Synthesis and Rearrangement of Hydrazidic Azides

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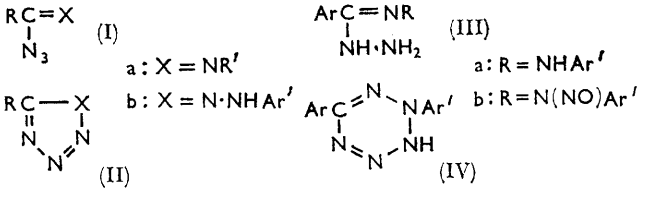
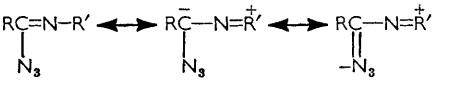
Hydrazidic azides have been synthesised by the reaction of hydrazidic halides with azide ion. The azides could not be converted into the isomeric tetrazoles under a variety of conditions. An earlier claim that the corresponding tetrazoles are products of the reaction of hydrazidines with nitrous acid must be regarded with doubt. On treatment with trifluoroacetic acid, or in acetic–sulphuric acid, hydrazidic azides rearrange to semicarbazides. In trifluoroacetic acid, both trifluoroacetyl semicarbazide and the parent semicarbazide are isolated, and the variation in yield with the nature of the hydrazidic azide has been investigated. We have also demonstrated, by use of an optically active hydrazidic azide substrate, that the migrating group in the azide rearrangement retains its configuration.

ACYL azides and similar compounds may have the open-chain structure (I) or a cyclic form (II), depending on the nature of X. Irrespective of the character of R, when X = O only form (I) is detected [1] and when X = S



only form (II) is detected.[2] When X is a substituted amino-group, both the azidine form (Ia) and the tetrazolyl form (IIa) can exist. The balance or equilibrium between the two forms is subtly dependent on the nature of R and R′.[3] Where R = aryl, with R′ = H, alkyl, or aryl the tetrazole tautomer is the more stable,[4] whereas with R′ = OH, alkoxy or acyloxy, only the azidine form is detectable.[5] There is presumably additional stabilisation of the azidine form in the latter instances, due to resonance, *e.g.*,



On that basis one would predict that the hydrazidic azides, in which R′ again possesses lone-pair electrons, would also be more stable in the open-chain form (Ib). Some data in the literature conflict with this prediction. The nitrosation of amidrazones is a standard route to azidines, and nitrosation of the hydrazidic hydrazines (or hydrazidines) (IIIa) has been reported. Burgess and Gibson [6] demonstrated that the products of this nitrosation were not the substituted azides (Ib), because they lacked the characteristic azide stretching absorption at 2150 cm.$^{-1}$. Of the alternatives (IV) [7] and (IIb),[8] they assigned the tetrazole structure to the three materials they examined.

We have repeated the work of Burgess and Gibson,[6] starting with hydrazidines (IIIa) having various substituents (Table 1), prepared by the reaction of hydrazidic bromides with hydrazine hydrate in 95% ethanol.

[1] E. Lieber and C. N. R. Rao, *Chem. Rev.*, 1965, **65**, 377.
[2] E. Lieber, E. Offendahl, and C. N. R. Rao, *J. Org. Chem.*, 1963, **28**, 164.
[3] Cf. W. P. Norris and R. A. Henry, *J. Org. Chem.*, 1964, **29**, 650, for discussions and relevant references.
[4] J. V. Braun and W. Rudolph, *Ber.*, 1941, 264; G. Schroeter, *ibid.*, 1909, **42**, 3356; C. Ainsworth, *J. Amer. Chem. Soc.*, 1953, **75**, 5728.
[5] F. Eloy, *J. Org. Chem.*, 1960, **26**, 952; M. S. Chang and A. J. Matuszko, *ibid.*, 1963, **28**, 2260.
[6] J. M. Burgess and M. S. Gibson, *Tetrahedron*, 1962, **18**, 1001.
[7] F. D. Chattaway and G. D. Parkes, *J. Chem. Soc.*, 1926, 113.
[8] R. Stolle, *J. prakt. Chem.*, 1926, **114**, 348.

They were nitrosated in hydrochloric acid using a four-fold excess of sodium nitrite at 0°, to give, in *ca.* 80% yields, the compounds formulated as tetrazoles (IIb) by Burgess and Gibson.[6] We have confirmed that they do not (with the exceptions noted) have azide infrared absorptions, but the spectra cannot be readily used to distinguish unequivocally between the two possible structures (IIb) and (IV). When the nitrosation was attempted with hydrazidines (IIIa) in which Ar contained electron-donating groups, *e.g.*, *p*-tolyl or *p*-isopropylphenyl, extensive decomposition occurred.

