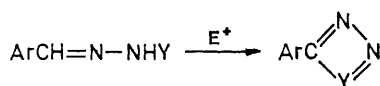


Ambident Oxidative Ring Closure of Semicarbazones †

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Oxidative cyclisation of a series of substituted benzaldehyde semicarbazones, with bromine in acetic acid in the presence of base or with lead tetra-acetate, yields 2-amino-1,3,4-oxadiazoles. With bromine in the absence of base there is a competition between cyclisations involving nitrogen and oxygen atoms, and the main products are triazolones arising from ring closure at a nitrogen atom. Ring closure at an oxygen atom appears to involve a nitrilimine intermediate as the product governing species, whereas the ring closure at nitrogen appears to be a carbonium-ion reaction. A methyl group at N-2 in the semicarbazone systems prevents the formation of a nitrilimine species and confines the subsequent cyclisation reaction to nitrogen atom attack. The rates of bromination (in 70%) acetic acid at 20 °C of a similar series of benzaldehyde semicarbazones proved to be independent of the bromine concentration. The slow step in the reaction measured was the *syn-anti* isomerisation of the semicarbazone. We favour a mechanism for this process involving rotation about the C=N bond, in light of (a) data on the effect of substituents on the rate of isomerisation and (b) comparison with related systems.

REACTIONS of aldehyde hydrazones with electrophiles such as bromine¹ and lead tetra-acetate² can lead to cyclisation products as shown in Scheme 1 if the group Y is suitable. Such processes are oxidative cyclisations; their mechanisms would be better understood, if key



SCHEME 1

intermediates (such as $\text{ArCE=N}\cdot\text{NHY}$) could be isolated and examined. With tetra-acetate as oxidant such species are as yet unknown, but with bromine the intermediates are hydrazonyl bromides ($\text{ArCBr=N}\cdot\text{NHY}$), compounds which we have reported on in detail elsewhere,¹ with Y as a ring system. We have also examined two other such classes of hydrazonyl halide. In the first, where Y is an amidino-function [C(=NH)-NH_2], the bromides can be readily isolated but their subsequent cyclisation reactions are not simple.³ The second of the two systems, where Y is a carbamoyl ($\text{CO}\cdot\text{NH}_2$) group is derived from arylmethylenesemicarbazides (I). Here not only have we been unable to obtain the cyclisation intermediate, but even the cyclisation process itself is complicated, involving ambident cyclisation patterns.⁴ The present paper details our studies on these systems.

RESULTS AND DISCUSSION

(a) *Products*.—Our intention was to study the oxidative cyclisation of the semicarbazones (I). Because of our previous extensive mechanistic work with bromine as electrophile, reactions with this reagent were studied first. Gibson had earlier reported⁵ that reactions of compounds (I) with bromine in acetic acid containing sodium acetate lead to oxadiazoles (IV) in high yield.

† This paper is our sixth describing studies on geometric isomerisation about azomethine bonds. The others are: A. F. Hegarty and F. L. Scott, *Chem. Comm.*, 1967, 521; A. F. Hegarty and F. L. Scott, *J. Org. Chem.*, 1968, **33**, 753; F. L. Scott, F. A. Groeger, and A. F. Hegarty, *Tetrahedron Letters*, 1968, 2463; F. L. Scott, F. A. Groeger, and A. F. Hegarty, *J. Chem. Soc. (B)*, 1971, 1141; J. C. Tobin, A. F. Hegarty, and F. L. Scott, *J. Chem. Soc. (B)*, 1971, 2198.

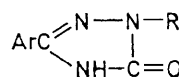
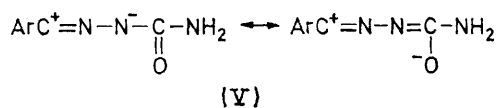
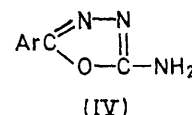
We confirmed his results for the two compounds he examined by use of the following similar technique. Bromine (1.1 mol. equiv.) was added during 15 min to the semicarbazone (I) suspended in glacial acetic acid containing anhydrous sodium acetate (4 mol. equiv.)



(I) R = H, X = H

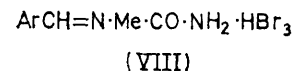
(II) R = H, X = Br

(III) R = Me, X = H



(VI) R = H

(VII) R = Me



a; Ar = Ph b; Ar = *p*-ClC₆H₄ c; Ar = *p*-BrC₆H₄
d; Ar = *p*-MeC₆H₄ e; Ar = *p*-MeO·C₆H₄

at room temperature. We extended this study to include an additional four semicarbazones. Similar cyclisations of semicarbazones (I) leading to oxadiazoles have been observed by Maggio *et al.*⁶ (with sodium hypobromite as oxidant) and Gehlen⁷ (with iodine-potassium iodide in aqueous sodium carbonate). Gibson suggested the presence of a nitrilimine intermediate (V) as the product-governing species in the reaction with bromine. Such a species could arise from the action of

¹ R. N. Butler and F. L. Scott, *Chem. and Ind.*, 1970, 1216.

² R. N. Butler, *Chem. and Ind.*, 1968, 437.

