201. *The Coupling of Quaternary Thiazolium Salts with* p-*Nitrobenzenediazonium Chloride.*

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Reaction of quaternary thiazolium salts with *p*-nitrobenzenediazonium chloride leads unexpectedly to attack, not at the reactive 2-position, but primarily at the negatively charged sulphur atom in the opened nucleus. The effect of the nature and position of substituents in the thiazole nucleus is discussed.

The development of colour on reaction of thiamine with diazonium salts has long been known and use made of it in the detection and estimation of the vitamin.[1] Buchmann [2] reported that, with diazotised sulphanilic acid, coupling is confined to quaternary salts derived from 5-2′-hydroxyethyl-4-methylthiazole, but Todd and Bergel [3] stated that reaction with diazonium compounds is a general property of thiazolium salts having a 5-2′-hydroxyethyl side chain and an unsubstituted 2-position. The latter apparent requirement is of interest in connection with the unexpected reactivity of this position in thiamine, implied in the very rapid exchange of its hydrogen atom with deuterium [4] (subsequently shown to be a general property of such thiazolium compounds [5]), and the

[1] Kinnersley and Peters, *Biochem. J.*, 1934, **28**, 667; 1935, **29**, 2369; Prebluda and McCollum, *Science*, 1936, **84**, 488; *J. Biol. Chem.*, 1939, **127**, 495; Willstaedt, *Naturwiss.*, 1937, **25**, 682; Melnick and Field, *J. Biol. Chem.*, 1939, **127**, 505.

[2] Buchmann, *J. Amer. Chem. Soc.*, 1936, **58**, 1803.

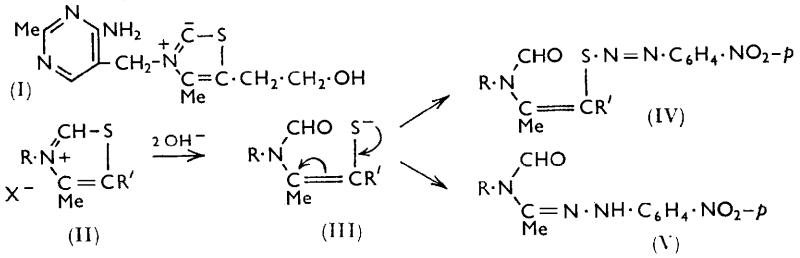
[3] Todd and Bergel, *J.*, 1936, 1559; 1937, 1504.

[4] Breslow, *J. Amer. Chem. Soc.*, 1957, **79**, 1762.

[5] Downes and Sykes, unpublished results.

suggested participation of the ylide (I), derived from it, in the catalytic decarboxylation of pyruvic acid.[6] The site and scope of coupling being as yet undecided, an attempt has been made to demonstrate the particular and peculiar reactivity of the 2-position by azo-coupling.

p-Nitrobenzenediazonium chloride was used throughout and coupling reactions were carried out in buffer solutions. It was found, unexpectedly, that coupling never took place in the 2-position; there was no reaction until the solution was sufficiently alkaline for the thiazolium nucleus to have begun to open in the usual way (II ⟶ III). Thus,