It was then considered that with compounds such as the hydrazidines (IIIa) the nitrosation technique might not be the most satisfactory route to the possible azides, because nitrosation of compound (IIIa) could occur at any (or all) of the hydrogen atoms of the $NH{\cdot}NH_2$ function, to produce an azide–tetrazole system, or alternatively at the NH adjacent to Ar′, *i.e.*, a process akin to the nitrosation of hydrazones. If the latter event happened, the intermediate (IIIb) might not lead to compounds (Ib) or (IIb). Accordingly, we used another standard route to azidines to prepare the systems (Ib)—(IIb). This involved reaction of a hydrazidic bromide with sodium azide in 80% aqueous dioxan. The products were different from those obtained in nitrosation reactions, and their infrared spectra showed them to be the required hydrazidic azides (Ib). These reactions with azide ion are complete in *ca.* 1 min. at room temperature. They presumably take place through an initially formed 1,3-dipolar ion, on loss of hydrogen bromide from the hydrazidic bromide (since the competing S_N1 reaction, with azocarbonium ion formation, is very much slower in this solvent mixture [9]). However, in the reactions to form the hydrazidic azides, there is competition with the solvent water, since small quantities (1—3%) of the equivalent hydrazides [9] were also isolated. The replacement reaction to form hydrazidic azides was successful in all cases (see Table 2), even for compounds whose hydrazidines could not be successfully nitrosated. All these azides (Ib) absorbed strongly at 2130 $cm.^{-1}$ with little or no variation due to substituents (R and Ar′) used, while the N–H stretching absorption was at 3350 $cm.^{-1}$.

Attempts to cyclise the azides (Ib) to either the tetrazole (IIb) or the dihydropentazine (IV), under a variety of conditions which effect this change in other systems,[10] were unsuccessful. Thus, on dissolution in 10% sodium hydroxide followed by reprecipitation by acid or warming for 3 hr. in methanol or in dioxan in the presence of sodium acetate, the azides (Ib) were recovered quantitatively. Also, cyclisation did not occur when they were treated in hydrochloric acid with sodium nitrite under the conditions used for the preparation of the cyclic materials. In fact, they have remarkable stability, comparable to that of azidoximes,[5] since they crystallise unchanged from aqueous acetone or ethanol. Under strongly acid conditions, rearrangement results in the formation of semicarbazides.[11]

Reactions of electrophilic agents with hydrazones which contain an *o*-nitro-group are sluggish (*e.g.*, with lead tetra-acetate [12]) or do not occur (*e.g.*, with nitrosobisulphate [13]), and the effect of an *o*-nitro-group (which is tightly bonded to the amino hydrogen of the hydrazone) has been compared, from kinetic studies,[14] to the effect of using an *NN*-disubstituted hydrazone. Busch *et al.*[15] showed that such *NN*-disubstituted hydrazones do not react with nitrous acid (to give nitroso-hydrazones). When a hydrazidine with an *o*-nitro-group [IIIa; Ar = Me_3C, Ar′ = 2,4-$(NO_2)_2C_6H_3$] was nitrosated under the conditions used for the preparation of the cyclic compounds, the hydrazidic azide (Ib) was formed rather than (IIb) or (IV). Thus, in a reaction where electrophilic attack (nitrosation) at one of the possible sites of the hydrazone is retarded (by the presence of the *o*-nitro-group), the azide is formed in good yield, presumably by nitrosation of the primary hydrazine nitrogen of (IIIa). This suggests that nitrosation of hydrazidines which have not this *o*-nitro-group and give cyclic materials occurs, not on the basic primary hydrazine nitrogen (which would be protonated under the acid conditions used), but at some site in the hydrazone part of (IIIa).

Thus, the tetrazole formulation (IIb) must be viewed with doubt; moreover, there are no reports in similar systems of the two routes (nitrosation of a hydrazino azomethine and replacement of an imidic halide by azide ion) giving two different relatively stable non-interconvertible products, (Ia) and (IIa).

As mentioned above, in an attempt to achieve azide–tetrazole equilibrium, the hydrazidic azide (Ib; R = Ph, Ar′ = 2-Br,4-$NO_2C_6H_3$) was suspended, for 24 hr. at room temperature, in trifluoroacetic acid.[16] However, in this solvent, nitrogen was evolved and a Schmidt-type rearrangement of the hydrazidic azide took place. Two compounds were isolated: one was the semicarbazide

RNH·CO·NH·NHAr (V)
RNH·CO·NH·N(CO·CF_3)Ar (VI)

(V; R = Ph, Ar = 2-Br,4-$NO_2C_6H_3$) which was synthesised unambiguously by the reaction of phenyl isocyanate with 2-bromo-4-nitrophenylhydrazine, and the other was its trifluoroacetyl derivative for which the infrared data point to structure (VI) rather than (VIII); moreover, (VIII) would be expected to rearrange (through a five-membered transition-state) to

[9] F. L. Scott and J. B. Aylward, *Tetrahedron Letters*, 1965, 841.
[10] R. Stolle and E. Helwerth, *Ber.*, 1914, **47**, 1132; R. Stolle and A. Netz, *ibid.*, 1922, **55**, 1297.
[11] A. F. Hegarty, J. B. Aylward, and F. L. Scott, *Tetrahedron Letters*, 1967, 1257.
[12] D. C. Iffland, L. Salisbury, and W. R. Schafer, *J. Amer. Chem. Soc.*, 1961, **83**, 747.
[13] H. J. Teuber and K. H. Dietz, *Angew. Chem., Internat. Edn.*, 1966, **5**, 1049.
[14] A. F. Hegarty and F. L. Scott, *Chem. Comm.*, 1967, 521.
[15] M. Busch and H. Kunder, *Ber.*, 1916, **49**, 317.
[16] C. Temple, W. C. Coburn, M. C. Thorpe, and J. A. Montgomery, *J. Org. Chem.*, 1965, **30**, 2395.