³ F. L. Scott and A. F. O'Mahony, unpublished work.

⁴ F. L. Scott, T. M. Lambe, and R. N. Butler, *Tetrahedron Letters*, 1971, 2669.

⁵ M. S. Gibson, *Tetrahedron*, 1962, **18**, 1377.

⁶ G. Valenti and F. Maggio, *Ann. Chim. (Italy)*, 1952, **42**, 18.

⁷ H. Gehlen and K. Mockel, *Annalen*, 1962, **651**, 133.

base on an intermediate hydrazone bromide* (II) and hence base might be expected to play an important product-governing role. We have found this to be the case; when the reaction was carried out in the absence of base the product balance was drastically changed. The main products in this case were the triazolones (VI) (Table I) arising from cyclisation at a nitrogen atom. These materials were identified from their i.r. spectra (urea-type carbonyl absorption¹⁰ at 1725–1735 cm⁻¹), and were identical with samples prepared by oxidising the materials (I) in ethanol with iron(III) chloride at 130°. In the reaction of compounds (I) with bromine in the absence of base, small quantities (up to 6%) of the oxadiazoles (IV) were also obtained, along with some decomposition products (the parent aldehyde and ammonium bromide). The possibility that the materials (IV) were formed initially and then converted into the triazolones (VI) was ruled out when control reactions of the

TABLE I

Reaction of the semicarbazones (I) with bromine in the absence of base^a

Substrate	Compound (VI) (%)	Compound (IV) (%)	NH ₄ Br (%)	Compound (I) (%)
(Ia) ^b	51	6.5	15.5	
(Ib)	43	3	11	26
(Ic)	47	4	12	23
(Id) ^c	42	5	13.5	12.5
(Ie)	41	7	13	14.5

^a The materials were stirred with bromine (1.5 mol. equiv.) in anhydrous acetic acid for 48 h at ambient temperature.

^b Benzaldehyde (4.5%) was isolated (see Experimental section). ^c *p*-Tolualdehyde (4%) was isolated.

materials (IV) with bromine and hydrobromic acid under the cyclisation conditions did not bring about this change. The possibility that the triazolones (VI) were the initial products of the reaction in the presence of base was also ruled out by control reactions. When the materials (I) were treated with bromine in aqueous 70% acetic acid in the absence of base, cyclisation at oxygen took place in 60–70% yields,¹² along with considerable decomposition, and cyclisation at nitrogen was detected. The addition of water to the system may have favoured the generation of a nitrilimine species by facilitating the loss of hydrogen bromide from a hydrazone bromide precursor.

To study further the possibility of a nitrilimine species being the key product-governing intermediate in the reaction involving closure at an oxygen atom, a methyl group was inserted at N-2 of the semicarbazone chain, thus rendering the formation of a nitrilimine impossible.

* Najer *et al.*,⁸ claimed the isolation of such a hydrazone bromide in low yield when *p*-chlorobenzaldehyde 4,4-dimethyl-semicarbazone was treated with bromine in glacial acetic acid containing sodium acetate. However, Weber *et al.*,⁹ repeated this work and could not isolate a hydrazone bromide; instead they obtained hydrobromide perbromides of the semicarbazones.

† Oxadiazoles of type (IV) cannot be formed from the substrates (III). However, related compounds, *e.g.* 2-amino-3-methyl-1,3,4-Δ²-oxadiazolines, could have been formed by attack on oxygen.

‡ This is no proof that a nitrilimine species was involved in the O-attack undergone by compounds (I), but is consistent with that supposition.

The methyl group in these compounds (III) had two effects: (a) it rendered the compounds much less reactive towards bromine and (b) it completely blocked cyclisation at oxygen. In no case was a product corresponding to attack on oxygen formed.† When compounds (III) were treated with bromine in glacial acetic acid containing sodium acetate under the same conditions as used with the materials (I), the starting materials (III) were recovered in 80% yields. Small quantities (up to *ca.* 10%) of the corresponding substituted benzoic acids were obtained, indicating that the course of the reaction had changed.

When the compounds (III) were treated with bromine in acetic acid, unstable reddish brown materials were obtained, which readily liberated bromine when exposed to the air or when they were being dried (over CaCl₂); it was impossible to obtain satisfactory analyses. We believe however, from (a) the approximate analyses obtained and (b) their general properties, that these materials are unstable perbromides.¹³ In accord with expectation they liberated iodine from potassium iodide in methanol, and when they were distributed between aqueous sodium thiosulphate and ether the semicarbazones (III) were recovered in *ca.* 80% yields from the ethereal layer. When they were heated with acetanilide in glacial acetic acid (*cf.* ref. 14) low yields of *p*-bromoacetanilide were obtained, as expected.

