The Reactions of Substituted Benzothiazol-2-ylhydrazones with Bromine: A Route to *s*-Triazolo[3,4-*b*][1,3]benzothiazoles

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The products of the reaction of *p*-substituted benzaldehyde benzothiazol-2-ylhydrazones with bromine depended on the molar ratio of the reactants and the reaction time. With 1 mol of bromine and short reaction times hydrazone bromonium bromides and perbromides were formed. With 0·5 mol of bromine and longer reaction times the products included hydrobromides, hydrazonyl bromides, and 6-bromobenzothiazol-2-ylhydrazones. Cyclisations of the hydrazonyl bromides were investigated and as well a single-step cyclisation of the parent hydrazones with bromine was developed as an efficient cyclisation route to *s*-triazolo[3,4-*b*][1,3]benzothiazoles.

THE oxidative cyclisation of heterocyclic aldehyde hydrazones has provided routes to a wide range of fused heterocyclic systems.[1,2] The value of the reaction may be limited by complicated competitive pathways which often depend on the heterocyclic portion and the reagent used for the oxidation. We have recently discussed the reactions of lead tetra-acetate with substituted benzothiazolylhydrazones where cyclisation was not the

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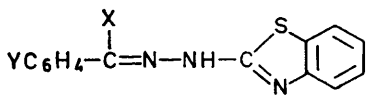
[1] For a review see R. N. Butler and F. L. Scott, *Chem. and Ind.*, 1970, 1216.

[2] For a review see R. N. Butler, *Chem. and Ind.*, 1968, 437.

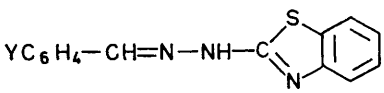
main reaction observed.[3] With lead tetra-acetate as oxidant the reaction can be viewed as a one-step process, from a practical point of view, because of the instability of the various intermediates involved. However, once the reaction was oriented unfavourably, *i.e.* at the expense of cyclisation, it is difficult to control. With bromine, this difficulty may often be overcome since the intermediates involved are frequently sufficiently stable for isolation. Hence, with a view to directing the oxidations of benzothiazolylhydrazones towards cyclisation, we investigated the oxidation of these materials with bromine.

RESULTS AND DISCUSSION

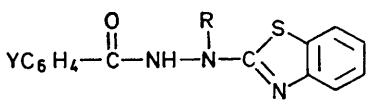
When the hydrazones (I) were treated with 1 mol of bromine for short periods (*ca.* 10 min) in glacial acetic acid, molecular complexes of bromine with the hydrazones were formed. For hydrazones with a *para*-electron-withdrawing substituent (Y = Cl, Br, or NO_2), the products had the formula of an *N*-bromonium bromide (II) (*i.e.* of the type $HyBr^+ Br^-$, where Hy = hydrazone) and for hydrazones where Y was H or Me, compounds with formulae closer to perbromides (III) (*i.e.* $HyH^+ Br_3^-$) were obtained. In each case the positive species is probably attached to the nitrogen atom of the benzothiazole group since this is more nucleophilic than the nitrogen atom of the 2-amino-



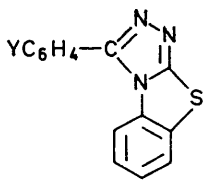
(I) X = H
(II) X = H. Br_2
(III) X = H. HBr_3
(IV) X = Br
(V) X = H. HBr



(VI)



(VII) R = Ac
(IX) R = H



(VIII)

Y = (a) H; (b) *p*-Cl; (c) *p*-Br; (d) *p*-Me; (e) *p*-NO_2

group.[4,5] Both types of compounds (II) and (III) liberated iodine from acidified potassium iodide solution. They gradually lost bromine on standing in the air. When they were distributed between chloroform and aqueous sodium thiosulphate solution, the original hydrazones (I) were regenerated quantitatively. In general, the compounds display properties similar to oxadiazolylhydrazone perbromides,[6] arylidenepyridylhydrazone bromonium bromides,[7] and open-chain azinium perbromides [8] which have previously been reported.

