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Nuclear Magnetic Resonance of Benzobisheterocyclic Compounds

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The nuclear magnetic resonance spectra of forty-nine benzobisheterocyclic compounds, containing various heterocycles, were determined. The observed spectral data made possible the elucidation of the structure and also clarified the influences of the heterocyclic substituents and of heterocyclic rings on chemical shift values of the aromatic protons.

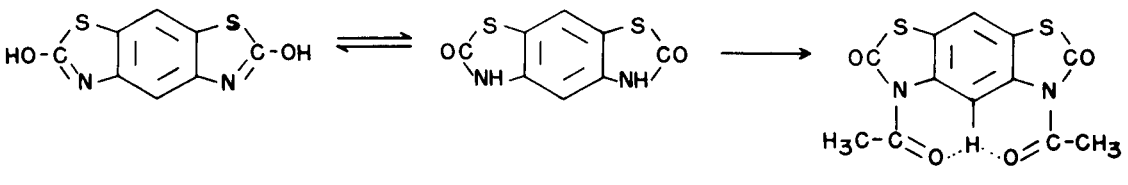
The synthesis of benzobisheterocyclic compounds on which we have previously reported in a number of papers, may lead to angular as well as to linear structures, depending on the course of cyclization as influenced by the orienting effects of functional groups. The structures of some benzobisheterocycles were assigned by us based upon alternative syntheses, however this method may not be generally applicable. Furthermore, in the benzobisheterocyclic field, U.V. spectroscopy cannot always give reliable information about an angular or linear structure (2,3).

In these researches, NMR spectroscopy constitutes the most simple and straight forward method for definitive resolution among the possible structures. Moreover, the influence of a number of heterocycles, with or without substituents, on the chemical shifts of the aromatic protons have been clarified.

As a result of the examination of a large number of spectra of benzobisheterocycles, we were able to decide between an angular and a linear structure by examining the pattern of aromatic proton signals. Indeed, in compounds possessing a linear structure (Table I), the two aromatic protons are in a *para*-relationship and because of the low value of their coupling constants ($J_{AB} \cong 0 - 1$ c.p.s.) give a two singlet pattern. In the compounds of linear structure in Table II, the protons referred to above are perfectly equivalent (excepting 31, 32 and 33), being flanked by a sulfur and a nitrogen atom, giving rise to a single signal. Compounds of angular structure (Table III) are characterized by a mutual *ortho*-relationship of the two protons considered and as a consequence, their NMR spectra show the presence of an AB-type quartet with the characteristic J-value of 9 c.p.s. Compounds 38 and 45 are however exceptional since they give a two-proton singlet (*i.e.*, both hydrogens have the same δ value); if however, the spectrum of compound 38 is taken in deuteriochloroform solution, different δ values are measurable and the characteristic AB-type pattern develops. Such a device could not be applied to compound 45, because of its insolubility in deuteriochloroform, however the acetyl derivative of compound 45, because of the altered charge distribution in the molecule, shows the expected quartet.

As far as the aromatic proton δ values for the

8 a 8 b



10 a 10 b 11

reported compounds are concerned, a considerable influence is exerted by substituents attached to the heterocyclic nucleus as well as by the heterocyclic-type nucleus and by the pattern of the heteroatoms linked to the benzene ring, however the signal type remains constant in each series of compounds (4).

Benzobisthiazoles.

Spectra of unsubstituted or methyl-substituted isomeric benzobisthiazoles have been recorded in trifluoroacetic acid as well as in deuteriochloroform solution. It is known that benzobisthiazoles behave as monoacid bases (5). However in trifluoroacetic acid solution, in which the molecule is protonated, there is no differentiation of the chemical shift of the aromatic protons (benzobisthiazoles in Table II) and of the protons of the thiazole substituents, which appear in the spectra as a single peak. It may then be concluded that there is no difference in the electronic density. This phenomenon could be also interpreted as if both nitrogen atoms were protonated (see experimental). In both solvents the spectra of benzobisthiazoles are very similar; however the NMR signals in trifluoroacetic acid solution are shifted further downfield than in deuteriochloroform. In the benzobisthiazoles, 1 and 2, the relative chemical shift is greater than that observed for other isomeric compounds which averages about 0.6 p.p.m.