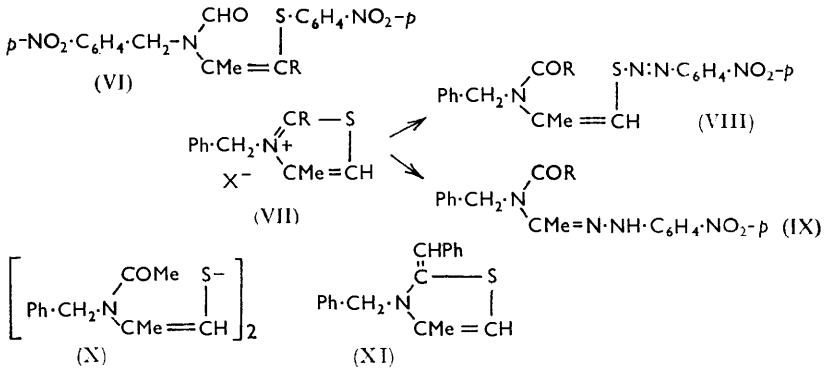
at pH 9·2, 3-benzyl-4-methylthiazolium chloride (II; R = Ph·CH_2, R′ = H, X = Cl) yielded a yellow, alkali-labile azo-compound, whose infrared spectrum exhibited absorption at 1670 cm.$^{-1}$ characteristic of the >N·CHO group in ring-opened thiazolium compounds; it is assigned the *S*-coupled structure (IV; R = Ph·CH_2, R′ = H). At pH 12·3 the coupling yielded, in addition, a yellow, sulphur-free product with infrared bands at 1642, 1664, and 3250 cm.$^{-1}$, corresponding to the >C=N–, >N·CHO, and >NH groups, respectively. This compound is believed to have the structure (V; R = Ph·CH_2); initial attack at the 4-position, resulting from the electronic shift shown in (III), being followed by an elimination similar to that observed by Quilico and Freri [7] in the coupling of *p*-nitrobenzenediazonium chloride with anethole to yield *p*-methoxybenzaldehyde *p*-nitrophenylhydrazone.

The introduction of an electron-withdrawing substituent might be expected to increase the inductive effect of the benzyl group and, by promoting the electronic shift in (III), to increase the product obtained by initial coupling at the 4-position. Thus coupling with 4-methyl-3-4′-nitrobenzylthiazolium bromide (II; R = *p*-NO_2·C_6H_4·CH_2, R′ = H, X = Br) doubles the yield of this product, whereas with 4-methyl-3-phenethylthiazolium bromide (II; R = Ph·CH_2·CH_2, R′ = H, X = Br), in which the introduction of a second methylene group inhibits any inductive effect of the phenyl group on the thiazolium nucleus, no such product is obtained at all, only the *S*-coupled product (IV; R = Ph·CH_2·CH_2, R′ = H) being isolated. The effect of rise of pH (9·5 ⟶ 11·5) in raising the yield of product (42 ⟶ 90%), owing to the increased proportion of the ring-opened form (III; R = Ph·CH_2·CH_2, R′ = H), is clearly marked with this compound.

Introduction of a substituent into the 5-position, as in 5-2′-hydroxyethyl-4-methyl-3-4′-nitrobenzylthiazolium bromide (II; R = *p*-NO_2·C_6H_4·CH_2, R′ = CH_2·CH_2·OH, X = Br), also inhibits coupling at position 4, despite the presence of a substituent in the 3-position with a promoting inductive effect. That this inhibition is not due to reversible addition of the hydroxyl group of the hydroxyethyl side chain across the 4,5-double bond (cf. ref. 8) is shown by the fact that 5-2′-acetoxy-4-methyl-3-4′-nitrobenzylthiazolium bromide (II; R = *p*-NO_2·C_6H_4·CH_2, R′ = CH_2·CH_2·OAc, X = Br) behaves analogously; it thus seems that the inhibition of attack at position 4 is due to steric hindrance by the 5-substituent. A further feature of the coupling reactions of these two compounds is that *S*-arylated compounds (VI; R = CH_2·CH_2·OH and CH_2·CH_2·OAc, respectively) are also

[6] Breslow, *J. Amer. Chem. Soc.*, 1958, **80**, 3719.
[7] Quilico and Freri, *Gazzetta*, 1928, **58**, 380.
[8] Yoshida and Unoki, *J. Pharm. Soc. Japan*, 1952, **72**, 1431.

obtained. These are not artefacts because, though the *S*-coupled products undergo ready decomposition at the pH of the coupling reaction, *S*-arylated compounds are not thereby produced.