Treatment of many aldehyde heterocyclic hydrazone systems with bromine leads to hydrazonyl bromides.[1] The benzothiazolylhydrazone system is somewhat exceptional insofar as it proved very difficult to obtain such materials from the brominations. However, by varying the conditions, low yields of the hydrazonyl bromides (IV) were isolated. Thus, when the compounds (I) were treated with 0·5 mol of bromine in glacial acetic acid, over long periods of time (from 5 h to 3 days), the bromides (IV) were obtained in low yields (9—37%); hydrobromides (V) (48—62%) and 6-bromobenzothiazol-2-ylhydrazones (VI) (4—9%) were also formed. The hydrobromides (V) were obtained separately by treating the hydrazones (I) with hydrobromic acid in glacial acetic acid. The compounds (VI) were characterised by independent synthesis from 2-amino-6-bromobenzothiazole *via* diazotisation and reduction to the hydrazine, which was then coupled with the appropriate aldehyde. The possibility that the molecular complexes (II), obtained after short reaction times, may be precursors to the products (IV)—(VI) from the extended reactions was considered. After the *p*-nitro-compound (IIe) had been stirred at 60° in glacial acetic acid for 5 h, it was recovered unchanged. However, when the process was carried out in the presence of 1 mol of the parent hydrazone, the compounds (Ve), (VIe), (VIIIe), and the acetoxylation product (VIIe) were formed in 56, 6, 9, and 13% yields respectively. The acetyl-compound (VIIe) was characterised as previously described.[3] Its presence and that of the cyclised product (VIIIe) can be attributed to reactions of the intermediate hydrazonyl bromide (IVe). It is clear that while the materials (II) may dissociate to some extent in solution, a large excess of free hydrazone is required for appreciable reaction to occur. Hence, the compounds (II) are not precursors of the compounds (IV)—(VI) in an intramolecular process. While they may be involved to a small extent in an intermolecular process, this process is slow and is probably not the main source of the other products.

Reactions of Hydrazonyl Bromides.—When the bromides (IV) were treated with triethylamine in benzene for 10 min, high yields (85—95%) of the triazolobenzothiazoles (VIII) were obtained. These compounds were identical with the samples obtained in low yields from the reaction of the hydrazones (I) with lead tetra-acetate previously reported.[3] The present reaction

[3] R. N. Butler, P. O'Sullivan, and F. L. Scott, *J. Chem. Soc.* (*C*), 1971, 2265.
[4] T. Wagner-Jauregg and R. Helmert, *Ber.*, 1942, **75**, 935.
[5] L. H. Conover and D. S. Tarbell, *J. Amer. Chem. Soc.*, 1950, **72**, 5221.
[6] F. L. Scott, T. M. Lambe, and R. N. Butler, *Tetrahedron Letters*, 1971, 1729.
[7] M. S. Gibson, *Tetrahedron*, 1963, **19**, 1587.
[8] F. L. Scott and P. A. Cashell, *J. Chem. Soc.* (*C*), 1970, 2674.

probably involves a nitrilimine intermediate with an electrocyclic [9] ring closure step involving the 1,5-dipolar form. The compounds (IV) were also cyclised by stirring at ambient temperatures in 70% (v/v) dioxan–water. Yields of the tricyclic products (VIII) ranged from 73—94%, the higher yields being associated with the electron-withdrawing Y substituents. This solvolytic cyclisation may involve a carbonium ion intermediate arising from heterolytic fission of the carbon–bromine bond.[10,11] Normally in such reactions the carbonium ion is partitioned between the various nucleophiles present and by introducing strong nucleophiles it has been possible to prevent cyclisation altogether.[12] Hence, the direct solvolysis product (IX) might be expected from the reactions in aqueous dioxan. However no such compounds were isolated and, indeed, when a reaction with a representative compound (IVe) was carried out in the presence of morpholine, the cyclised material (VIIIe) was the only identifiable product.