TABLE 1

The hydrazidines $RC(NH{\cdot}NH_2){:}N{\cdot}NHAr$ and their benzylidene derivatives

R	Ar	M. p.	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
Ph	2-Br,4-$NO_2C_6H_3$	176°	44·4	3·6		$C_{13}H_{12}BrN_5O_2$	44·6	3·4	
Benzylidene derivative		197	54·9	3·7		$C_{20}H_{16}BrN_5O_2$	54·8	3·6	
4-$Me_2CH{\cdot}C_6H_4$	2-Br,4-$NO_2C_6H_3$	167	49·1	4·1	17·6	$C_{16}H_{18}BrN_5O_2$	48·8	4·5	17·8
Benzylidene derivative		190	57·5	3·2		$C_{23}H_{22}BrN_5O_2$	57·5	3·2	
4-$Cl{\cdot}C_6H_4$	2-Br,4-$NO_2C_6H_3$	187	40·2	2·7	18·4	$C_{13}H_{11}BrClN_5O_2$	40·6	2·9	18·2
Benzylidene derivative		203	50·5	3·3		$C_{20}H_{15}BrClN_5O_2$	50·8	3·2	
Ph	4-$NO_2{\cdot}C_6H_4$	158	57·3	5·4	25·8	$C_{13}H_{13}N_5O_2$	57·5	5·0	25·8
Benzylidene derivative		194	66·5	4·9		$C_{20}H_{17}N_5O_2$	67·0	4·8	
4-$Me{\cdot}C_6H_4$	4-$NO_2{\cdot}C_6H_4$	149	59·2	4·2	24·0	$C_{14}H_{12}N_5O_2$	59·5	4·3	24·5
Benzylidene derivative		193	68·3	4·3		$C_{21}H_{16}N_5O_2$	68·7	4·3	
4-$Br{\cdot}C_6H_4$	4-$NO_2{\cdot}C_6H_4$	169	44·0	3·5	20·1	$C_{21}H_{12}BrN_5O_2$	44·4	3·4	20·0
Benzylidene derivative		198	54·5	3·8		$C_{20}H_{16}BrN_5O_2$	54·8	3·6	
Me	2,4-$(NO_2)_2C_6H_3$	172	37·6	3·8	32·8	$C_8H_{10}N_6O_4$	37·8	3·9	33·0
MeEtCH	2,4-$(NO_2)_2C_6H_3$	180	44·9	5·6	28·2	$C_{11}H_{16}N_6O_4$	44·6	5·5	28·4
Me_3C	2,4-$(NO_2)_2C_6H_3$	198	44·9	5·6	28·2	$C_{11}H_{16}N_6O_4$	44·6	5·4	28·4

TABLE 2

The hydrazidic azides $RC(N_3){:}N{\cdot}NHAr$

R	Ar	M. p.	Yield (%)	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
Ph	2-Br,4-$NO_2C_6H_3$	111°	74	43·4	2·9	23·2	$C_{13}H_9BrN_6O_2$	43·2	2·5	23·4
4-$Cl{\cdot}C_6H_4$	2-Br,4-$NO_2C_6H_3$	125	87	39·4	2·3	21·3	$C_{13}H_8BrClN_6O_2$	39·5	2·0	21·3
4-$Me_2CH{\cdot}C_6H_4$	2-Br,4-$NO_2C_6H_3$	118	79	47·4	3·4	20·4	$C_{16}H_{15}BrN_6O_2$	47·4	3·9	20·8
Ph	4-$NO_2{\cdot}C_6H_4$	130	83	55·5	3·5	30·0	$C_{13}H_{10}N_6O_2$	55·3	3·5	29·8
4-$Me{\cdot}C_6H_4$	4-$NO_2{\cdot}C_6H_4$	131	75	56·9	4·4	28·4	$C_{14}H_{12}N_6O_2$	56·7	4·1	28·4
4-$Br{\cdot}C_6H_4$	4-$NO_2{\cdot}C_6H_4$	142	76	43·6	2·5	22·9	$C_{13}H_9BrN_6O_2$	43·2	2·5	23·2
Ph	2,4-$Br_2C_6H_3$	96	86	39·8	2·5	17·5	$C_{13}H_9Br_2N_5$	39·4	2·3	17·7
Me	2,4-$(NO_2)_2C_6H_3$	131	76	36·7	2·2	36·7	$C_8H_7N_7O_4$	36·25	2·7	37·1
MeEtCH	2,4-$(NO_2)_2C_6H_3$	141	82	43·3	4·5	32·3	$C_{11}H_{13}N_7O_4$	43·0	4·3	31·9
Me_3C	2,4-$(NO_2)_2C_6H_3$	151	88	42·7	4·2	31·9	$C_{11}H_{13}N_7O_4$	43·0	4·3	31·9

the *N*-acetyl compound (VI), and such hydrazidic acetates have not been isolated.[17]

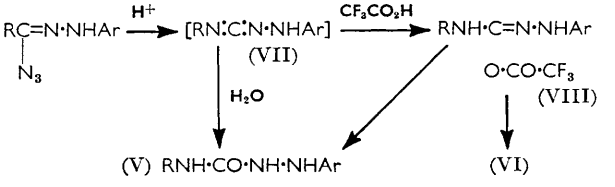
The influence of substituents in R and Ar on the speed of the rearrangement and the relative amounts of (V) and (VI) was also investigated (Table 3; analytical