The protons of the thiazole substituents exhibit similar chemical shifts in the three series. This fact indicates that they are not unduly influenced by the disposition of the hetero atoms in the benzene nucleus; the above disposition on the contrary strongly influences the protons in the benzenoid ring. Moreover electron-acceptor substituents induce chemical shifts downfield while electron-donor substituents produce upfield shifts of the aromatic protons. In view of the above fact it is not possible to use unsubstituted benzobisthiazoles as reference standards because in those compounds the chemical shifts of the aromatic protons are situated downfield with respect to the corresponding protons of all the substituted derivatives. This fact is probably due to the accentuated electron-attractive characteristics of the thiazole nucleus unperturbed by substituents, and also to the greater aromatic character of unsubstituted benzobisthiazoles, because of their inability to sustain a ring current. Therefore, only by simple comparison with the unsubstituted benzobisthiazoles is it possible to observe that the phenyl group causes an upfield shift in the aromatic protons of 0.23 and 0.11 p.p.m. in compound 6, of 0.11 p.p.m. in compound 29 and 0.06 p.p.m. in the angular compound 36, while the methyl group causes an upfield shift of 0.29 and 0.55 p.p.m. in compound 2, of 0.24 p.p.m. in compound 28 and of 0.19 p.p.m. in the angular compound 35.

Protonation of one of the two nitrogen atoms does not produce a significant effect on the chemical shift of the aromatic protons (as in compounds 3 and 5), while a noticeable, although small, effect is visible in the left part of the spectrum of the substituent on the protonated heterocycle: this fact may be taken as a confirmation of the above statement. The presence of an unsaturated substituent, as in compound 4, causes a displacement of the signal upfield due to the proton lying between the two nitrogen atoms; this effect is reversed by protonation (compound 5). The amino substituent (compound 8) may give rise to two tautomeric forms 8a and 8b. Examination of the NMR spectrum of this compound shows that in trifluoroacetic acid solution, only form 8a exists; the aromatic protons are shifted 1.50-1.59 p.p.m. upfield, with respect to the values for the unsubstituted compounds. If the amino group is acetylated, the signals ascribable to the above protons are shifted again downfield. This occurs in all of the instances examined. For compound 10 two tautomeric formulas 10a and 10b must also be taken into consideration. The observed chemical shift values for the aromatic protons in this compound, if compared with those of compounds 12 and 13, are in agreement with thiazole structure 10b, as already demonstrated by one of us with U.V. spectroscopy (2). In fact these values are 7.70 and 7.52 p.p.m., and hence notably lower than those found for the other compounds of the series. This fact is readily explained on the basis of the non basic character of the nitrogen atom. In the acetyl derivative 11, we note a shift towards the left of the 4-proton of 1.95 p.p.m. with respect to 10; this effect is due to the introduction of the electronegative acetyl substituent on the nitrogen atom. We may also propose that the unusually large shift is partly due to an increased rigidity of the molecule as a result of hydrogen bonding. These findings substantiate the structure attributed to 10.

The spectra of compounds 12, 13, 14 and 15 support the structures assigned to them on the basis of their synthesis. The chemical shift values are in good agreement with the above considerations. It is noteworthy that in compounds belonging to the angular series, the asymmetric disposition of the two heterocycles on the benzene nucleus causes a slight differentiation of the chemical shifts of the two substituents.

Thiazoloketodihydrothiazinobenzenes.

NMR spectra are markedly affected by substituting the thiazole ring with a ketodihydrothiazine ring. Aromatic proton signals are shifted upfield, this shift being over 1 p.p.m. in the unsubstituted derivatives or those bearing a methyl or a phenyl group (Table I). Smaller shifts are observed in the amino derivatives.

In the thiazoloketodihydrothiazinobenzenes in Table II, the two aromatic protons are no longer equivalent, and two distinct singlets arise. Likewise in this series, the signals are shifted upfield, although less than 1 p.p.m. The six angular compounds in Table III exhibit the same behavior.