Finally, an unsubstituted 2-position is not essential for coupling to take place, for 3-benzyl-2,4-dimethylthiazolium bromide (VII; R = Me, X = Br) yields products (VIII; R = Me and IX; R = Me), though yields are low. This incidentally establishes that simple 2-alkylated thiazolium salts undergo ring-opening in alkali which had previously been open to doubt;[9] further confirmation is provided by characterisation of a disulphide (X) on oxidation of compound (VII; R = Me, X = Br). That not all 2-alkylthiazolium salts undergo such ring-opening, however, is demonstrated by the fact that 2,3-dibenzyl-4-methylthiazolium chloride (VII; R = Ph·CH_2, X = Cl) is converted by alkali into the unstable anhydro-base (XI), characterised as its phenylurethane (cf. the behaviour of 2-substituted benzothiazolium compounds [10]).

The behaviour of thiamine and its analogues on coupling is more complex. Though model experiments lead us to think that the pyrimidine nucleus is probably not attacked, the original coupled products are extremely unstable and complex mixtures of products are obtained which have not yet been separated or characterised.

Experimental

Preparation of Quaternary Thiazolium Bromides.—The thiazole (0·020 mole) and the halide (0·022 mole) in dry toluene (10 ml.) were heated at 120° until no more solid was deposited. The separated solid was filtered off, washed with toluene, dried, and recrystallised from ethanol or ethanol–ether. The following *thiazolium bromides* (II) were so obtained: 4-*methyl*-3-4′-*nitrobenzyl*-, prisms, m. p. 208° (Found: C, 41·8; H, 3·6; N, 8·8. $C_{11}H_{11}O_2N_2BrS$ requires C, 42·1; H, 3·5; N, 8·9%), 4-*methyl*-3-*phenethyl*- (28%, 72 hr.), needles, m. p. 196° (Found: C, 50·7; H, 4·9; N, 4·7. $C_{12}H_{14}NBrS$ requires C, 50·7; H, 4·9; N, 4·9%), 5-2′-*hydroxyethyl*-4-*methyl*-3-4′-*nitrobenzyl*-, (72%, 3 hr.), rods, m. p. 150° (Found: C, 43·5; H, 4·5; N, 7·7. $C_{13}H_{15}O_3N_2BrS$ requires C, 43·5; H, 4·2; N, 7·8%), and 5-2′-*acetoxyethyl*-4-*methyl*-3-4′-*nitrobenzyl*- (59%, 15 hr.), needles, m. p. 178° (Found: C, 44·8; H, 4·6; N, 6·8. $C_{15}H_{17}O_4N_2BrS$ requires C, 44·9; H, 4·2; N, 7·0%).

Coupling Reactions.—Reaction of diazotised *p*-nitroaniline with the following compounds was investigated:

(a) *With* 3-*benzyl*-4-*methylthiazolium chloride.* (i) The chloride [11] (1·0 g.), in phosphate buffer (pH 9·2; 100 ml.), at 5°, was treated with a solution obtained by diazotising *p*-nitroaniline (0·64 g., 1·05 mol.). A yellow flocculent precipitate separated which was collected after 5 min., dissolved in ethyl acetate, and immediately chromatographed on activated alumina.

[9] Albert, " Heterocyclic Chemistry," Athlone Press, London, 1959, p. 224.
[10] König and Meier, *J. prakt. Chem.*, 1925, **109**, 324.
[11] Karimullah, *J.*, 1937, 961.

A broad yellow band eluted in ethyl acetate yielded, on evaporation and recrystallisation from warm ethanol (refluxing results in almost complete decomp.), N-*benzyl*-N-*formyl*-1-*methyl*-2-(p-*nitrophenyldiazothio*)*vinylamine* (IV; R = Ph·CH_2, R′ = H) (0·82 g., 52%) as yellow prisms, m. p. 87° (decomp.) (Found: C, 57·1; H, 4·7; N, 15·8. $C_{17}H_{16}O_3N_4S$ requires C, 57·3; H, 4·5; N, 15·7%). A further narrow red band, eluted slowly in ethyl acetate, proved to be 4,4′-dinitrodiazoaminobenzene,[12] m. p. and mixed m. p. 232° (decomp.), corresponding to *ca.* 2% of the *p*-nitroaniline. This was also obtained in all subsequent coupling reactions.