When the materials (III) were treated with bromine in glacial acetic acid in the absence of base under more vigorous conditions (90°) cyclisation at nitrogen occurred to give the triazolones (VII) in yields up to 80%. These materials were identified from their i.r. spectra [ν_{max} (CO) 1693–1700 cm⁻¹, about 30 cm⁻¹ lower than for the unmethylated triazolone; see ref. 15 for a similar effect], and were identical with samples prepared by oxidising the materials (III) with iron(III) chloride in ethanol.¹⁶ Thus no cyclisation at oxygen was observed where a nitrilimine intermediate cannot be formed.‡

Addition of either sodium acetate or water to bromine in acetic acid influences the reaction with semicarbazones in two ways: it causes rapid acceleration in the overall rate, together with the exclusion of *N*-attack. We envisage that both *O*- and *N*-attack arise from initial bromination (to form ArCBr=N·NH·CO·NH₂) and that the products can then undergo either of two reactions. We have established elsewhere¹⁷ that hydrazone

⁸ H. Najer, R. Guidicelli, C. Morel, and J. Menin, *Bull. Soc. chim. France*, 1965, 153.

⁹ G. Weber, M. C. Aversa, and F. Buccheri, *Ann. Chim. (Italy)*, 1969, 59, 912.

¹⁰ K. Nakanishi, 'Infrared Absorption Spectroscopy,' Holden-Day, San Francisco, 1962, 2nd edn., p. 47.

¹¹ E. Hoggarth, *J. Chem. Soc.*, 1949, 1918.

¹² F. Maggio, G. Werber, and G. Lombardo, *Ann. Chim. (Italy)*, 1960, 50, 491.

¹³ (a) F. L. Scott and P. A. Cashell, *Chem. and Ind.*, 1969, 1343; (b) F. L. Scott and P. A. Cashell, *J. Chem. Soc. (C)*, 1970, 2674.

¹⁴ M. S. Gibson, *Tetrahedron*, 1963, 19, 1587.

¹⁵ H. Schilbknecht and G. Hatzmann, *Annalen*, 1969, 724, 226.

¹⁶ G. Young and W. H. Oates, *J. Chem. Soc.*, 1901, 79, 659.

¹⁷ A. F. Hegarty, M. P. Cashman, and F. L. Scott, *J.C.S. Perkin II*, 1972, 44.

halides can undergo either ionization (to yield carbonium ions, *e.g.* $\text{Ar}\overset{\oplus}{\text{C}}=\text{N}-\text{NH}\cdot\text{CO}\cdot\text{NH}_2$) and 1,3-dipolar elimination (to yield nitrilimines, *e.g.* $\text{Ar}\overset{\oplus}{\text{C}}=\text{N}-\bar{\text{N}}\cdot\text{CO}\cdot\text{NH}_2$), depending especially upon the pH of the medium. We regard the attack on an oxygen atom in base or water [leading to product (IV)] as arising from a 1,5-dipolar addition process, involving a nitrilimine, whereas the concurrent *N*-attack and *O*-attack in anhydrous acetic acid can be regarded as ambident nucleophilic attack at a carbonium ion centre. The presence of hydrazonyl halides as precursors to the nitrilimine intermediates which yield oxadiazoles indeed seems likely. We have recently¹⁸ prepared oxadiazoles by selective displacement of halogen atoms from trihalogenodiazabutadienes; this reaction necessitated the intermediacy of a semicarbazone species with a halogen atom at the methine carbon atom, thereby implying that a hydrazonyl halide could indeed lead to an oxadiazole product. This is in full agreement with our present results, since hydrazonyl halides are well known precursors of nitrilimines.¹⁹

The rapid acceleration in bromine uptake caused by base or water as just noted must be due to the influence of these reagents on the electrophilic attack stage; this effect probably arises from some change in the nature of the attacking electrophile. For that reason we briefly examined the cyclisation pattern with a different electrophile, lead tetra-acetate.²⁰ Reactions of substrates (I) with lead tetra-acetate in glacial acetic acid (conditions which lead to *N*-attack with bromine) afforded no *N*-attack, the products being the oxadiazoles (IV), obtained in high yields. We regard the lead tetra-acetate reaction as proceeding through a nitrilimine, and thus its rapidity (complete in 15 min at ambient temperature) and exclusive *O*-attack are completely consistent with our results with bromine as oxidant. Interestingly, with the 2-methylsemicarbazones (III) the lead tetra-acetate was inert; no *N*-attack was observed.

(b) *Kinetic Studies*.—The oxidative cyclisations discussed are clearly multi-stage processes, electrophilic attack being followed by internal nucleophilic attack, each of which may possibly proceed through several stages as well. Having available electrometric techniques for studies of rapid reactions with bromine in aqueous 70% acetic acid,²¹ and knowing that the reaction of substrates (I) with bromine under these conditions leads to exclusive *O*-attack we used the bromometric technique to examine the mechanism of *O*-attack.

The kinetics of bromination of a series of substituted benzaldehyde semicarbazones were studied; the results are given in Table 2. The rates were independent of the concentration of bromine. Moreover, variation in the

concentration of potassium bromide (at constant ionic strength) (Table 3) which in effect varies the relative amounts of the two electrophiles present (Br_2 and Br_3^-), did not change the observed rate of bromination to any

TABLE 2

Rates of *syn-anti* interconversion of semicarbazones ($\text{XC}_6\text{H}_4\cdot\text{CH}=\text{N}\cdot\text{NH}\cdot\text{CO}\cdot\text{NH}_2$) (solvent: 70% acetic acid containing 0.1M-KBr; 20 °C)

X	$10^4k/s^{-1}$	X	$10^4k/s^{-1}$	X	$10^4k/s^{-1}$
<i>p</i> -MeO	4.6	<i>p</i> -Cl	2.15	<i>o</i> -F	1.8
<i>p</i> -Me	4.05	<i>p</i> -Br	2.05	<i>o</i> -Cl	1.55
<i>p</i> -Pri	3.9	<i>m</i> -Br	1.8	<i>o</i> -I	1.17
H	3.2	<i>o</i> -Me	1.9		

Each k_{obs} quoted is the average from 3 experiments.

