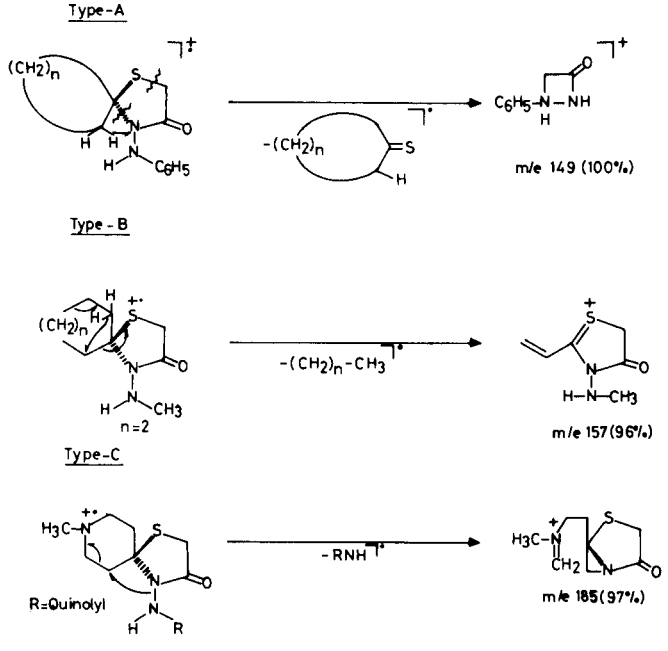
Finally, methylation of VII with methyl iodide afforded the methyl derivative IX which was identical with the *N*-methyl-*N*-phenyl compound prepared unambiguously from *N*-methyl-*N*-phenyl hydrazone X.

Oxidation of VII with sodium *meta* periodate in methanol yielded the sulfoxide XI. Attempted sulfone preparation was unsuccessful. When VII was refluxed with 10% hydrochloric acid the ring system was unstable and decomposed into several products, however, the compound was unaffected by refluxing with alkali.

With a view to studying the substituent effects on the reaction mode and also the structure activity relationships, we have investigated the reaction with different substituted hydrazines such as alkyl and heterocyclic hydrazines. It is interesting to note that change of substituents in the hydrazine moiety or the cycloalkyl part (cyclohexanone to cyclopentanone and *N*-methylpiperidone) has not altered the reaction mode and resulted in the formation of the corresponding thiazolidines as sole products. The different 3-substituted aminospirothiazolidines thus prepared are listed in the Table.

Mass fragmentation of the compounds under study, fol-

lows three major paths, A, B and C. The substituent at the 4-position appears to have a marked influence on the fragmentation pattern. Compounds with a 4-arylamino substituent show type A fragmentation whereas the methylamino compounds undergo fragmentation in the alicyclic ring (Path B). In the case of the *N*-methylpiperidino compounds the major fragment is at m/e 185 formed by the elimination of a substituent at the 4-position (Type C).



The preliminary screening results of these compounds revealed promising antifungal and antibacterial activity.

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EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. The ir spectra were recorded on Perkin-Elmer 283E model spectrometer. Mass spectra were taken on Micromass 70-70H and the ^{13}C nmr and ^{1}H nmr spectra were recorded on JEOL JNM-FX 90Q FT NMR spectrometer with a dual probe in deuteriochloroform and using TMS as the internal standard.

General Procedure for the Synthesis of Spirothiazolidinones. Method A.

A mixture of (0.02 mole) of cycloalkanone hydrazones **1-12**, (cycloalkanone hydrazones were prepared following the standard procedure by reacting equimolar amounts of cycloalkanones and the corresponding hydrazines in alcohol) and 0.02 mole of mercaptoacetic acid in (100 ml) of benzene and refluxed for 20 hours and the water formed was removed azeotropically using benzene. The solvent was removed under reduced pressure. The residue was washed with 10% sodium carbonate solution (100 ml) followed by water and recrystallized from methanol. Melting points, yields and analyses are listed in the Table.

Method B.