(ii) Coupling was repeated, with double the above quantities, in phosphate buffer at pH 12·3. A brown precipitate separated which was dissolved in ethyl acetate and chromatographed as above. A pale yellow band yielded the above *S*-coupled product (1·56 g., 50%), and a second, deep yellow band, eluted in 9 : 1 ethyl acetate–acetone yielded, on evaporation and repeated recrystallisation from ethanol, N-*benzyl*-N-*formylacetamide* p-*nitrophenylhydrazone* (V; R = Ph·CH_2) (0·1 g., 4%) as deep yellow needles, m. p. 163° (decomp.) (Found: C, 61·2; H, 5·0; N, 17·6. $C_{16}H_{16}O_3N_4$ requires C, 61·5; H, 5·1; N, 17·9%).

(b) *With* 4-*methyl*-3-4′-*nitrobenzylthiazolium bromide.* The thiazolium salt (2·38 g.) was coupled with diazotised *p*-nitroaniline (1·29 g., 1·05 mol.) in phosphate buffer at pH 12·3, as above. The yellow precipitate was chromatographed in ethyl acetate on activated alumina. A bright yellow band, eluted in ethyl acetate, yielded, on evaporation and recrystallisation from acetone, N-*formyl*-1-*methyl*-N-4′-*nitrobenzyl*-2-(p-*nitrophenylazothio*)*vinylamine* (IV; R = *p*-NO_2·C_6H_4·CH_2, R′ = H) (2·32 g., 77%) as yellow prisms, m. p. 108° (decomp.) (Found: C, 51·2; H, 3·2; N, 17·2. $C_{17}H_{15}O_5N_5S$ requires C, 50·9; H, 3·7; N, 17·5%).

A second, deep yellow band, eluted in 7 : 3 ethyl acetate–acetone, yielded, on evaporation and recrystallisation from acetone, N-*formyl*-N-4′-*nitrobenzylacetamide* p-*nitrophenylhydrazone* (V; R = *p*-NO_2·C_6H_4·CH_2) (0·23 g., 8%) as orange needles, m. p. 179° (decomp.) (Found: C, 53·4; H, 4·3; N, 19·6. $C_{16}H_{15}O_5N_5$ requires C, 53·8; H, 4·2; N, 19·6%).

(c) *With* 4-*methyl*-3-*phenethylthiazolium bromide.* The thiazolium salt (0·5 g.) was coupled with diazotised *p*-nitroaniline (0·245 g., 1 mol.) in phosphate buffer at pH 9·5, as above. The brown precipitate was treated as above and yielded, on recrystallisation from acetone, N-*formyl*-1-*methyl*-2-(p-*nitrophenylazothio*)-N-*phenethylvinylamine* (IV; R = Ph·CH_2·CH_2, R′ = H) (0·27 g., 42%) as golden leaflets, m. p. 93° (decomp.) (Found: C, 58·2; H, 4·9; N, 14·7. $C_{18}H_{18}O_3N_4S$ requires C, 58·4; H, 4·9; N, 15·1%). Repetition at pH 11·5 increased the yield of this product to 98%.

(d) *With* 5-2′-*hydroxyethyl*-4-*methyl*-3-p-*nitrobenzylthiazolium bromide.* The thiazolium salt (2·0 g.) was coupled with diazotised *p*-nitroaniline (0·77 g., 1 mol.) in phosphate buffer at pH 9·2, as above. The brown precipitate was chromatographed as previously and then yielded, on recrystallisation from ethanol, N-*formyl*-2-2′-*hydroxyethyl*-1-*methyl*-2-N-4′-*nitrobenzyl*-(p-*nitrophenylthio*)*vinylamine* (VI; R = CH_2·CH_2·OH) (0·09 g., 4%) as colourless needles, m. p. 226° (Found: C, 54·8; H, 4·9; N, 10·0. $C_{19}H_{19}O_6N_3S$ requires C, 54·7; H, 4·6; N, 10·1%).