TABLE 3

Variation of [KBr] at constant ionic strength for $p\text{-ClC}_6\text{H}_4\cdot\text{CH}=\text{N}\cdot\text{NH}\cdot\text{CO}\cdot\text{NH}_2$

[KBr]/M	[KNO ₃]/M	$10^4k/s^{-1}$
0.1	0.0	2.15
0.05	0.05	2.55
0.025	0.075	2.5
0.01	0.09	2.6

appreciable extent. Hence the observed rate must reflect some molecular transformation in the semicarbazone prior to bromination. Azoalkane formation (*i.e.* to give $\text{ArCH}_2\cdot\text{N}=\text{N}\cdot\text{CO}\cdot\text{NH}_2$) can be ruled out because (a) Simon and Moldenhauer²² have shown that such a reaction is very slow compared to those studied here, and, (b) the bromination of the 2-methyl compound ($\text{PhCH}=\text{N}-\text{NMe}\cdot\text{CO}\cdot\text{NH}_2$), for which such a transformation is impossible under our experimental conditions, was found to be fast ($k\ 3.0 \times 10^{-5}\ \text{s}^{-1}$), and like its unmethylated analogue showed a zero-order rate in bromine. Our present kinetic data best fit a rate-determining geometric isomerisation of the semicarbazones prior to halogenation. While there has been some controversy²³ about which isomer (*syn*- or *anti*-) predominates in such acidic media at 70% acetic acid, our data indicate that the minor isomer present must be brominated very rapidly; it is therefore the conversion of the less reactive isomer to the reactive form which is rate-determining.

The rate data apply to a steric change of the type depicted in Scheme 2 for which there are two extremes of mechanism,²⁴ inversion path (A) or rotation path (B). Inversion involves displacement of the group Y through a transition state in which the group is collinear with the C=N bond. The alternative mechanism (rotation) involves the group Y rotating out of the plane of the molecule with a concurrent transitory reduction in the carbon-nitrogen imine bond order. This results in strong polarisation of this bond, with a considerable degree of charge separation developed in the transition state.

¹⁸ F. L. Scott, J. O'Donovan, and J. K. O'Halloran, *Tetrahedron Letters*, 1970, 4079.

¹⁹ R. Huisgen, *Angew. Chem. Internat. Edn.*, 1963, 2, 633, 565.

²⁰ T. M. Lambe, R. N. Butler, and F. L. Scott, *Chem. and Ind.*, 1971, 996.

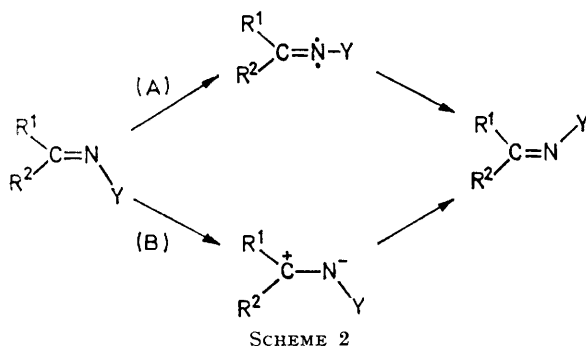
²¹ A. F. Hegarty and F. L. Scott, *J. Chem. Soc. (B)*, 1966, 672.

²² H. Simon and W. Moldenhauer, *Chem. Ber.*, 1967, 100, 1949.

²³ (a) G. J. Karabatsos, J. D. Graham, and F. M. Vare, *J. Amer. Chem. Soc.*, 1962, 84, 753; (b) V. I. Stenberg, P. A. Burks, D. Bays, D. D. Hammargren, and D. V. Rao, *J. Org. Chem.*, 1968, 33, 4402.

²⁴ H. Kessler, *Angew. Chem. Internat. Edn.*, 1970, 9, 219.

While either of these mechanisms may operate in particular circumstances,²⁵ there most probably exists a continuum of gradations between these extremes,²⁶ and the key issue with regard to any particular system is to assign it a place somewhere along that continuum.