TABLE 3

Reaction of hydrazidic azides $RC(N_3){:}N{\cdot}NHAr$

R	Ar	In trifluoroacetic acid (V) (%)	In trifluoroacetic acid (VI) (%)	In trifluoroacetic acid Time (hr.)	In sulphuric–acetic acid (V) (%)	In sulphuric–acetic acid Time (min.)
Ph	2-Br,4-$NO_2C_6H_3$	58	33	24	87	15
4-$Me_2CH{\cdot}C_6H_4$	2-Br,4-$NO_2C_6H_3$	18	73	1	84	5
4-$Cl{\cdot}C_6H_4$	2-Br,4-$NO_2C_6H_3$	86	6	72	90	1440
Ph	4-$NO_2{\cdot}C_6H_4$	5	81	1	84	10
4-$Me{\cdot}C_6H_4$	4-$NO_2{\cdot}C_6H_4$	3	86	0·5	84	5
4-$Br{\cdot}C_6H_4$	4-$NO_2{\cdot}C_6H_4$	12	79	48	86	720
Ph	2,4-$Br_2C_6H_3$	53	35	24	89	20

data in Tables 4 and 5). The reaction times in Table 3 are presumably a measure of the relative ease of formation of the *N*-amino-carbodi-imide (VII), and the observed substituent effects are consistent with data for the Schmidt rearrangements of acyl azides[18] and 1,5-disubstituted tetrazoles.[19] The predominance of (V) over (VI) in the slower reactions is not due to the hydrolysis of a first-formed *N*-acetyl compound (VI), since (VI) was stable in trifluoroacetic acid under the conditions used for the rearrangement of the hydrazidic azides. Moreover, the relative amounts of (V) and (VI) were approximately the same if reaction times were shorter than those in Table 3. Compound (VI) was also not formed by trifluoroacetylation of (V), since the latter was recovered quantitatively from trifluoroacetic acid solution after 24 hr.



Although the formation of relatively larger amounts of (V) from (VII) with electron-withdrawing groups in Ar or R could be explained by the existence of competitive

[17] F. L. Scott and R. N. Butler, *J. Chem. Soc.* (*C*), 1966, 1202; J. M. Burgess and M. S. Gibson, *ibid.*, 1964, 1500; J. T. Edward and S. A. Samad, *Canad. J. Chem.*, 1963, **41**, 1638.

[18] P. A. S. Smith, *J. Amer. Chem. Soc.*, 1948, **70**, 320.

[19] J. Vaughan and P. A. S. Smith, *J. Org. Chem.*, 1958, **23**, 1909.

acid-catalysed hydration [20] and reaction with trifluoroacetic acid,[21] the results may also be explained by the occurrence of the latter process alone. The reaction of carbodi-imides with carboxylic acids occurs readily,[22] giving mixtures of ureas (formed by reaction of a second molecule of the acid with an intermediate *C*-acetate; the acid anhydride is another product) and the corresponding *N*-acyl-urea (by rearrangement of the *C*-acetate). The relative amounts of rearranged product (VI) formed are consistent with this; electron-withdrawing groups aid the rearrangement (VIII) ⟶ (VI) [23] relative to the displacement of the trifluoroacetyl group by a second molecule of trifluoroacetic acid [formation of (V)].[22] The presence of an *o*-bromo-group in the hydrazine ring increases the relative yield of the semicarbazide (Table 3), presumably by slowing the rearrangement of the acetate (VIII) to the *N*-acetyl compound (VI). Similar effects have been noted in the usually facile rearrangements of imidic acetates; only those imidic acetates with very large groups to slow the rearrangement to the isomeric *N*-acetyl compounds having been isolated.[23]

The rearrangement of the hydrazidic azide (Ia) to the semicarbazide (V) was achieved in good yield and without product complications by suspending the azide in 2·2M-sulphuric acid in acetic acid at room temperature until the evolution of nitrogen had ceased. Again the reaction was slower when hydrazidic azides with electron-withdrawing substituents were used (see Table 3), but the overall reaction times required were much shorter than for the corresponding reactions in trifluoroacetic acid.

As shown above, the isolation of hydrazidic azides and their demonstrated failure to cyclise to give tetrazoles casts doubt on the tetrazole structure for the compounds isolated from the nitrosation of hydrazidines. Moreover, if these compounds were tetrazoles (IIb) they might be expected to rearrange in the manner suggested [24] for 1,5-disubstituted tetrazoles, particularly since, as we have shown, the reactive open azide form (Ia) is far more stable when R′ = NHAr than when R′ = alkyl. But when compound (IIb; R = Ph, Ar′ = 2-Br,4-$NO_2C_6H_3$) was dissolved in trifluoroacetic acid or in acetic–sulphuric acid solution for 3 weeks no rearrangement occurred and the starting material was recovered unchanged.