While the cyclisation of the bromides (IV) was effected in high yields, the process does not afford an efficient route to the tricyclic compounds (VIII) because of the initial low yields of the bromides (IV). In seeking a direct single-step cyclisation of the hydrazones (I) with bromine a number of procedures were investigated. The most successful involved a slow addition of 1 mol of bromine in chloroform to a mixture of the hydrazone in the same solvent containing an excess of sodium carbonate at ambient temperatures. The compounds (VIII) were obtained in 65—94% yields. When sodium acetate was used in place of sodium carbonate, the reaction gave mixtures of the tricyclic materials (VIII) and the *N*-acetylhydrazides (VII) and was less effective.* The formation of compounds (VII) in this instance may be attributed to a displacement of bromide ion from the materials (IV) by acetate ion followed by a 1,4 O → N acyl migration. This is a well-known reaction of hydrazonyl halides in the presence of acetate ion.[1]

Kinetic studies on the processes described will be reported elsewhere in conjunction with other data.

EXPERIMENTAL

M.p.s were measured on an Electrothermal apparatus. I.r. spectra were measured on a Perkin-Elmer Infracord (model 137E) spectrophotometer with sodium chloride optics. Microanalytical determinations were carried out by Mrs. K. M. Duggan and Miss D. Healy of this Department. The hydrazone substrates (I) were prepared as previously described.[3]

Brominations.—(a) *With* 1 *mol of bromine.* The following is a typical example: bromine (0·175 ml) in glacial acetic acid (2 ml) was added over 2 min to a stirred suspension of *p*-nitro-compound (Ie) (1 g) in 30 ml of the same solvent. The mixture was stirred for 5—10 min and the flocculent p-*nitrobenzaldehyde* 1,3-*benzothiazol*-2-*ylhydrazone* N-*bromonium bromide* (IIe) (1·05 g; 69%), m.p. 265—270° (Found: C, 38·5; H, 2·6; Br, 34·5; N, 13·2. $C_{14}H_{10}N_4O_2S,Br_2$ requires C, 36·7; H, 2·2; Br, 34·9; N, 12·2%), was washed with cold ether. This material was unstable † and evolved bromine on standing. It liberated iodine from acidified potassium iodide solutions and, when distributed between chloroform and aqueous sodium thiosulphate, *p*-nitrobenzaldehyde 1,3-benzothiazol-2-ylhydrazone (Ie) was recovered quantitatively. The following *benzaldehyde* 1,3-*benzothiazol*-2-*ylhydrazone* N-*bromonium bromides*, which displayed similar properties, were obtained from the corresponding hydrazones by a similar procedure: p-*chloro*- (IIb) (65%), m.p. 160° to a cloudy, viscous liquid clearing at 210° (Found: C, 37·9; H, 2·5; Br, 39·5; N, 9·4. $C_{14}H_{10}ClN_3S,Br_2$ requires C, 37·6; H, 2·2; Br, 40·0; N, 9·4%); p-*bromo*- (IIc) (60%), m.p. 175° clearing at 211° (Found: C, 34·3; H, 2·0; Br, 49·2; N, 8·7. $C_{14}H_{10}BrN_3S,Br_2$ requires C, 34·1; H, 2·0; Br, 49·7; N, 8·5%). With the hydrazones (Ia) and (Id) the products had compositions closer to the perbromides (III); *benzaldehyde* 1,3-*benzothiazol*-2-*ylhydrazone hydroperbromide* (IIIa) (76%), m.p. 145° clearing at 175° (Found: C, 36·5; H, 2·8; Br, 45·6; N, 9·2. $C_{14}H_{11}N_3S,HBr_3$ requires C, 34·0; H, 2·4; Br, 49·6; N, 8·5%) and the p-*chloro-derivative* (IIIb) (80%), m.p. 150° clearing at 250° (Found: C, 36·4; H, 2·9; Br, 44·5; N, 8·5. $C_{15}H_{13}N_3S,HBr_3$ requires C, 35·4; H, 2·75; Br, 47·2; N, 8·25%).