We regard the *syn-anti* isomerisation of the semicarbazones (I) as having considerable rotational character in the transition state on the basis of the following facts. First, the kinetic data (Table 2), which fit a Hammett ρ value of -0.65 ($r = 0.996$), indicate that electron release to the imine carbon atom facilitates the

isomerisation, a fact consistent with a $-\overset{+}{C}-\overset{-}{N}$ polarisation in the transition state. We have recently reported²⁷ a similar ρ value (-0.69) for the *syn-anti* isomerisation of 5-(arylmethylenhydrazino)tetrazoles. These ρ values are substantially greater (numerically) than the ρ values recorded for systems where the mechanism of *syn-anti* isomerism is inversion. Second, and more significantly, the kinetics of isomerisation of a series of *ortho*-substituted compounds (Table 2) have the following sequence $o\text{-F} > o\text{-Cl} > o\text{-Br} > o\text{-I}$ (data which fit a Taft steric susceptibility constant, δ , of 0.29). These data imply that increase in substituent size decreases the rate of isomerisation, a fact again in accordance with the rotation mechanism but one inconsistent with the inversion mechanism.²⁴

Two other features are noteworthy. First, the thermodynamic data which we derived for some of our runs (Table 4) show that while the enthalpies of activation

TABLE 4

Kinetic and thermodynamic data for the *syn-anti* isomerisation of benzaldehyde semicarbazones ($\text{XC}_6\text{H}_4\text{CH}=\text{N}\cdot\text{NH}\cdot\text{CO}\cdot\text{NH}_2$)

X	$10^4k/s^{-1}$ (20°)	$10^4k/s^{-1}$ (40°)	$E^\ddagger/$ kcal mol ⁻¹	$\Delta H^\ddagger/$ kcal/mol ⁻¹	$\Delta S^\ddagger/$ kcal mol ⁻¹ K ⁻¹
H	3.2	15.2	14.19	13.61	-28.6
<i>p</i> -Cl	2.15	10.0	14.0	13.42	-29.4
<i>p</i> -Br	2.05	9.96	14.4	13.8	-29.52

(*ca.* 13–14 kcal mol⁻¹) are of the expected magnitude, the entropies involved (*ca.* -29 kcal mol⁻¹ K⁻¹) are

²⁵ H. Kessler and D. Leibfritz, *Chem. Ber.*, 1971, **104**, 2143, 2158; see also F. Kerek, G. Ostragovitch, and Z. Simon, *J. Chem. Soc. (B)*, 1971, 541.

²⁶ M. Raban and E. Carlson, *J. Amer. Chem. Soc.*, 1971, **93**, 685.

surprisingly large (numerically) for such a process as we have described.²⁸ Solvation effects (in our relatively polar medium, aqueous 70% acetic acid) must thus play a considerable part in our hydrazone isomerisations, and we are investigating this further for some of the other systems we have studied (Table 5). Second, the majority of *syn-anti* isomerisations of the imine type that have been studied involve inversion mechanisms. Whence then does the rotational character arise in our hydrazone reactions? Perhaps it arises from one, or all, of three factors: the high polarity of the medium in which our studies have been made, protonation effects (because of the acidic character of the same medium) which would inhibit inversion, or perhaps even from the anomeric effect²⁹ (*i.e.* the effect of lone pairs in the group Y), which certainly raises isomerisation barriers significantly.

TABLE 5

Data on the isomerisations of various systems of type $\text{ArCH}=\text{N}\cdot\text{Y}$

Y	ρ	δ	$\Delta G^\ddagger/\text{kcal}$ mol ⁻¹	k_1 range (temp.)
$\text{NH}\cdot\text{C}_6\text{H}_3(\text{NO}_2)_2$	0.0(ρ^*)	0.49		$5\text{--}30 \times 10^{-4}$ (20°)
$\text{NMe}\cdot\text{C}_6\text{H}_3\cdot\text{NO}_2\text{-}p$	-0.29	0.15	23	$1\text{--}4 \times 10^{-5}$ (20°)
$\text{NH}\cdot\text{CN}_4\cdot\text{CH}_2\text{Ph}^a$	-0.69	+0.44		$1\text{--}4 \times 10^{-4}$ (25°)
$\text{NH}\cdot\text{CO}\cdot\text{NH}_2$	-0.65	0.29	22	$1\text{--}4 \times 10^{-4}$ (20°)

^a The benzyl group may be at the 1- or 2-position.

As already mentioned we have examined a number of such migrations where Y is a substituted amino-group, for example $\text{NH}\cdot\text{C}_6\text{H}_3(\text{NO}_2)_2$; $\text{NMe}\cdot\text{C}_6\text{H}_4\cdot\text{NO}_2\text{-}p$; or 1- or 2-benzyltetrazol-5-ylamino (see footnote to Title); the data obtained (Table 5) all fitted best a transition state which contained considerable rotational character. On the basis of these earlier data we had concluded that special circumstances, *e.g.* ring size, ring type, *etc.*, were responsible for such isomerisation kinetics. It is surprising that semicarbazones fit the same pattern. The comparison of results in Table 5 shows the similar pattern of Y migration throughout the various systems studied.

(c) *Conclusions.*—We have established that both *N*- and *O*-attack can occur in the oxidation by bromine of arylmethylenesemicarbazides, depending upon the solvent and other reagents used. Efforts to examine at least one of these processes, (*O*-attack) under conditions where it occurs exclusively were frustrated because the rate-determining step with respect to bromine uptake was in fact a geometric inversion of the substituted hydrazone. However, these rate data constituted in themselves the first such kinetic study involving semicarbazones.

EXPERIMENTAL

M.p.s lower than 360° were measured on an electrochemical apparatus and those greater than 360° on a Mel-Temp apparatus (0–500°). I.r. spectra were measured on

²⁷ J. C. Tobin, A. F. Hegarty, and F. L. Scott, *J. Chem. Soc. (B)*, 1971, 2198.