In all the compounds of this kind considered, it may be further noted that the methylene and the imidic NH of the ketodihydrothiazinobenzene nucleus are influenced to a limited extent by both the thiazole substituents and the benzobisheterocycle structure. The protons of the thiazole substituent are themselves shifted upfield, hence it is evident that the positive effect of the benzothiazole residue (6) is lowered by the opposite effect produced by the ketodihydrothiazine heterocycle linked to it. We can logically deduce the existence of a mutual influence between the two heterocycles. It is known, indeed, that the ring currents in one ring of a fused aromatic system affect the line positions of protons in the other ring (7, 8). In the present case such an effect is transmitted through the benzene ring.

Miscellaneous benzobisheterocycles.

Linear compounds are reported in Table I and angular compounds are reported in Table III.

In compound 21 (benzobisketodihydrothiazine), the aromatic protons are shifted upfield about 2.02 and 2.82 p.p.m. compared with the shift of the benzobisthiazole 1. It is logical to suppose that the larger shift should be that of the aromatic proton between the two imidic nitrogen atoms (compound 21). Since in the thiazoloketodihydrothiazinobenzene, 16, the shift upfield is about 1.35 p.p.m. for both protons, we must conclude that the whole molecule is influenced by the basic nitrogen atom of the thiazole moiety. When the latter is lacking, remarkable shifts are experienced by the proton flanked between the two nitrogen atoms. This shift, in the cases reported, is 0.8 p.p.m. higher than that of the hydrogen flanked by the two sulfur atoms. The aromatic protons of the linear compounds 22, 25 and 26, containing the thiazaepine nucleus, are shifted downfield with respect to the benzobisketodihydrothiazine 21. This observation confirms the character of the thiazaepine nucleus, since it is known to be a weaker electron-donor than the thiazine ring. It is then obvious that the proton between the two sulfur atoms is shifted to a greater extent. The dithiane nucleus in compound 23 shifts the aromatic protons 0.26 p.p.m. downfield with respect to 21. In the spectrum of thiazinoquinoline, 24, the signals of the aromatic protons are considerably downfield compared to those in compound 16. This effect can be predicted easily if the stronger basic character of pyridine with respect to thiazole is considered.

As far as angular heterocyclic compounds are concerned (Table III) we note that the isothiazole ring (compound 43) shows an effect similar to that of thiazole, while the thiophene ring (compound 44), as expected, shifts the aromatic protons upfield. Another heterocycle taken into consideration in this work is α-thiopyrone; in the thiazolothiocoumarines, 45 and 46, the aromatic protons have the same δ value, but, as mentioned above, the signal at 7.86 p.p.m. is a singlet (area = 2 protons), and hence in this compound, both protons are equivalent. The α-thiopyrone ring, as far as its influence on aromatic protons shifts is concerned, occupies an intermediate position between thiazine and thiazole. The spectra of the imidazolothiocoumarines, 47 and 48, show that the presence of a methyl substituent on the imidazole ring has, with respect to the parent compound 47, the same effect reported above for the thiazole compounds. Finally, the spectrum of benzobisthiochromanone, 49, described as linear, shows a quartet centered at δ = 7.66 (J = 9 c.p.s.); this points to an angular structure for it. This finding supports the preferential formation of angular rather than linear structures (9).

EXPERIMENTAL

All NMR spectra were determined in the solvents indicated with tetramethylsilane as the internal reference using a Varian A-60 spectrometer. The melting points are uncorrected.

2,3-Tetrahydro-4(5*H*)-ketothiazepine[7,6-g]benzo-2*H*-(1,4)-thiazin-3(4*H*)-one (22).

This compound was prepared from 2,4-dinitro-1,5-dichlorobenzene by first substituting one chlorine atom with a thiopropionyl moiety, then the second chlorine atom with a thio acetyl group. Reduction of the dinitro acid obtained, gave an amino acid which by cyclo-condensation gave the desired product.

2,4-Dinitro-5-chlorobenzenethiopropionic Acid.

Dinitrochlorobenzene (10 g.) was dissolved in ethanol (150 ml.) and sodium bicarbonate (10.5 g.) and β-thiopropionic acid (4.5 g.) were added and heated on a steam bath for about 1 hour. The ethanol was removed by distillation until only a small volume remained and then water was added. The solution was filtered and the filtrate was acidified with dilute hydrochloric acid. A waxy precipitate that solidifies readily separated. The product was recrystallized from ethanol, yellow needles, m.p. 164-166°.