(b) *With* 0·5 *mol of bromine.* The following is a typical example: bromine (0·406 ml) in acetic acid (8 ml) was added over 15 min to a well-stirred suspension of the hydrazone (Ia) (4 g) in 50 ml of the same solvent. The mixture was stirred for 5 h at ambient temperatures and the *hydrobromide* (Va) (2·55 g; 48%), m.p. 259—260° (Found: C, 49·8; H, 3·75; Br, 23·8; N, 12·7. $C_{14}H_{11}N_3S,HBr$ requires C, 50·25; H, 3·6; Br, 23·9; N, 12·6%), which separated, was removed (filtrate A) and washed with ether. The filtrate (A) was solidified in an ice bath. Slow re-melting of the acetic acid yielded a solid, which was leached with dry ether (100 ml). The ether-insoluble material (0·5 g; 9·5%), m.p. 255—258° (from ethanol), was *benzaldehyde* 6-*bromo*-1,3-*benzothiazol*-2-*ylhydrazone* (VIa) (Found: C, 50·1; H, 3·4; Br, 24·4; N, 12·7. $C_{14}H_{10}BrN_3S$ requires C, 50·6; H, 3·0; Br, 24·05; N, 12·6%). The ethereal extract was evaporated to low volume and, on cooling, crystals (700 mg; 13·5%) of N-(1,3-*benzothiazol*-2-*yl*)*benzohydrazonyl bromide* (IVa) separated, m.p. 140° (Found: C, 51·0; H, 3·2; Br, 23·6; N, 12·2%. $C_{14}H_{10}BrN_3S$ as above). Further work-up of the acetic acid mother liquor yielded a small quantity of a sticky material.

Similar reactions with a range of the hydrazones (I) yielded the corresponding products. With the materials (Ib), (Ic), and (Ie) the products (IV) and (V) separated as mixtures. In each case the hydrazonyl bromide (IV) could be readily removed by leaching the mixture with ether.

* We have recently learned of a similar cyclisation being effected with bromine in the presence of sodium acetate and also with ferric chloride (V. Ranga Rao, University of North Carolina, personal communication).

† Because of this instability it was not possible to achieve satisfactory analyses of some of these compounds. Analytical results therefore correspond to approximations to the original pure form of the compound before decomposition becomes appreciable.

[9] H. Reimlinger, *Chem. Ber.*, 1970, **103**, 1900.
[10] F. L. Scott, D. A. Cronin, and J. K. O'Halloran, *J. Chem. Soc.* (*C*), 1971, 2769.
[11] F. L. Stcot, M. Cashman, and A. F. Hegarty, *J. Chem. Soc.* (*B*), 1971, 1607.
[12] R. N. Butler and F. L. Scott, *J. Chem. Soc.* (*C*), 1967, 239.