²⁸ G. E. Hall, W. J. Middleton, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1971, **93**, 4778.

²⁹ S. Wolfe, A. Rauk, L. M. Tel, and I. F. Csizmadia, *J. Chem. Soc. (B)*, 1971, 136.

Perkin-Elmer Infracord (models 137E and 257) spectrophotometers with sodium chloride optics. Solids were examined as potassium bromide discs. Microanalytical determinations were carried out by Mrs. K. M. Duggan and Miss D. Healy of this department.

Product Studies

Preparation of Substrates.—The semicarbazones (I) were prepared by a procedure previously described (*cf.* ref. 30). The compounds were recrystallised from ethanol and had the following m.p.s: compound (Ia), m.p. 222—223° (lit.,³¹ m.p. 222°); compound (Ib), m.p. 231° (lit.,³¹ m.p. 230°); compound (Ic), m.p. 228—229° (lit.,³¹ 228°); compound (Id), m.p. 221° (lit.,³¹ m.p. 221°); compound (Ie), m.p. 210—211° (lit.,³¹ m.p. 210°).

The 2-methylsemicarbazones (III) were prepared in a similar manner (*cf.* ref. 30) from 2-methylsemicarbazide in place of semicarbazide hydrochloride. An improved method of preparing 2-methylsemicarbazide was as follows. Powdered potassium cyanate (20.25 g) was added slowly to a stirred ice-cold solution of potassium hydrogen sulphate (34 g) in water (500 ml), and the mixture was treated with methylhydrazine (11.5 g), added dropwise during 1 h at ca. 0°. The resulting clear solution was set aside for 24 h at this temperature and then evaporated. The residue was leached with ethanol in a Soxhlet apparatus for 3 h; evaporation of the extract gave 2-methylsemicarbazide (12.3 g, 55%), m.p. 115—117° (lit.,³² 115°) (from chloroform). The materials (III) were recrystallised from ethanol and had the following characteristics: compound (IIIa), m.p. 163—164° (lit.,³² 163); *p*-chlorobenzaldehyde 2-methylsemicarbazone (IIIb), m.p. 175—176° (Found: C, 51.4; H, 4.9; N, 19.95. C₉H₁₀ClN₃O requires C, 51.05; H, 4.7; N, 19.85%); *p*-bromobenzaldehyde 2-methylsemicarbazone (IIIc), m.p. 177—179° (Found: C, 42.35; H, 3.8; N, 16.8. C₉H₁₀BrN₃O requires C, 42.2; H, 3.9; N, 16.4%).

Oxidation of the Semicarbazones (I).—(a) *With bromine in the presence of sodium acetate.* The following is a typical example. Bromine (0.57 ml) in glacial acetic acid (5 ml) was added dropwise during 10 min to a stirred suspension of compound (Ib) (2 g) and anhydrous sodium acetate (3.3 g) in the same solvent (20 ml). The mixture was stirred for a further 10 min and then carefully added to ice-cold water (150 ml). The white solid (m.p. 270—272°; 1.82 g, 91%) which separated was the oxadiazole (IVb). Recrystallisation from ethanol gave material of m.p. 272—274° (lit.,³³ 273—274°), identical (mixed m.p. and i.r. spectra) with an authentic sample.⁷

Similar reactions with a series of compounds (I) yielded the following oxadiazoles in yields greater than 90%: compound (IVa), m.p. 242° (lit.,³³ 242°); compound (IVc), m.p. 275—276° (lit.,³³ 273—275°); compound (IVd), m.p. 265—267° (lit.,³³ 263—264°); compound (IVe), m.p. 250—251° (lit.,³³ 250—251°). These materials were identical (mixed m.p. and i.r. spectra) with authentic samples.⁷

(b) *With bromine in 70% acetic acid.* The following is a typical example. Bromine (1.04 ml) in 70% acetic acid (15 ml) was added dropwise during 20 min to a stirred suspension of compound (Ib) (2 g) in 70% acetic acid (50 ml). The mixture was then stirred for a further 20 min and the resultant clear solution upon dilution with ice-cold water (200 ml) yielded compound (IVb) (1.25 g, 62.5%; m.p.

260—264°) [filtrate (A)]. Recrystallisation from ethanol gave a sample of m.p. 272—274° (mixed m.p. 272—274°).

Work-up of filtrate (A) yielded mostly intractable gums, *p*-chlorobenzaldehyde (10%) [2,4-dinitrophenylhydrazone, m.p. 268—269° (lit.,³¹ 270°)], and ammonium bromide (11%).

Similar results were obtained with compounds (Ia), (Ic), and (Id); in all cases greater than 50% yields of the corresponding oxadiazoles (IVa), (IVb), and (IVc) were obtained.