A further band yielded, after recrystallisation from acetone and then ether, N-*formyl*-N-2-2′-*hydroxyethyl*-1-*methyl*-2-4′-*nitrobenzyl*-(p-*nitrophenyldiazothio*)*vinylamine* (IV; R = *p*-NO_2·C_6H_4·CH_2, R′ = CH_2·CH_2·OH) (0·26 g., 11%) as yellow prisms, m. p. 107° (decomp.) (Found: C, 51·0; H, 4·4; N, 15·6. $C_{19}H_{19}O_6N_5S$ requires C, 51·2; H, 4·3; N, 15·7%). Repetition at pH 10·8 increases the yield of both products.

The *S*-coupled compound decomposes extremely readily in contact with alkali, but on rechromatography of material that has been treated in this way, no *S*-arylated compound was isolated.

(e) *With* 5-2′-*acetoxyethyl*-4-*methyl*-3-4′-*nitrobenzylthiazolium bromide.* The thiazolium salt (1·5 g.) was coupled with diazotised *p*-nitroaniline (0·52 g., 1 mol.) in phosphate buffer at pH 9·2. The precipitate was chromatographed as above, and then yielded, on repeated crystallisation from acetone, 2-2′-*acetoxyethyl*-N-*formyl*-1-*methyl*-N-4′-*nitrobenzyl*-2-(p-*nitrophenylazothio*)*vinylamine* (IV; R = *p*-NO_2·C_6H_4·CH_2, R′ = CH_2·CH_2·OAc) (0·66 g., 38%) as yellow prisms, m. p. 93° (decomp.) (Found: C, 51·5; H, 4·6; N, 14·4. $C_{21}H_{21}O_7N_5S$ requires C, 51·7; H, 4·3; N, 14·4%). Repetition with the same quantities at pH 11·0 yielded 56% of the above product and, in addition, as a first fraction from the column, 2-2′-*acetoxyethyl*-N-*formyl*-1-*methyl*-N-4′-*nitrobenzyl*-2-(p-*nitrophenylthio*)*vinylamine* (VI; R = CH_2·CH_2·OAc) (0·08 g., 5%), obtained after recrystallisation from acetone and then ethanol as pale yellow needles, m. p. 171° (Found: C, 55·0; H, 4·8; N, 9·3. $C_{21}H_{21}O_7N_3S$ requires C, 54·9; H, 4·6; N, 9·2%).

[12] Meldola and Streatfield, *J.*, 1886, **49**, 627.

The *S*-coupled product was extremely alkali-labile but did not yield the *S*-arylated compound as an artefact.

(f) *With* 3-*benzyl*-2,4-*dimethylthiazolium bromide*. The thiazolium salt (2·0 g.) was coupled with diazotised *p*-nitroaniline (0·97 g., 1 mol.) in phosphate buffer at pH 12·3. The brown precipitate was chromatographed as previously and yielded, on recrystallisation from ethanol, N-*acetyl*-N-*benzyl*-1-*methyl*-2-(p-*nitrophenylazothio*)*vinylamine* (VIII; R = Me) (0·37 g., 17%) as yellow leaflets, m. p. 104° (decomp.) (Found: C, 58·1; H, 5·1; N, 15·0. $C_{18}H_{18}O_3N_4S$ requires C, 58·4; H, 4·9; N, 15·1%). A second, deep yellow, band from the column yielded, after crystallisation from ethanol, N-*benzyldiacetamide* p-*nitrophenylhydrazone* (IX; R = Me) (0·07 g., 4%), as orange prisms, m. p. 154° (decomp.) (Found: C, 62·3; H, 5·5; N, 16·9. $C_{17}H_{18}O_3N_4$ requires C, 62·6; H, 5·5; N, 17·2%).