To clarify further the mechanism of the migration reaction, an optically active hydrazidic azide was prepared and its rearrangement in acid solution studied. D-(−)-2-methylbutan-1-ol was oxidised to D-(+)-2-methylbutyraldehyde, whose 2,4-dinitrophenylhydrazone was brominated in acetic acid solution with complete retention of configuration, to give the hydrazidic bromide [(IX); R = MeEtCH, Ar = 2,4-$(NO_2)_2C_6H_3$].[25] This, on treatment with azide ion, gave a hydrazidic azide which was suspended in acetic–sulphuric acid for 4 min., to yield the semicarbazide (V), $[\alpha]_{578}^{25}$ +36·5°, which was also prepared unambiguously by another route starting with the same optically active alcohol. D-(+)-2-

TABLE 4

The semicarbazides RNH·CO·NH·NHAr

R	Ar	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N
Ph	2-Br,4-$NO_2C_6H_3$	236°	44·5	3·35	15·8	$C_{13}H_{11}BrN_4O_3$	44·4	3·1	15·95
4-$Me_2CH{\cdot}C_6H_4$	2-Br,4-$NO_2C_6H_3$	221	48·9	4·1	14·5	$C_{16}H_{17}BrN_4O_3$	48·8	4·3	14·2
4-$Cl{\cdot}C_6H_4$	2-Br,4-$NO_2C_6H_3$	250	41·0	4·0	14·5	$C_{13}H_{10}BrClN_4O_3$	40·5	2·6	14·5
Ph	4-$NO_2{\cdot}C_6H_4$	224	57·4	4·4	—	$C_{13}H_{12}N_4O_3$	57·3	4·4	—
4-$Me{\cdot}C_6H_4$	4-$NO_2{\cdot}C_6H_4$	232	58·5	5·0	—	$C_{14}H_{14}N_4O_3$	58·8	4·9	—
4-$Br{\cdot}C_6H_4$	4-$NO_2{\cdot}C_6H_4$	239	44·4	3·3	16·1	$C_{13}H_{11}BrN_4O_3$	44·4	3·1	16·0
Ph	2,4-$Br_2C_6H_3$	213	41·5	2·8	10·8	$C_{13}H_{11}Br_2N_3O$	41·6	2·8	11·1

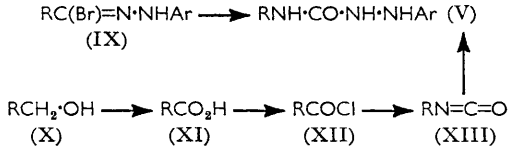
TABLE 5

The *N*-trifluoroacetyl semicarbazides RNH·CO·NH·N(CO·CF_3)Ar

R	Ar	M. p.	Found (%) C	H	F	N	Formula	Required (%) C	H	F	N
Ph	2-Br,4-$NO_2C_6H_3$	162°	40·4	2·6	13·0	12·2	$C_{15}H_{10}BrF_3N_4O_4$	40·2	2·3	12·8	12·5
4-$Me_2CH{\cdot}C_6H_4$	2-Br,4-$NO_2C_6H_3$	160	44·6	3·5	11·7	11·2	$C_{18}H_{16}BrF_3N_4O_4$	44·2	3·2	11·6	11·4
4-$Cl{\cdot}C_6H_4$	2-Br,4-$NO_2C_6H_3$	193	37·1	1·5	11·9	11·7	$C_{13}H_9BrClFN_4O_4$	37·4	1·9	11·8	11·6
Ph	4-$NO_2{\cdot}C_6H_4$	216	49·3	3·4	14·9	15·0	$C_{15}H_{11}F_3N_4O_4$	48·9	3·0	15·4	15·2
4-$Me{\cdot}C_6H_4$	4-$NO_2{\cdot}C_6H_4$	214	50·5	3·6	14·5	14·6	$C_{16}H_{13}F_3N_4O_4$	50·3	3·4	14·9	14·8
4-$Br{\cdot}C_6H_4$	4-$NO_2{\cdot}C_6H_4$	210	39·7	2·5	11·7	12·6	$C_{15}H_{10}BrF_3N_4O_4$	40·3	2·2	12·0	12·5
Ph	2,4-$Br_2C_6H_3$	158	38·6	2·0	9·5	9·2	$C_{15}H_{10}Br_2F_3N_3O_2$	38·2	2·2	9·1	8·9

[20] S. Hunig, H. Lehmann, and G. Grimmer, *Annalen*, 1953, **579**, 77, 87.
[21] D. B. Jones and D. C. Wigfield, *Canad. J. Chem.*, 1966, **44**, 2517.
[22] M. Smith, J. G. Moffatt, and H. G. Khorana, *J. Amer. Chem. Soc.*, 1958, **80**, 6204.
[23] D. Y. Curtin and L. L. Miller, *Tetrahedron Letters*, 1965, 1869; *J. Amer. Chem. Soc.*, 1967, **89**, 637.
[24] P. A. S. Smith and E. Leon, *J. Amer. Chem. Soc.*, 1958, **80**, 4647.
[25] A. F. Hegarty and F. L. Scott, to be published.

Methylbutan-1-ol (X; R = MeEtCH) was carefully oxidised to the corresponding acid (XI) which was converted into the acid chloride (XII) using thionyl



chloride. Treatment of this with azide ion followed by rearrangement gave the isocyanate (XIII; R = MeEtCH), which reacted with 2,4-dinitrophenylhydrazine to give the same semicarbazide [V; R = MeEtCH, Ar = 2,4-$(NO_2)_2C_6H_3$] as prepared by the rearrangement of the hydrazidic azide with the same (within experimental error) specific rotation. Since the formation of the isocyanate (XIII) by this reaction sequence is known to occur with almost complete retention of configuration at the asymmetric centre [26] and racemisation is unlikely to have occurred in the final step to form compound (V) which was carried out in anhydrous ether, the semicarbazide (V) formed by this route would essentially retain its optical activity (certainly <3% racemisation). Thus, in the rearrangement of hydrazidic azides to semicarbazides, migration occurs with retention of optical and geometric configuration.