(c) *With bromine in the absence of base.* The following is a typical example. Bromine (1.1 ml) in anhydrous glacial acetic acid (7 ml) was added dropwise during 10 min to a stirred suspension of compound (Ib) (2.8 g) in the same solvent (15 ml). The mixture was stirred for 48 h at ambient temperature and the white solid (1.05 g) [filtrate (A)] which separated was removed. Ammonium bromide (100 mg) was removed from this solid by stirring in water. The water-insoluble material (900 mg), m.p. 410—412° (from glacial acetic acid) was compound (VIb) (lit.,¹¹ m.p. 406°) (Found: C, 49.25; H, 3.05; N, 21.3. Calc. for C₈H₆ClN₃O: C, 49.1; H, 3.05; N, 21.5%), and was identical (mixed m.p. and i.r. spectrum) with an authentic sample.¹¹

When the filtrate (A) was evaporated to about one-third of its volume under a stream of cold air a further crop (220 mg, total yield 43%) of compound (VIb) was obtained. The filtrate from this crop was added to ice-cold water (100 ml); starting material (Ib) (720 mg) contaminated with some of its hydrobromide, precipitated. This was removed, and when the filtrate was brought to pH 9 with dilute sodium carbonate solution, a white precipitate [80 mg, 2.8%; m.p. 273—274° (from ethanol)] [filtrate (B)] separated. This material was the oxadiazole (IVb), and was identical (mixed m.p. and i.r. spectrum) with an authentic sample. When the filtrate (B) was extracted with ether (3 × 50 ml) and the combined extracts were dried and evaporated, a small quantity of an intractable gum was obtained. In similar reactions with compounds (Ia) and (Id) these ethereal extracts contained small quantities of the parent aldehyde, which was isolated as a 2,4-dinitrophenylhydrazone derivative.

The results of a series of these reactions are summarised in Table 1. The materials (VI) obtained were soluble in dilute aqueous sodium carbonate or dilute sodium hydroxide and could be recovered quantitatively from the basic solutions by acidification with dilute hydrochloric acid. The i.r. spectra showed strong triazolone carbonyl absorption at 1725—1735 cm⁻¹ and N—H absorption at 3120 cm⁻¹. The materials which were identical with authentic samples,¹¹ had the following characteristics: compound (VIa), m.p. 332—333° (lit.,¹¹ 324°) (Found: C, 59.6; H, 4.5; N, 26.3. Calc. for C₈H₇N₃O: C, 59.6; H, 4.35; N, 26.1%); 3-*p*-bromophenyl-1,2,4-triazol-5(4H)-one (VIc), m.p. 425—428° (Found: C, 39.65; H, 2.5; N, 17.65. C₈H₆BrN₃O requires C, 40.0; H, 2.5; N, 17.5%); 3-*p*-tolyl-1,2,4-triazol-5(4H)-one, m.p. 375—377° (Found: C, 61.7; H, 5.05; N, 23.75. C₉H₉N₃O requires C, 61.7; H, 5.15; N, 24.0%); compound (VIe), m.p. 349—347° (lit.,¹¹ 334°) (Found: C, 56.2; H, 4.3; N, 21.55. Calc. for C₉H₉N₃O₂: C, 56.55; H, 4.7; N, 22.0%).

(d) *With lead tetra-acetate (LTA).* The following is a typical example. LTA (5.5 g) in glacial acetic acid (5 ml)

³¹ Ref. 30, p. 320.

³² C. Voegelé, *Rec. Trav. chim.*, 1943, **62**, 5.

³³ G. Blankenstein and K. Mockel, *Z. Chem.*, 1962, **2**, 69.

³⁰ R. L. Shriner, R. C. Fuson, and D. Y. Curtin, 'The Systematic Identification of Organic Compounds,' Wiley, New York, 1964, 5th edn., p. 253.

was added during 3 min to a stirred suspension of compound (Id) (2 g) in the same solvent (15 ml). The mixture was stirred for 15–20 min at ambient temperature and the white solid (1.3 g; m.p. 262–265°) [filtrate (A)] which had separated was removed. This material, [m.p. 265–267° (from ethanol)] was identical (mixed m.p. and i.r. spectra) with an authentic sample of compound (IVd).

When the filtrate (A) was carefully added to ice-cold water (100 ml) a second crop (550 mg) of compound (IVd) was obtained (total yield 92%). Further work-up of the mother liquor by the procedure developed in ref. 34 yielded only intractable gums.

The yields of other oxadiazoles were prepared similarly as follows: (IVa) 87%; (IVb) 65%; (IVc) 63%; (IVe) 89%. For compounds with electron-withdrawing substituents [*i.e.* (Ib and c)] the reaction was slower and it was necessary to heat the mixture gently. For these two materials up to 30% of starting material was recovered unchanged.

(e) *Interconversion of products.* When the products (IV) and (VI) were treated under any of the various conditions which brought about cyclisation of the parent semicarbazones (I), the materials were quantitatively recovered unchanged and there was no evidence for interconversion.

Oxidation of the 2-Methylsemicarbazones (III).—(a) *With bromine in the presence of sodium acetate.* The following is a typical example. Bromine (0.26 ml) in glacial acetic acid (2 ml) was added to stirred solution of compound (IIIb) (1 g) and anhydrous sodium acetate (1.5 g) in the same solvent (10 ml). The mixture was stirred for 6 h and poured into ice-cold water (100 ml), whereupon starting material (710 mg) separated. The filtrate was set aside for 12 h and white crystals [80 mg, 11%; m.p. 241–242° (from ethanol) (lit.,³⁵ 242°)] of *p*-chlorobenzoic acid separated, identical (mixed m.p. and i.r. spectrum) with an authentic sample.