A mixture of cycloalkanones (0.02 mole), the corresponding hydrazines (0.02 mole) and mercaptoacetic acid (0.02 mole) in benzene (100 ml) was refluxed and the water generated was collected in an azeotropic collector for a period of 20 hours. The solvent was removed, the residue was washed with 10% sodium carbonate solution (100 ml) followed by water and recrystallised from methanol.

Methylation of VII.

A mixture consisting of compound VII (0.01 mole, 262 mg), methyl iodide (10% molar excess, 1 ml) and sodium hydride (0.01 mole, 24 mg) in dry benzene (25 ml) was heated and refluxed for 4 hours. The precipitate was removed by filtration and the filtrate was concentrated under reduced pressure. The crude product was crystallised from methanol, mp 101°, yield 80% (221 mg); ir (potassium bromide): ν max 1690 cm^{-1} (C=O); ^{1}H nmr: 1.6-2.3 (10H, m), 3.33 (3H, s), 3.47 (2H, s), 6.7-7.0 (3H, m), 7.1-7.3 (2H, m).

Anal. Calcd. for $C_{15}H_{20}N_2OS$: C, 65.22; H, 7.25; N, 10.14. Found: C, 65.14; H, 7.15; N, 10.16.

Preparation of Sulfoxide.

Spirothiazolidinone VII (0.01 mole, 2.62 g) was dissolved in 30 ml of methanol. The solution was cooled to 5° and an aqueous methanolic solution of sodium *meta*-periodate (3.21 g, 0.015 mole) in 30 ml of aqueous methanol was added dropwise with stirring during a period of 30 minutes. The reaction mixture was stirred at 5° for one hour. The precipitated sodium iodide was removed by filration and the filtrate was extracted with chloroform. The chloroform was dried over anhydrous sodium sulfate. The solvent extract was removed under reduced pressure and recrystallised from methanol, mp 139°, yield 1.95 g (70%); ir (potassium bromide): ν max 1690 cm^{-1} (C=O), 1050 (S→O), 3220 cm^{-1} (NH); nmr 1.4-2.2 (10H, m), 3.6 (2H, s), 6.2 (1H, s), 6.8-7.0 (3H, m), 7.2-7.4 (2H, m).

Anal. Calcd. for $C_{14}H_{18}N_2O_2S$: C, 60.43; H, 6.47; N, 10.07. Found: C, 60.45; H, 6.34; N, 10.09.

4-(*N*-Methyl-*N*-phenyl)-1-thia-4-azaspiro[4.5]decan-3-one (IX).

A mixture of cyclohexanone *N*-methyl-*N*-phenylhydrazone (0.01 mole, 2.02 g) and mercapto acetic acid (0.01 mole, 0.94 g) in benzene (100 ml) was refluxed for 20 hours during which time the water formed was removed azeotropically using benzene. The solvent was removed under reduced pressure. The residue was washed with 10% sodium carbonate solution (100 ml) followed by water and recrystallised from methanol; mp 101° yield (80%, 2.21 g); ir (potassium bromide): ν max 1690 cm^{-1} (C=O); ^{1}H nmr: 1.6-2.3 (10H, m), 3.33 (3H, s), 3.47 (2H, s), 6.7-7.0 (3H, m), 7.1-7.3 (2H, m).

Anal. Calcd. for $C_{15}H_{20}NOS$: C, 65.22; H, 7.25; N, 10.14. Found: C, 65.14; H, 7.15; N, 10.16.

REFERENCES AND NOTES

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[5] The ^{13}C nmr data of spirothiazolidinones is not available in the literature. Therefore, we have prepared the 3-phenyl derivatives VIII according to ref [3] and recorded the ^{13}C nmr spectrum for comparison; 170.78 (C=O), 73.05 (C-5), 31.26 (C-2), 136.26 (C-1'), 128.35 (C-4'), 129.00 (C-2'-C-6'), 130.09 (C-3' and C-5'), 24.00 (C-6 and C-10), 38.90 (C-7 and C-9) and 23.19 (C-4).

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