Di-[2-(N-*benzylacetamido*)*propenyl*] *Disulphide* (X).—3-Benzyl-2,4-dimethylthiazolium bromide [13] (2·0 g.) in water (20 ml.) was treated with N-sodium hydroxide (14·0 ml., 2 mol.) and aqueous 0·1N-iodine (70 ml., 1 mol.). The separated gum was extracted in chloroform (3 × 15 ml.), and the extract dried (Na_2SO_4). Removal of the solvent at 25° and recrystallisation from light petroleum (b. p. 60—80°) yielded the *disulphide* (1·1 g., 71%), as pale yellow plates, m. p. 100° (Found: C, 65·4; H, 6·5; N, 6·4. $C_{24}H_{28}O_2N_2S_2$ requires C, 65·5; H, 6·4; N, 6·3%). Schöberl and Stock [14] have reported an oxidation product derived from this thiazolium salt, but give no analysis.

N-*Benzyl*-α-*phenyl*(*thioacetamide*).—*N*-Benzylphenylacetamide (5·0 g.) was ground in a mortar with phosphorus pentasulphide (1·0 g., 1 mol.) and then heated to 140—150° for 10 min. with vigorous stirring. The resultant solid was recrystallised from ethanol to yield the thioamide (2·3 g., 43%) as colourless prisms, m. p. 79° (Found: C, 74·9; H, 6·5; N, 5·8. Calc. for $C_{15}H_{15}NS$: C, 74·7; H, 6·2; N, 5·8%). The method of Klingsberg and Papa [15] failed to convert the amide into the thioamide, and the product obtained by King and Freeman [16] by a Willgerodt reaction has m. p. 85—86°.

2,3-*Dibenzyl*-4-*methylthiazolium Chloride* (VII; R = Ph·CH_2, X = Cl).—The above thioamide (2·0 g.) and chloroacetone (3 ml.; excess) were heated to 110°; a vigorous reaction took place and the mixture became dark green. After being heated for 10 min., the solution was cooled, and the separated solid filtered off and washed with acetone, then with ether. Recrystallisation from ethanol–ether yielded the *thiazolium chloride* (0·75 g., 27%) as colourless rods, m. p. 170° (Found: C, 65·1; H, 5·9; N, 4·1. $C_{18}H_{18}NClS,H_2O$ requires C, 64·8; H, 6·0; N, 4·2%).

Action of Alkali on 2,3-*Dibenzyl*-4-*methylthiazolium Chloride*.—The thiazolium chloride (0·40 g.) in water (20 ml.) was treated with an excess of N-sodium hydroxide; a precipitate at once separated which was filtered off and washed with water. Recrystallisation from ethanol yields 3-*benzyl*-2-*benzylidene*-4-*methylthiazoline* (XI) (0·31 g., 90%) as pale yellow needles, m. p. 118° (decomp.) (Found: C, 77·1; H, 6·2; N, 4·9. $C_{18}H_{17}NS$ requires C, 77·4; H, 6·1; N, 5·0%). Reaction in benzene with phenyl isocyanate yielded the *phenylurethane* (83%) as pale yellow needles (from ethanol), m. p. 186° (Found: C, 75·2; H, 5·5; N, 6·9. $C_{25}H_{22}ON_2S$ requires C, 75·4; H, 5·6; N, 7·0%).

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[13] Todd, Bergel, and Karimullah, *Ber.*, 1936, **69**, 217.
[14] Schöberl and Stock, *Ber.*, 1941, **73**, 1240.
[15] Klingsberg and Papa, *J. Amer. Chem. Soc.*, 1951, **73**, 4988.
[16] King and Freeman, *ibid.*, 1946, **68**, 2335.