The products obtained from the corresponding hydrazones were as follows: (i) the p-*chloro-hydrazone hydrobromide* (Vb) (49%), m.p. 263—265° (Found: C, 45·4; H, 2·8; Br, 21·6; N, 11·3. $C_{14}H_{10}ClN_3S$,HBr requires C, 45·6; H, 3·0; Br, 21·7; N, 11·4%); the p-*chloro-hydrazonyl bromide* (IVb) (18·5%), m.p. 160—190° (Found: C, 46·0; H, 2·7; Br, 22·3; N, 11·25. $C_{14}H_9BrClN_3S$ requires C, 45·8; H, 2·7; Br, 22·5; N, 11·45%); ring bromination in this case to form compound (VIb) was not encountered; (ii) the p-*bromo-hydrazone hydrobromide* (Vc) (48·5%), m.p. 280—282° (Found: C, 40·7; H, 2·75; Br, 38·4; N, 10·4. $C_{14}H_{10}BrN_3S$,HBr requires C, 40·7; H, 2·65; Br, 38·7; N, 10·15%); the p-*bromo-hydrazonyl bromide* (IVc) (20%), m.p. 180—190° (Found: C, 40·75; H, 2·4; Br, 38·5; N, 10·55. $C_{14}H_9Br_2N_3S$ requires C, 40·9; H, 2·2; Br, 38·85; N, 10·2%); p-*bromobenzaldehyde* 6-*bromo*-1,3-*thiazol*-2-*yl-hydrazone* (VIc) (7%), m.p. 270—272° (Found: C, 40·5; H, 2·15; Br, 39·1; N, 10·3. $C_{14}H_9Br_2N_3S$ requires C, 40·9; H, 2·2; Br, 39·0; N, 10·2%); (iii) the p-*methyl-hydrazone hydrobromide* (Vd) (62%), m.p. 274—276° (Found: C, 51·7; H, 3·8; Br, 22·5; N, 11·75. $C_{15}H_{13}N_3S$,HBr requires C, 51·7; H, 4·0; Br, 23·0; N, 12·05%); the p-*methyl-hydrazonyl bromide* (IVd) (9%), m.p. 145—180° (Found: C, 51·7; H, 3·4; Br, 22·9; N, 11·95. $C_{15}H_{12}BrN_3S$ requires C, 52·0; H, 3·5; Br, 23·1; N, 12·15%); the p-*methyl* 6-*bromo-hydrazone* (VId) (4%), m.p. 254—255° (from aqueous acetic acid) (Found: C, 52·4; H, 3·6; Br, 22·8; N, 12·2. $C_{15}H_{12}BrN_3S$ as above); (iv) the p-*nitro-hydrazone hydrobromide* (Ve) (50%), m.p. 293—295° (Found: C, 44·6; H, 3·0; Br, 21·0; N, 15·0. $C_{14}H_{10}N_4O_2S$,HBr requires C, 44·3; H, 2·9; Br, 21·1; N, 14·8%); the p-*nitro-hydrazonyl bromide* (IVe) (37%), m.p. 184—185° (from acetic acid) (Found: C, 45·9; H, 2·55; Br, 21·6; N, 15·1. $C_{14}H_9BrN_4O_2S$ requires C, 45·85; H, 2·45; Br, 21·85; N, 15·3%). For this latter reaction methanol was used as solvent because the bromide (IVe) reacted with acetic acid during the long reaction time (2—3 days). In methanol the reaction was complete in *ca.* 45 min at ambient temperatures. The m.p.s of some of the bromides (IV) were spread over a range, which was not diminished by repeated recrystallisations from ether. The spread is probably due to a slow decomposition of the compounds on heating.

(c) *Characterisation of products.* The hydrazonyl bromides (IV) did not liberate iodine from acidified potassium iodide solution in agreement with a structure involving carbon–bromine bonds only. When heated under reflux in 95% alcohol for short periods, they liberated the theoretical quantity of bromide ion in accordance with expectation for a labile carbon–bromine bond. The materials are further characterised by the reactions described below. The hydrobromides (V) were also prepared by treating the hydrazones (I) with hydrobromic acid in glacial acetic acid. On addition of ether the hydrobromides (V) separated. They were identical (mixture m.p. and i.r. spectra) with the samples obtained from the brominations.

The ring-brominated products (VI) were characterised by unequivocal preparation as follows; a solution of 2-amino-6-bromo-1,3-benzothiazole [13] (4·58 g) in 89% phosphoric acid (45 ml) was cooled to 0° and treated first with concentrated nitric acid (18 ml) and then carefully with a solution of sodium nitrite (1·50 g) in water (3·6 ml) with stirring. The mixture was stirred for a further 10 min and then carefully added to a mixture of stannous chloride dihydrate (12 g), water (36 ml), and concentrated hydrochloric acid (9 ml) cooled with crushed ice (*ca.* 40 g). The orange product was leached with boiling water (200 ml) and the insoluble gummy material removed. The aqueous solution was made basic with sodium hydroxide and the solid which separated was leached with boiling alcohol (30 ml). A small amount of an insoluble gummy residue was removed. The alcoholic solution was evaporated to half volume and treated with water (10 ml), when 6-bromo-2-hydrazino-1,3-benzothiazole separated (1·22 g; 25%), m.p. 221—223° (from aqueous alcohol) (Found: C, 34·2; H, 2·35; Br, 33·15; N, 17·4. $C_7H_6BrN_3S$ requires C, 34·45; H, 2·45; Br, 32·8; N, 17·2%). This hydrazine was condensed with the appropriate aldehydes to give the hydrazones (VI). The samples obtained by this procedure were identical (mixture m.p. and i.r. spectra) with those isolated from the brominations.