Further work-up of the reaction solution yielded starting material (IIIb) (30 mg; total recovery 74%) and small quantities of gums. Similar results were obtained when compounds (IIIa) and (IIIc) were treated with bromine and sodium acetate, *i.e.* up to 75% of starting material was recovered along with small amounts of decomposition products.

(b) *With bromine in the absence of base.* The following are typical examples. (i) *Ambient temperature.* Bromine (0.58 ml) in glacial acetic acid (1 ml) was added dropwise during 15 min to a stirred solution of compound (IIIa) (1 g) in the same solvent (4 ml), and the mixture was stirred for 2 h at ambient temperature. The reddish solid (1.35 g, 71%; m.p. 118–125°) which separated was washed with dry ether and dried (CaCl₂) *in vacuo*. It lost bromine continuously and proved impossible to purify. However, analytical data suggested that the material was *benzaldehyde 2-methylsemicarbazone hydrobromide perbromide* (VIIIa) (Found: C, 28.15; H, 3.1; Br, 55.7; N, 10.8. C₉H₁₂Br₃N₃O requires C, 25.85; H, 2.85; Br, 57.0; N, 10.05%).

Similar reactions with compound (IIIb and c) yielded the corresponding materials (VIII) in greater than 70% yields. Compound (VIIIb) had m.p. 143–148° (Found: C, 25.8; H, 2.65; Br, 51.5; Cl, 8.6; N, 10.6. C₉H₁₁Br₃ClN₃O re-

quires C, 23.85; H, 2.45; Br, 53.05; Cl, 7.85; N, 9.3%); compound (VIIIc) had m.p. 148–153° (Found: C, 23.8; H, 2.3; Br, 61.55; N, 10.0. C₉H₁₁Br₄N₃O requires C, 21.75; H, 2.2; Br, 64.4; N, 8.45%).

The materials (VIII) liberated iodine from potassium iodide in methanol and when they were distributed between aqueous sodium thiosulphate and ether the semicarbazones (VI) were recoverable quantitatively from the ethereal layers. When they were heated with acetanilide in glacial acetic acid,¹⁴ low yields (less than 50%) of *p*-bromoacetanilide were obtained, as expected.

(ii) *Higher temperature.* Bromine (0.49 ml) in glacial acetic acid (4 ml) was added during 15 min to a stirred solution of compound (IIIb) (1 g) in the same solvent (5 ml) at 90–95°, and the mixture was stirred for a further 15 min at this temperature. It was then cooled and carefully added to ice-cold water (100 ml), whereupon white crystals (780 mg, 78%; m.p. 288–290°) of 3-*p*-chlorophenyl-1-methyl-1,2,4-triazol-5(4H)-one (VIIb) separated [m.p. 289–291° (from glacial acetic acid)] (Found: C, 51.9; H, 3.65; N, 20.5. C₉H₈ClN₃O requires C, 51.55; H, 3.8; N, 20.05%), identical (mixed m.p. and i.r. spectrum) with an authentic sample.¹⁶ Similar reactions with the compounds (IIIa and c) yielded the corresponding materials (VII). Compound (VIIa) had m.p. 218–219° (lit.,¹⁶ 218°) (from ethanol) (Found: C, 61.65; H, 5.05; N, 24.3. Calc. for C₉H₉N₃O: C, 61.7; H, 5.15; N, 24.0%). Compound (VIIc) had m.p. 318–320° (from glacial acetic acid) (Found: C, 42.6; H, 3.15; N, 16.85. C₉H₈BrN₃O requires C, 42.5; H, 3.15; N, 16.55%).

In accordance with expectation the materials (VIII) were soluble in dilute base and could be recovered quantitatively by acidification with dilute acid. Their i.r. spectra showed a strong triazolone carbonyl absorption at 1695–1703 cm⁻¹.

(c) *With lead tetra-acetate.* When the materials (IIIa–c) were treated with LTA in the manner already described, there was no evidence of reaction, and when the solutions were added to water large-scale decomposition of unchanged LTA occurred. Careful work-up of the mixtures yielded over 85% of the starting semicarbazones unchanged.

Rate Study

The reaction solvent aqueous 70% acetic acid, prepared from 70 volumes of acetic acid (AnalaR) (refluxed over chromium trioxide then distilled; the portion with b.p. 117–118° was used) and 30 volumes of deionised water (twice distilled from alkaline potassium permanganate to remove traces of impurity capable of reacting with bromine). AnalaR potassium bromide was added to this to make a 0.1M-solution. All inorganic chemicals (potassium bromide and potassium nitrate) were of AnalaR grade and were dried at 120° before use. The kinetic method itself, using as its basis an amperometric method and a Metrohm Polarocord (E261R), has been dealt with in a previous paper.²¹

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³⁴ F. L. Scott and R. N. Butler, *J. Chem. Soc. (C)*, 1966, 1202.

³⁵ Ref. 30, p. 315.