Anal. Calcd. for $C_9H_7ClN_2O_6S$: N, 9.14; S, 10.46. Found: N, 9.25; S, 10.53.

2,4-Dinitrobenzene-1-thiopropionic-5-thioglycolic acid.

To a solution of 2,4-dinitro-5-chlorobenzenethiopropionic acid (10 g.) in ethanol (200 ml.), sodium bicarbonate (9 g.) and thioglycolic acid (3.1 g.) were added and the mixture was heated on a steam bath for 1 hour. The precipitate that forms after cooling was filtered and dissolved in water, treated with charcoal, and precipitated with hydrochloric acid. The product obtained was then recrystallized from acetic acid to give yellow needles melting at 224°.

Anal. Calcd. for $C_{11}H_{10}N_2O_8S_2$: S, 17.68. Found: S, 17.81.

2,4-Diaminobenzene-1-thiopropionic-5-thioglycolic Acid and 6-Aminobenzo-2*H*-(1,4)-thiazin-3(4*H*)-one-7-thiopropionic Acid.

To a stirred solution of the above dinitrobenzenethiopropionicthioglycolic acid (20 g.) in concentrated ammonium hydroxide, was slowly added an aqueous solution of ferrous sulfate (215 g.), taking care that the resulting mixture always remained strongly alkaline. The solution was filtered and the filtrate was acidified (*p*H = 4). A mixture of the corresponding diamino acid and the benzodihydroketothiazine-aminothiopropionic acid was obtained and extracted with ethanol. The diamino acid was easily recrystallized from ethanol, white prisms, melting at 217°.

Anal. Calcd. for $C_{11}H_{14}N_2O_4S_2$: S, 21.24. Found: 21.38.

This diamino acid, heated above the melting point, was rapidly transformed into the benzodihydroketothiazine-aminothiopropionic acid.

The portion insoluble in ethanol was recrystallized from aqueous ethylene glycol to yield the benzodihydroketothiazine-aminothiopropionic acid, m.p. > 300°. The product was soluble in both acidic and basic media.

Anal. Calcd. for $C_{11}H_{12}N_2O_3S_2$: S, 22.58. Found: S, 22.70.

The mixture of the two products obtained from the above reduction

TABLE I (a)*

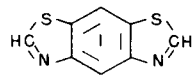
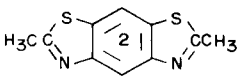
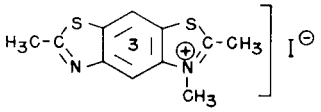
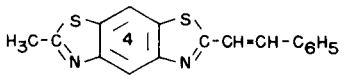
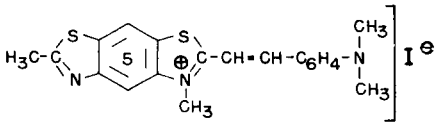
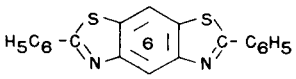
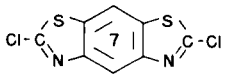
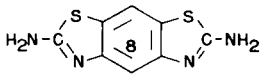
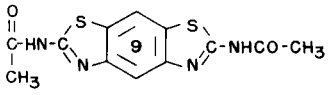
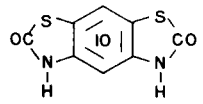
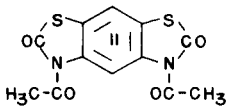
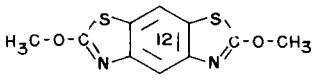
Compound	Reference	Aromatic Protons (c)		Thiazole Substituent	Other Protons
	(5)	9.36	9.66	10.58	
		(e) 8.50	8.92	9.10	
	(5)	9.07	9.11	3.39	
		(e) 8.18	8.50	2.85	
	(5)	9.06	9.16	3.36 3.44 N-CH_3 = 4.51	
	(5)	9.04	8.99	3.39	
	(5)	9.04	9.16	3.43 N-CH_3 = 4.63	-$N(CH_3)_2$ = 3.51
	(5)	9.13	9.55	~8 (f)	
	(10)	8.60	8.88		
	(5, 10)	7.86	8.07	8.45 (b)	
	(10)	8.57	8.68	2.64	
	(10)	7.70	7.52		
	(10)	7.58	9.47	2.92	
	(10)	8.61	8.71	4.71	