EXPERIMENTAL

Melting points were measured on an Electrothermal apparatus. Infrared spectra were measured on a Perkin-Elmer Infracord model 137E spectrophotometer with sodium chloride optics. Solids were examined as potassium bromide discs.

Preparation of Hydrazidines (IIIa).—The preparation of one of the hydrazidines (IIIa; Ar = Ph, Ar′ = 2-Br,4-$NO_2C_6H_3$) is described; the others (Table 1) were similarly prepared. *N*-(2-Bromo-4-nitrophenyl)benzhydrazidic bromide (7·0 g.) [9] was stirred as a slurry in 95% ethanol (40 ml.) at room temperature, hydrazine hydrate (5 ml.) in water (5 ml.) was added dropwise, and the mixture was stirred for 12 hr. The deep red solid which had separated was filtered off (5·4 g., 87%), and recrystallisation from 95% ethanol gave the required *hydrazidine*, m. p. 176°. This hydrazidine (500 mg.) was suspended in 95% ethanol (30 ml.), benzaldehyde (0·2 ml.) was added, and the mixture was refluxed for 5 min. On cooling, the bright red *benzylidene derivative* precipitated (*ca.* 100%), m. p. 197° (from ethanol).

Nitrosation of Hydrazidines.—(*a*) *N*-(2-Bromo-4-nitrophenyl)benzhydrazidine (5·5 g.) was ground to a thin yellow paste with concentrated hydrochloric acid (*d* 1·18; 30 ml.) and water (12 ml.). The mixture was cooled to 0° and vigorously stirred while sodium nitrite (3·5 g.) in water (10 ml.) was added during 20 min. The mixture was set aside for a further 15 min. and the light brown precipitate which had formed (77%) was filtered off. Recrystallisation yielded the material previously [6] formulated as 1-(2-bromo-4-nitroanilino)-5-phenyltetrazole, m. p. 201—202° (lit.,[8] 201°). Its infrared spectrum was identical with that described [6] and azide absorptions were absent.

(*b*) *N*-(2-Bromo-4-nitrophenyl)-*p*-chlorobenzhydrazidine was similarly nitrosated, to give 1-(2-*bromo*-4-*nitroanilino*)-5-p-*chlorophenyltetrazole* (74%), m. p. 164° (Found: C, 39·3; H, 2·0; Br, 20·25; Cl, 9·0; N, 21·1. $C_{13}H_8BrClN_6O_2$ requires C, 39·5; H, 2·0; Br, 20·0; Cl, 8·8; N, 21·3%). Similarly, the compound formulated [6,7] as 1-(2,4-dibromoanilino)-5-phenyltetrazole was prepared (82%), m. p. 168—171° (lit.,[6] 172°).

(*c*) Extensive decomposition resulted when the other hydrazidines in Table 1 (with the exceptions listed below) were treated under these conditions with sodium nitrite. For example, *N*-(2-bromo-4-nitrophenyl)-*p*-isopropylbenzhydrazidine (3 g.) was stirred to a fine paste with concentrated hydrochloric acid (15 ml.) and water (7 ml.) and treated at 0° with sodium nitrite (2 g.) in water (8 ml.). The light brown material which formed was filtered off, m. p. 32—62°, but rapidly decomposed to a black tar-like solid either on standing or when treated with solvents such as benzene, chloroform, or dioxan. Its infrared spectrum taken before decomposition, showed most of the bands associated [6] with the tetrazole formulation (IIb) together with weak azide absorption at 2130 and carbonyl absorption at 1690 cm.$^{-1}$. Variation of the acid concentration, nitrite concentration, or the mode of addition of the nitrite solution (*e.g.*, addition of the concentrated acid to a mixture of the hydrazidine and sodium nitrite in water) gave similar results.

(*d*) *N*-(2,4-Dinitrophenyl)-*C*-t-butylhydrazidine [IIIa; Ar = Me_3C, Ar′ = 2,4-$(NO_2)_2C_6H_3$] (0·30 g.) was stirred to a fine yellow paste with concentrated hydrochloric acid (*d* 1·18; 2 ml.) and water (4 ml.) at 0°, and sodium nitrite (0·14 g.) in water (2 ml.) was added dropwise. The bright yellow solid which formed immediately (0·26 g., 82%), m. p. 148—149°, was N-(2,4-*dinitrophenyl*)-C-*t-butylhydrazidic azide* [Ib; R = Me_3C, Ar′ = 2,4-$(NO_2)_2C_6H_3$] which was also unambiguously prepared by the reaction of the hydrazidic bromide with sodium azide (see below). The analytical data are in Table 2 with data for the two other *N*-(2,4-dinitrophenyl)hydrazidic azides prepared by both routes.

