618. *Thiadiazoles. Part XIII.* Isomerisation of "Hector's Bases."*

By FREDERICK KURZER and PHYLLIS M. SANDERSON.

Ethanolic ammonia at 140° isomerises "Hector's bases" to 3,5-diarylamino-1,2,4-thiadiazoles. The latter are obtainable by oxidation of *N*-aryl-*N'*-arylamidinothioureas, the structure of which is confirmed.

THE interaction of phenyl isothiocyanate and phenylguanidine yields a product formulated [1] as *N*-phenyl-*N'*-phenylamidinothiourea (I; Ar = Ph). This structural assignment was based on the assumed preferential addition of the isothiocyanate at the free amino- rather than the anilino-group of phenylguanidine, but the alternative possible structure (II) was not excluded with certainty.

The correctness of the original formulation has now been confirmed by the results of the hydrazinolysis of the *S*-alkyl-derivative of the amidinothiourea concerned. Thus, cyclisation of the hydrazino-compound (VII) derived from *S*-benzyl-*N*-phenyl-*N'*-phenylamidinoisothiourea (V) can yield, theoretically, either 3,5-dianilino-1,2,4-triazole (IX) or 3-imino-2-phenyl-5-anilino-1,2,4-triazoline (X) by loss of ammonia, or 3-amino-5-anilino-1,2,4-triazole (XI) by loss of aniline. By the same reaction sequence, the isomeric amidinothiourea (II) would yield 3-amino-5-anilino-4-phenyl-1,2,4-triazole (XII).

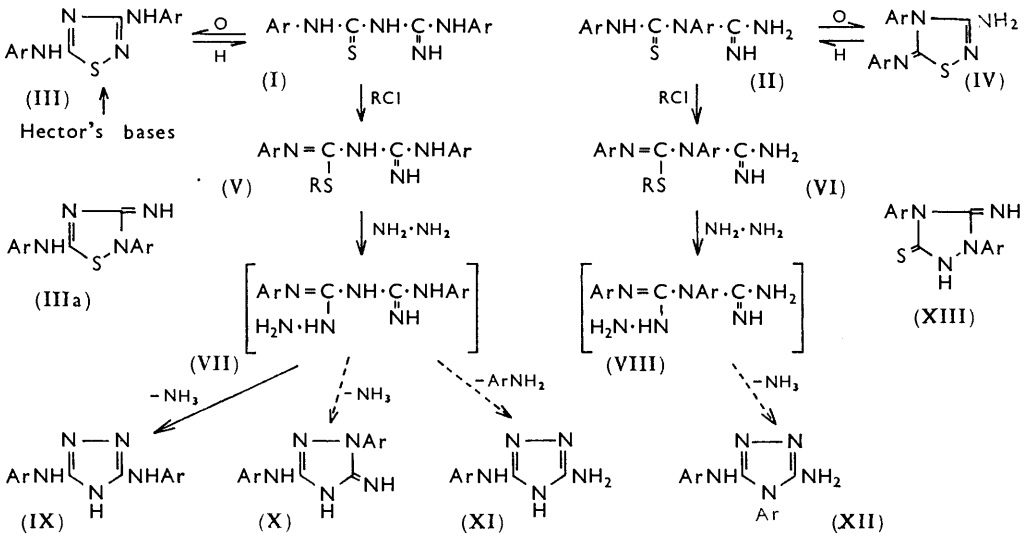
S-Benzyl-*N*-phenyl-*N'*-phenylamidinoisothiourea (V; Ar = Ph, R = $PhCH_2$), obtained from the parent compound (I) on benzylation, was converted by ethanolic hydrazine into 3,5-dianilino-1,2,4-triazole (IX; Ar = Ph) in one stage in good yield. The identity of this product was confirmed by its comparison with authentic material synthesised from 2-methyl-1,5-diphenyldithioisobiuret.[2,3]

This result thus excludes the alternative formulation of the amidinothiourea as (II). It also confirms with great probability the structure of the product of its oxidative cyclisation as 3,5-dianilino-1,2,4-thiadiazole (III). Thus, the alternative structure (IV) is ruled out with certainty; the possible representation of the product as (IIIa) is rejected on

* Part XII, Kurzer and Taylor, *J.*, 1962, 4191.

[1] Kurzer, *J.*, 1956, 2345.
[2] Johnson and Elmer, *Amer. Chem. J.*, 1903, **30**, 167, 176.
[3] Underwood and Dains, *Univ. Kansas Sci. Bull.*, 1936, **24**, 5.

the grounds that oxidative ring-closure of the amidinothiourea (I) is considered to occur between its mercapto- and free imino- rather than the anilino-group. Although anilino-groupings have in fact been observed [4] to participate in cyclisations of this



type, no alternative site for oxidative attack was available in such cases [*e.g.*, RNH·CS·NH·C(:NR)NHR].