(d) *Reaction of compound* (IIe) *with the parent hydrazone.* A suspension of compounds (IIe) (1·35 g) and (Ie) (2·0 g) in glacial acetic acid (100 ml) was heated at 60° for 5 h and cooled. The hydrobromide (Ve) (1·82 g; 56%), m.p. 293—295°, which separated, was removed. The filtrate was evaporated to 15 ml and, on cooling, compound (VIe) (200 mg; 6%), m.p. 258—260° (Found: C, 46·2; H, 2·7; Br, 21·6; N, 15·4. $C_{14}H_9BrN_4O_2S$ requires C, 45·85; H, 2·45; Br, 21·85; N, 15·3%) separated (filtrate A). This material was identical (mixture m.p. and i.r. spectra) with a sample prepared as described above.

The filtrate (A) was carefully added to water and the precipitate which slowly separated was leached with boiling alcohol (30 ml). The insoluble material was 1-(p-*nitrophenyl*)-s-*triazolo*[3,4-b][1,3]*benzothiazole* (VIIIe) (250 mg; 9%), m.p. 288—290° (from ethanol) (Found: C, 56·4; H, 2·6; N, 19·0. $C_{14}H_8N_4O_2S$ requires C, 56·7; H, 2·7; N, 18·9%). The alcoholic solution was evaporated to 10 ml and treated with water. The solid which separated was recrystallised from chloroform to give N′-*acetyl*-N′-(1,3-*benzothiazol*-2-*yl*)-p-*nitrobenzohydrazide* (VIIe) (400 mg; 13%), m.p. 231—233° (Found: C, 53·5; H, 3·5; N, 15·8. $C_{16}H_{12}N_4O_4S$ requires C, 53·9; H, 3·4; N, 15·7%). Both compounds (VIIIe) and (VIIe) thus obtained were identical (mixture m.p. and i.r. spectra) with samples obtained from the reaction of the hydrazone (Ie) with lead tetra-acetate in the manner previously described.[3]

Reactions of the Hydrazonyl Bromides (IV).—(a) *With triethylamine in benzene.* Typically, a solution of compound (IVc) (200 mg) in benzene (20 ml) was treated with triethylamine (1 ml) in benzene (10 ml) and the mixture was stirred for 10 min at ambient temperatures. Insoluble triethylamine hydrobromide was removed and the solvent evaporated. The residue, when recrystallised from ethanol, yielded the material (VIIIc) (90%), m.p. 164—166°. Similar reactions with compounds (IV) yielded the products (VIII) in 85—95% yields. The triazolobenzothiazoles (VIII) isolated from these reactions were identical (mixed m.p. and i.r. spectra) with samples obtained previously.[3] When morpholine was used in place of triethylamine for the reaction with compound (IVe), the cyclised product (VIIIe) was obtained in 43% yield. The only other products encountered were intractable gums.

(b) *In* 70% (*v/v*) *dioxan–water.* Typically, a solution of compound (IVc) (250 mg) in 70% aqueous–dioxan (250 ml) was stirred and stood for 3 days. It was then treated with water (1 l) and extracted with ether (2 × 400 ml). The

[13] R. F. Hunter, *J. Chem. Soc.*, 1930, 125.

ethereal extracts were combined, dried, and evaporated. The residue, when recrystallised from aqueous alcohol, yielded compound (VIIIc) (83%). Similar reactions with the bromides (IV) yielded the triazolobenzothiazoles (VIII) in 73—94% yields. Despite extensive searches for amides of type (IX), using t.l.c. on the product solution, such materials were not encountered in these reactions.

(c) *Single-step cyclisation of the hydrazones* (I). Typically, bromine (0·195 ml) in chloroform (10 ml) was added to a stirred suspension of compound (Ie) (1 g) and sodium carbonate (3 g) in 100 ml of the same solvent. The mixture was stirred at ambient temperatures for 30 min and heated at 40° for 5 min. Insoluble sodium salts were removed and the solvent was evaporated. The residue, on recrystallisation from 95% ethanol, yielded compound (VIIIe) (94%). This reaction proved effective with all the hydrazones (I). The yields of the materials (VIII) were in the range 65—94%. When sodium acetate was used instead of sodium carbonate, mixtures of the materials (VII) and (VIII), which were difficult to separate, were encountered.

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