Hydrazidic Azides (Ib).—As this is a general method for the preparation of the hydrazidic azides in Table 2, it will be described in detail for only one compound. *N*-(2-Bromo-4-nitrophenyl)benzhydrazidic bromide (1·0 g.) was added to dioxan–water (80 : 20) (70 ml.) and gently warmed (to about 35°) until a clear solution was obtained. To this was added sodium azide (0·22 g.) dissolved in the same solvent mixture (10 ml.); the mixture was rapidly cooled in an ice–salt bath and immediately a bright yellow material, m. p. 106—109° (decomp.), separated (0·65 g., 74%). On recrystallisation from acetone it gave N-(2-*bromo*-4-*nitrophenyl*)*benzhydrazidic azide*, m. p. 111° (Table 2). This had the strong characteristic azide absorption at 2130 cm.$^{-1}$. Addition of water to the filtrate from the reaction mixture precipitated further yellow material (103 mg.), m. p. 63—98°. Recrystallisation from acetone yielded further hydrazidic azide (78 mg., 8%) with the same m. p. (111°). The filtrates remaining were combined and extracted with ether. Titration of the aqueous layer showed that 96% of the theoretical amount of bromide ion (from the hydrazidic bromide) was present. Evaporation of the dried ethereal extracts yielded a sticky black material (186 mg.). This was boiled with pentane (20 ml.) for 10 min. and the remaining solid crystallised from acetone to

[26] P. A. S. Smith, 'Molecular Rearrangements,' ed. P. de Mayo, Wiley, New York, 1963, ch. 8.

give further hydrazidic azide (38 mg., 4%), while concentration of the acetone solution gave *N*-(2-bromo-4-nitrophenyl)benzhydrazide (23 mg., 3%), m. p. and mixed m. p. 196—199° (lit.,[9] 202°).

Attempted Cyclisation of Hydrazidic Azides.—(*a*) *N*-(2-Bromo-4-nitrophenyl)benzhydrazidic azide (Ib; R = Ph, Ar′ = 2-Br,4-$NO_2C_6H_3$) (0·50 g.) was suspended in a solution of concentrated hydrochloric acid (*d* 1·18; 5 ml.) and water (2 ml.) and treated with sodium nitrite (0·35 g.) in water (5 ml.) at 0°. The solution was stirred and the solid filtered off after 20 min. Unreacted starting material (the hydrazidic azide) was recovered (97%), m. p. 110°.

(*b*) The same hydrazidic azide (0·50 g.) was suspended in methanol (30 ml.) and warmed at 40° for 3 hr. The solution was then poured into cooled water, and a bright yellow material (0·48 g., 95%), m. p. 110°, precipitated; it was the starting hydrazidic azide. A similar reaction in dioxan (30 ml.) containing anhydrous sodium acetate (0·16 mg.) at 50° for 5 hr. returned the starting material in 97% yield.

(*c*) The same hydrazidic azide (0·50 g.) readily dissolved in 10% sodium hydroxide (15 ml.). The solution was set aside overnight and neutralised with 2N-hydrochloric acid; the starting material was reprecipitated (97%), m. p. 109–110°.

Rearrangements of Hydrazidic Azides.—(a) *In trifluoroacetic acid solution.* *N*-(2-Bromo-4-nitrophenyl)benzhydrazidic azide (0·50 g.) was suspended in trifluoroacetic acid (30 ml.) (Koch-Light; purity >99%) and left at room temperature for 24 hr. The solid had then dissolved and the solution was poured into water (400 ml.); the light yellow solid (0·45 g.) which precipitated was recrystallised several times from 95% ethanol, to give 1-(2-*bromo*-4-*nitrophenyl*)-4-*phenylsemicarbazide* (V; R = Ph, Ar = 2-Br,4-$NO_2C_6H_3$), m. p. 236° (58%) (Table 4), identical (mixed m. p., infrared spectra) with that prepared unambiguously by the reaction of equimolar quantities of phenyl isocyanate and 2-bromo-4-nitrophenylhydrazine in dry ether catalysed by a drop of pyridine.

The 95% alcohol from which the above semicarbazide was obtained was concentrated, and a second material (27%) separated, m. p. 162° (from acetone–water) (Table 5), infrared (carbonyl bands at 1675 and 1750 $cm.^{-1}$). It was a *trifluoroacetyl derivative* of the semicarbazide (VI; R = Ph, Ar = 2-Br,4-$NO_2C_6H_3$).

(b) *In sulphuric–acetic acid solution.* *N*-(2-Bromo-4-nitrophenyl)benzhydrazidic azide (0·50 g.) was suspended in acetic acid (25 ml.) containing concentrated sulphuric acid (3 ml.). The mixture was stirred and the compound dissolved with the evolution of a gas. When the gas evolution had ceased (15 min.), the solution was filtered through a sintered glass funnel into water (100 ml.) and immediate precipitation occurred. The solid (0·42 g., 87%) was recrystallised from aqueous ethanol, giving 1-(2-bromo-4-nitrophenyl)-4-phenylsemicarbazide, m. p. 236°. Neutralisation of the aqueous acetic acid solution followed by ether extraction did not yield any further pure material.

The other hydrazidic azides in Table 2, when treated similarly, in sulphuric–acetic acid solution also gave semicarbazides (Table 4). However, different reaction times were required (at room temperature) as judged by the completion of nitrogen evolution; compounds containing electron-withdrawing groups in R and Ar requiring longer times in the acid mixture to complete the reaction (Table 3).

In trifluoroacetic acid [method (a) above] the time taken to complete the reaction also depended on the substrate used (Table 3); the variation in the relative amounts of the semicarbazide and its trifluoroacetyl derivative (Table 5) is also in Table 3.