TABLE I (Continued)

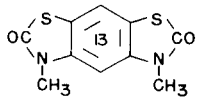
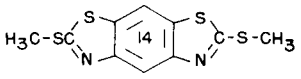
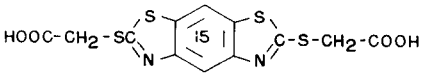
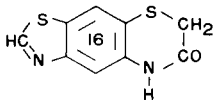
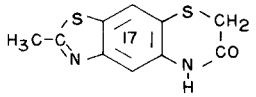
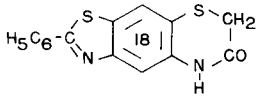
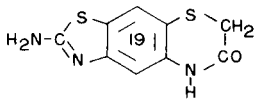
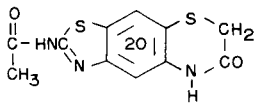
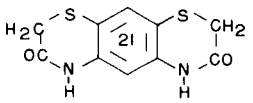
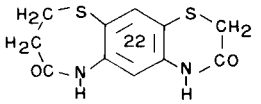
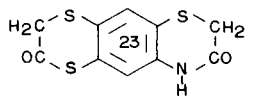
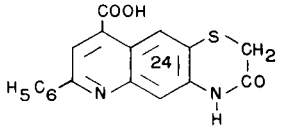
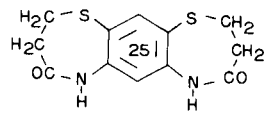
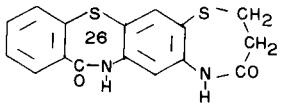
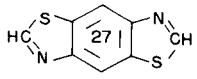
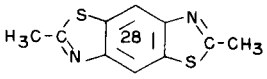
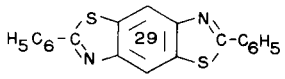
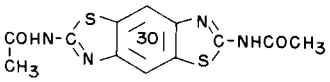
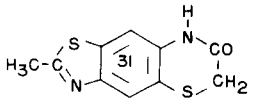
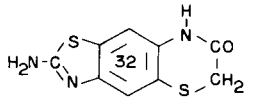
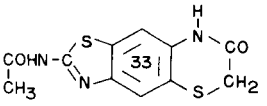
Compound	Reference	Aromatic Protons (c)		Thiazole Substituent	Other Protons
	(10)	7.72	7.24	$N-CH_3$ = 3.72	
	(10)	8.68	8.80	3.14	
	(10)	8.74	8.86	$-CH_2-$ = 4.52	
	(11)	8.01	8.30	10.13	$-CH_2-$ = 3.78 -NH-CO = 10.15
	(11)	7.76	8.09	3.21	$-CH_2-$ = 3.71 -NH-CO = 10.04
	(11)	between 7.70-8.20		~8 (f)	$-CH_2-$ = 3.74 -NH-CO = 10.11
	(11)	7.27	7.64	8.20 (b)	$-CH_2-$ = 3.64
	(11)	7.69	8.01	2.60	$-CH_2-$ = 3.70
	(5, 12)	7.34	6.84		$-CH_2-$ = 3.61 -NH-CO = 9.80
		7.62	7.00		$-CH_2-$ = 3.62 $-(CH_2)_2-$ = 3.18 (g)
	(13)	7.60	7.10		$-CH_2-$ = 3.58 -NH-CO = 9.90 $-CH_2-$ = 3.65
	(14)	8.83	9.21		$-CH_2-$ = 3.87 -NH-CO = 10.50

TABLE I (Continued)

Compound	Reference	Aromatic Protons (c)		Thiazole Substituent	Other Protons
	(15)	8.03	7.25		$-(CH_2)_2-$ = 3.23 (g)
		7.97	7.31		$(-CH_2)_2-$ = 3.20 (g) -NH-CO- = 9.58 $-C_6H_4-$ = 7.64 (f)

* See bottom of Table III for legend.