Under appropriate conditions, the oxidation of aromatic thioureas yields so-called " Hector's bases," for which a 4-aryl-3-arylimino-5-imino-1,2,4-thiadiazolidine structure is suggested.[5] Using ethanolic ammonia at 150°, Dost [6] isomerised the phenyl and *p*-tolyl homologues of this series to non-basic products, but did not at the time assign a structure to the isomers. They were indexed [7] arbitrarily as 1,4-diaryl-5-imino-3-thiono-1,2,4-triazolidines (XIII). We have confirmed Dost's experimental results,[8] obtaining the isomerisation products in 32—50% yield. They proved to be identical with the oxidation products of *N*-aryl-*N'*-arylamidinothioureas (I) and are therefore formulated as 3,5-diarylamino-1,2,4-thiadiazoles (III).

This isomerisation is not a mere thermal effect, because attempts to perform the reaction in boiling xylene (at 135—140°) failed. The use of other bases, both stronger or weaker than ammonia (*e.g.*, piperidine,[9] $k_b = 1—1{\cdot}6 \times 10^{-3}$; 3-methylpyridine,[10] $k_b = 1 \times 10^{-8}$), was also unsuccessful. The significance of the isomerisation in relation to the structure of " Hector's bases " is briefly discussed in the succeeding paper.[5]

Experimental

Light petroleum had b. p. 60—80°. *p*-Tolyl isothiocyanate was obtained in 40—45% yield by the general method of Dains, Brewster, and Olander.[11] Ultraviolet absorption measurements were made with a Unicam S.P. 500 spectrophotometer and approximately 0·00005M-ethanolic solutions.

S-*Benzyl*-N-*phenyl*-N'-*phenylamidinoisothiourea.*—A solution of *N*-phenyl-*N'*-phenylamidinothiourea [1] (5·4 g., 0·02 mole) in ethanol (60 ml.) at 60° was treated with benzyl chloride (3·05 g.,

[4] Kurzer and Sanderson, *J.*, 1960, 3240.
[5] See succeeding paper, Part XIV.
[6] Dost, *Ber.*, 1906, **39**, 863.
[7] Beilstein's Handbuch, Hauptwerk, 4th edn., 1937, Vol. 27, pp. 661, 663.
[8] See also Kurzer, *Chemistry and Industry*, 1956, 526.
[9] Bredig, *Z. phys. Chem.*, 1894, **13**, 289, 306; Hantzsch and Sebaldt, *Z. phys. Chem.*, 1899, **30**, 258, 297; Prideaux and Gilbert, *J.*, 1927, 2164.
[10] Constam and White, *Amer. Chem. J.*, 1903, **29**, 1, 35.
[11] Dains, Brewster, and Olander, *Org. Synth.*, Coll. Vol. I, 1941, p. 448.

0·024 mole), followed by 3N-sodium hydroxide (6·7 ml., 0·02 mole). The mixture was shaken at room temperature during 1 hr. and then stirred into water (500 ml.), and the (emulsified) product, which solidified gradually to a granular precipitate on occasional stirring, collected next day. Crystallisation from ethanol–acetone–light petroleum (40, 10, 10 ml.) gave prisms of the S-*benzyl derivative*, m. p. 152—153° (4·7—5·4 g., 65—75%) (Found: C, 69·6; H, 6·1; N, 15·0; S, 8·35. $C_{21}H_{20}N_4S$ requires C, 70·0; H, 5·55; N, 15·55; S, 8·9%).

3,5-*Dianilino*-1,2,4-*triazole*.—*S*-Benzyl-*N*-phenyl-*N'*-phenylamidinoisothiourea (1·8 g., 0·005 mole), suspended in ethanol (15 ml.) and hydrazine hydrate (2·5 ml., 0·05 mole), dissolved rapidly on being heated. The solution was refluxed for 1 hr. and then stirred into water (50 ml.) (smell of toluene-ω-thiol), and the precipitate collected after storage at 0°. Crystallisation from acetone–ethanol (1 : 1; and partial evaporation) gave felted needles (0·95 g., 75%) of 3,5-dianilino-1,2,4-triazole, m. p. and mixed m. p. with authentic [3] material 251—252° (Found: C, 66·6; H, 5·0; N, 28·3. Calc. for $C_{14}H_{13}N_5$: C, 66·9; H, 5·2; N, 27·9%). It had $\lambda_{min.}$ 225 mμ (log ε 3·94); $\lambda_{max.}$ 261 (4·59), its ultraviolet absorption curve being identical with that of an authentic sample.[3]

The compound was further identified by its conversion,[3] in 85% yield, into the monobenzoyl derivative, forming yellow needles (from ethanol), m. p. and mixed m. p. with authentic [3] material 132—134° (Found: C, 70·7; H, 4·9. Calc. for $C_{21}H_{17}N_5O$: C, 71·0; H, 4·8%).