Attempted Reaction of Compound (IIb) *in* (a) *Trifluoroacetic Acid and* (b) *Sulphuric–Acetic Acid.*—(*a*) Compound (IIb; R = Ph, Ar′ = 2-Br,4-$NO_2C_6H_3$) (0·50 g.) was dissolved in trifluoroacetic acid (50 ml.) and set aside in a stoppered flask for 7 days. The solution was poured into water and starting material (96%) was returned, m. p. 200°.

(*b*) The same compound (0·50 g.) was dissolved in glacial acetic acid (25 ml.) containing concentrated sulphuric acid (10 ml.), and the solution was set aside at room temperature for 7 days, and poured into water; 93% of the starting material was recovered. Extraction of the aqueous layer with ether, followed by evaporation of the dried ethereal extracts, yielded, on purification, a further 3% of the starting material.

Attempted Hydrolysis of Compounds (VI) *in Trifluoroacetic Acid.*—The trifluoroacetyl derivative of the semicarbazide (VI; R = Ph, Ar = 2-Br,4-$NO_2C_6H_3$) (0·20 g.) was dissolved in trifluoroacetic acid (10 ml.) at room temperature. After 24 hr. the solution was poured into water and starting material (81%), m. p. 161°, precipitated. A further 14% was obtained on neutralisation of the acid solution followed by extraction with ether. The other materials in Table 5 were treated similarly, and starting materials were returned in *ca.* 100% yields.

The semicarbazide (V; R = Ph, Ar = 2-Br,4-$NO_2C_6H_3$) was treated similarly in trifluoroacetic acid; after 24 hr. at room temperature, addition of water gave the starting semicarbazide (95%); no trifluoroacetyl derivative was detected.

1-(2,4-*Dinitrophenyl*)-4-(1-*methylpropyl*)*semicarbazide.*—(*a*) D-(−)-2-Methylbutan-1-ol ($[\alpha]_{578}^{25}$ −5·80°) was oxidised to the corresponding aldehyde [27] and coupled with 2,4-dinitrophenylhydrazine. Bromination of the hydrazone gave *N*-(2,4-dinitrophenyl)-*C*-(1-methylpropyl)hydrazidic bromide, $[\alpha]_{578}^{25}$ +21·0° (*c* in acetone). The hydrazidic bromide (400 mg.) was added to dioxan–water (80 : 20) (8 ml.) and the mixture was heated at 25° until a clear solution was obtained. To this was added sodium azide (38 mg.) in the same solvent (2 ml.), and a yellow solid immediately precipitated. The solid (320 mg., 90%) crystallised from acetone to give *N*-(2,4-dinitrophenyl)-*C*-(1-methylpropyl)hydrazidic azide [Ib; R = EtMeCH, Ar′ = 2,4-$(NO_2)_2C_6H_3$], m. p. 140—141°, $[\alpha]_{578}^{25}$ +55·0° (*c* 1·0 in acetone) (Table 2). The hydrazidic azide (300 mg.) was stirred with ' AnalaR ' glacial acetic acid (10 ml.), and concentrated sulphuric acid (3·0 ml.) was added dropwise. The solution was stirred rapidly, and when nitrogen evolution had stopped (about 4 min.), was poured into water (20 ml.) to precipitate the semicarbazide (250 mg., 86%). Recrystallisation (twice) from aqueous ethanol gave 1-(2,4-*dinitrophenyl*)-4-(1-*methylpropyl*)*semicarbazide*, m. p. 220° (Found: C, 46·3; H, 5·2; N, 20·1. $C_{11}H_{14}N_4O_5$ requires C, 46·8; H, 5·0; N, 19·9%), $[\alpha]_{578}^{25}$ +36·5° (*c* 1 in acetic acid).

(*b*) D-(−)-2-Methylbutan-1-ol was oxidised [28] to the corresponding acid and then converted into D-(+)-methyl-

[27] E. J. Badin and E. Pascu, *J. Amer. Chem. Soc.*, 1945, **67**, 1352; L. Lardicci and R. Rossi, *Atti. Soc. Toscana Sci. Nat. Pisa Proc. Verbali Mem. Ser. A*, 1962, **68**, 23.

[28] K. J. Sax and W. Bergmann, *J. Amer. Chem. Soc.*, 1955, **77**, 1910; K. H. Wiberg and T. W. Hutton, *ibid.*, 1956, **78**, 1640.

butyryl chloride. The acid chloride (1·2 g.) was dissolved in acetone (7·5 ml.) and added dropwise (10 min.) to a cooled (ice-bath) solution of sodium azide (0·91 g.) in water (7·5 ml.). When the addition was complete, the temperature of the mixture was allowed to rise to 15° and the mixture was rapidly stirred for 30 min. The upper (organic) layer was carefully separated and added dropwise to benzene (20 ml.) at 60°. The benzene solution was maintained at this temperature for 1 hr. and added to dried ether (1 l.) containing finely ground 2,4-dinitrophenylhydrazine (1·0 g.). The mixture was vigorously refluxed for 3 hr. after which time a small amount of (red) undissolved starting material was filtered off. The solution was set aside overnight and a yellow solid separated (0·62 g., 42%). Recrystallisation from aqueous ethanol gave 1-(2,4-dinitrophenyl)-4-(1-methylpropyl)semicarbazide, m. p. 220°, identical (mixed m. p., infrared spectra) with the material prepared by method (*a*). The semicarbazide prepared by route (*b*) had $[\alpha]_{578}^{25}$ +37·0° (*c* 1 in acetic acid).

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