TABLE II (a)*

Compound	Reference	Aromatic Protons (c)		Thiazole Substituent	Other Protons
	(16)	8.22 (e)	8.79	9.01 (e) 10.44	(e) (e)
	(17)	7.95 (e)	8.55	2.85 (e) 3.39	(e) (e)
	(17)	8.68		~ 8 (f)	
	(18)	8.24		2.64	
	(16)	7.79	8.09	3.21	$-CH_2-$ = 3.71 -NH-CO = 10.15
	(16)	7.41	7.56	8.20 (b)	$-CH_2-$ = 3.56
	(16)	7.68	7.94	2.62	$-CH_2-$ = 3.71 -NH-CO = 10.03

* See bottom of Table III for legend.

TABLE III (a) *

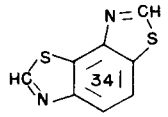
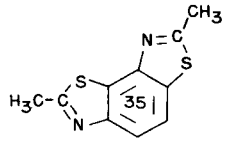
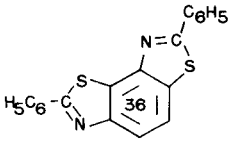
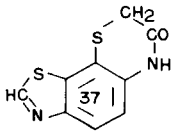
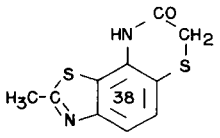
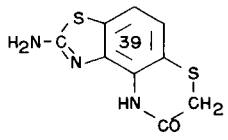
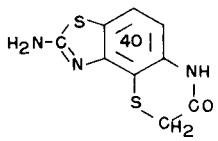
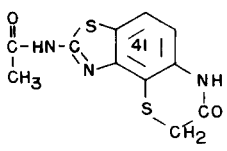
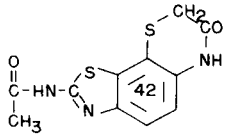
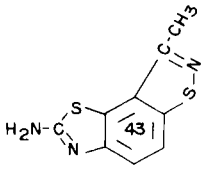
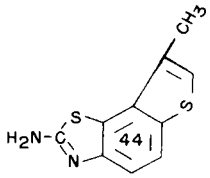
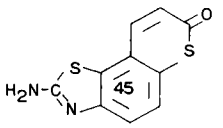
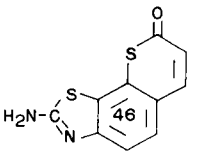
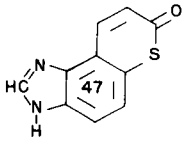
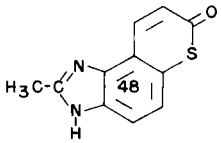
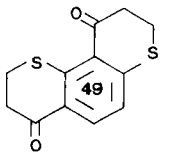
Compound	Reference	Aromatic Protons (h)	δ_A	δ_B	J_{AB} (i)	Thiazole Substituent		Other Protons
	(19)	8.69 (q)	8.66	8.72	9	10.23	10.46	
		(e) 8.12 (q)	8.05	8.19	9	9.09	9.15	(e)
	(19)	8.50 (q)	8.47	8.53	9	3.38	3.40	
		(e) 7.85 (q)	7.82	7.88	9	2.85	2.87	
	(19)	8.63 (q)	8.60	8.66	9	~8 (f)		
	(16)	8.0 (q)	7.74	8.26	9	10.32		$-CH_2-$ = 3.94 -NH-CO = 10.25
	(16)	7.79				3.26		$-CH_2-$ = 3.72
		(e) 7.47 (q)	7.38	7.57	9	2.83		$-CH_2-$ = 3.53 -NH-CO = 9.65
	(16)	7.70 (q)	7.51	7.89	9	3.26		$-CH_2-$ = 3.82 -NH-CO = 10.05
	(11)	7.34 (q)	7.14	7.54	9	8.30 (b)		$-CH_2-$ = 3.73
	(11)	7.58 (q)	7.35	7.81	9	2.60		$-CH_2-$ = 3.74 -NH-CO = 10.02

TABLE III (Continued)