3,5-*Dianilino*-1,2,4-*thiadiazole*.—Finely powdered 5-imino-4-phenyl-3-phenylimino-1,2,4-thiadiazolidine (" Hector's base " from phenylthiourea) (2·68 g., 0·01 mole), suspended in 10% ethanolic ammonia (40 ml.) was kept in a closed vessel at 135—140° during 2·5 hr. The resulting pale purple liquid was re-heated to redissolve the separated crystalline product, and to remove the ammonia, and was distilled to quarter-bulk under reduced pressure. The residual filtered orange liquid deposited a powdery solid which consisted, after crystallisation from ethanol (carbon), of platelets of 3,5-dianilino-1,2,4-thiadiazole, m. p. and mixed m. p.[1] 200—202° (1·28 g., 48%) (Found: C, 62·3; H, 4·5. Calc. for $C_{14}H_{12}N_4S$: C, 62·7; H, 4·5%). Its ultraviolet absorption curve was coincident with that [12] of authentic material [1] ($\lambda_{min.}$ 232 mμ; log ε 3·78; $\lambda_{max.}$ 270; 4·64).

The compound was further identified by its conversion [1] into the acetyl-derivative (85%), m. p. and mixed m. p.[1] 238—240° (Found: C, 62·4; H, 4·4. Calc. for $C_{16}H_{14}N_4OS$: C, 61·9; H, 4·5%), and the di(toluene-*p*-sulphonyl) derivative (35%), m. p. and mixed m. p.[1] 240—242°.

Treatment of the reactant as above at 105—110° during 4—6 hr., gave diminished yields (10—15%). Boiling 3-picoline (2 hr. at 140°) or piperidine (6 hr. at 105°) did not effect the desired isomerisation. Prolonged refluxing of a solution of the reactant (2·68 g.) in xylene (30 ml.) (3 hr. at 135°) gave an intractable orange oil.

N-p-*Tolyl*-N'-p-*tolylamidinothiourea*. This was prepared from *p*-tolyl isothiocyanate (0·05 mole) and *p*-tolylguanidine nitrate [13] (0·05 mole) in the presence of sodium alkoxides (0·045 mole) by the general method previously [1] described. It formed lustrous needles (10·7 g., 72%), m. p. 165—167° (from ethanol) (Found: C, 63·95; H, 5·95; N, 18·5. $C_{16}H_{18}N_4S$ requires C, 64·4; H, 6·0; N, 18·8%).

3,5-*Di*-p-*toluidino*-1,2,4-*thiadiazole*.—(*a*) *N*-*p*-Tolyl-*N'*-*p*-tolylamidinothiourea (2·98 g., 0·01 mole) in nearly boiling ethanol (80 ml.) decolorised bromine (1·6 g., 0·01 mole; in a little chloroform) instantly. The clear liquid was distilled *in vacuo* to one-third bulk and added to ice–water (150 ml.). The white precipitate consisted, after crystallisation from ethanol (25 ml. per g.), of lustrous needles of 3,5-*di*-p-*toluidino*-1,2,4-*thiadiazole*, m. p. 203—205° (2·12 g., 72%) (Found: C, 64·4; H, 5·5; N, 19·2; S, 11·3. $C_{16}H_{16}N_4S$ requires C, 64·9; H, 5·4; N, 18·9; S, 10·8%). It had $\lambda_{min.}$ 232 mμ (log ε 3·82), $\lambda_{max.}$ 272 mμ (4·64).

(*b*) Oxidation with hydrogen peroxide of the above amidinothiourea by the usual procedure [1] gave the same thiadiazole, m. p. and mixed m. p. (with material *a*) 203—204°, in 51% yield.

(*c*) Treatment of 5-imino-4-*p*-tolyl-3-*p*-tolylimino-1,2,4-thiadiazolidine (" Hector's base " from *p*-tolylthiourea) (1·5 g., 0·005 mole) with 10% ethanolic ammonia (30 ml.) at 135—140°; and isolation of the product as described for the phenyl homologue (see above), gave 3,5-di-*p*-toluidino-1,2,4-thiadiazole, m. p. and mixed m. p. 202—204° (from ethanol) (25—32%). Its ultraviolet absorption curve was coincident with that of sample (*a*).

[12] Kurzer and Taylor, *J.*, 1962, 4191.
[13] Kämpf, *Ber.*, 1904, **37**, 1681.

Derivatives.—The following derivatives were prepared by the methods [1] used for the phenyl analogue: *monoacetyl derivative*, white crystalline powder, m. p. 204—206° (85%), from ethanol (Found: C, 63·5; H, 5·4; N, 16·7; S, 9·7. $C_{18}H_{18}N_4OS$ requires C, 63·9; H, 5·3; N, 16·6; S, 9·5%). *Monobenzoyl derivative*, needles, m. p. 223—225° (80%), from acetone–ethanol (Found: C, 68·5; H, 4·9; N, 14·0; S, 8·05. $C_{23}H_{20}N_4OS$ requires C, 69·0; H, 5·0; N, 14·0; S, 8·0%). *Ditoluene-*p*-sulphonyl derivative*, refractive cubes, m. p. 231—232° (decomp.) (25%), from acetone–ethanol (Found: C, 59·8; H, 4·9; N, 9·4; S, 15·6. $C_{30}H_{28}N_4O_4S_3$ requires C, 59·6; H, 4·6; N, 9·3; S, 15·9%).

ROYAL FREE HOSPITAL SCHOOL OF MEDICINE,
(UNIVERSITY OF LONDON), W.C.1.

[*Received, September 28th*, 1962.]