Compound	Reference	Aromatic Protons (h)	δ_A	δ_B	J_{AB} (i)	Thiazole Substituent	Other Protons
	(16)	7.58 (q)	7.37	7.79	9	2.62	$-CH_2-$ = 3.80 -NH-CO = 10.10
	(20)	8.29 (q)	8.22	8.37	9		$-N=C-CH_3$ = 3.22
	(21)	7.67 (q)	7.45	7.89	9	~8.05 (b)	$=C=\overset{|}{C}-CH_3$ = 2.57 (d, j) $-\overset{|}{C}=C-$ = 7.37 (k)
	(22)	7.86				8.63 (b)	$-\overset{O}{\overset{\|}{C}}-CH=CH-$ = 7.50 (q, l)
	(23)	7.84 (q)	7.76	7.92	9	8.84 (b)	$-\overset{O}{\overset{\|}{C}}-CH=CH-$ = 7.50 (q, l)
	(24)	8.08 (q)	7.98	8.19	9		$-\overset{O}{\overset{\|}{C}}-CH=CH-$ = 8.03 (q, l) -N=CH-N= = 9.37
	(24)	8.01 (q)	7.91	8.12	9		$-\overset{O}{\overset{\|}{C}}-CH=CH-$ = 7.98 (q, l) $-N=\overset{|}{C}-N=$ = 3.15
	(25)	7.66 (q)	7.14	8.18	9		$-CO-CH_2-$ = 3.27 (t) $-S-CH_2-$ = 3.12

Notes to the Tables I, II and III

(a) The values are expressed in δ units. Unless otherwise indicated, values refer to singlet absorptions; for multiplet signals the following abbreviations are used: d = doublet; t = triplet, q = quartet, b = broad signal centered at the value cited. (c) The signal in the first column has been assigned to the proton between the two sulfur atoms and those in the second column to the other aromatic proton. (e) Spectra were determined in deuteriochloroform solution; all the others were measured in trifluoroacetic acid solution. (f) Center of the complex multiplet. (g) Center of the sextuplet. (h) The value indicated is the center of a quartet. (i) In c.p.s. (j) J = 1 c.p.s. (k) Partially super-imposed on one peak of a quartet. (l) J = 10 c.p.s.

heated 30 minutes in an oil-bath at 300-305°, gave the product 22, insoluble in either acidic or basic media. Purification by recrystallization from ethylene glycol afforded white prisms, m.p. > 300°.

Anal. Calcd. for $C_{11}H_{10}N_2O_2S_2$: N, 10.53; S, 24.06. Found: N, 10.61; S, 23.97.

Benzothiazepin-4(5*H*)-one[b]benzo[8,7-h]-2',3'-tetrahydrothiazepin-4'(5'*H*)-one (26).

This compound was obtained from the intermediates described below.

2,4-Dinitrobenzene-1-thiopropionic-5-thiosalicylic Acid.

To an alcoholic solution of 2,4-dinitro-5-chlorobenzenethiopropionic acid (10 g.) were added sodium bicarbonate (8.2 g.) and thiosalicylic acid (5 g.). The mixture was heated on a steam bath for about 2 hours. After almost all of the ethanol was removed by distillation, water was added and the mixture was filtered. On acidification, the product separated from the solution and was recrystallized from acetic acid in yellow prisms melting at 211-213°.

Anal. Calcd. for $C_{16}H_{12}N_2O_8S_2$: S, 15.09. Found: S, 15.18.

2,4-Diaminobenzene-1-thiopropionic-5-thiosalicylic Acid.

It was obtained from the above nitro acid by reduction with ferrous sulfate in ammonium hydroxide solution. The mixture was filtered and neutralized giving the amino acid, which was recrystallized from ethanol, white needles melting at 191°.

Anal. Calcd. for $C_{16}H_{16}N_2O_4S_2$: S, 17.62. Found: S, 17.80.

The above diamino acid, heated for about 2 hours in a oil bath at 190-200°, washed with a sodium carbonate solution, and crystallized from ethylene glycol, gave white microcrystals melting above 300°, compound 26.

Anal. Calcd. for $C_{16}H_{12}N_2O_2S_2$: N, 8.54; S, 19.51. Found: N, 8.62; S, 19.36.

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The bulk of the compounds reported in the present study have been synthesized earlier by us; the NMR data presented here confirm the structures previously reported. Only in the cases of compounds 44, 46 and 49 do the structures previously reported need revision. Some of the new compounds will be reported elsewhere. The synthesis of the remainder is described in the experimental part of the present paper.

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