

322. Reactions of Benzthiazole Derivatives. Part V. Observations on the Formation of 2-Acetylbenzthiazole.*

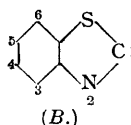
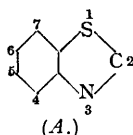
By M. A. THOROLD ROGERS and W. A. SEXTON.

2 : 2'-Diaminodiphenyl disulphide condenses with ethyl acetoacetate to give 3-*keto*-2-*acetyl*-2 : 3-*dihydrobenzthiazine* (IV) and 2-*acetylbenzthiazole* (V) (with its derived 2-methylbenzthiazole) in approximately equimolecular proportion. Zinc and acetic acid convert (IV) into (V) and sodium hydroxide hydrolyses it to 3-*keto*-2 : 3-*dihydrobenzthiazine* (VI). A similar series is derived from ethyl benzoylacetate. Mechanisms are suggested.

THE formation of 2-acetylbenzimidazole by condensation of *o*-phenylenediamine with ethyl acetoacetate or by reduction of acetoacet-*o*-nitroanilide has been demonstrated by one of us (Sexton, *J.*, 1942, 303) and its ability to couple with diazonium salts prompted us to investigate the analogous benzthiazole derivative (V).

2 : 2'-Dinitrodiphenyl disulphide was reduced by iron in alcohol to the diamine, this method giving, in contrast to those hitherto recorded, satisfactory yields of pure material with little trouble. Condensation with ethyl acetoacetate in chlorobenzene gave three products, 2-*acetylbenzthiazole* (V) (26.7%), 2-methylbenzthiazole (VII) (21.6%), and 3-*keto*-2-*acetyl*-

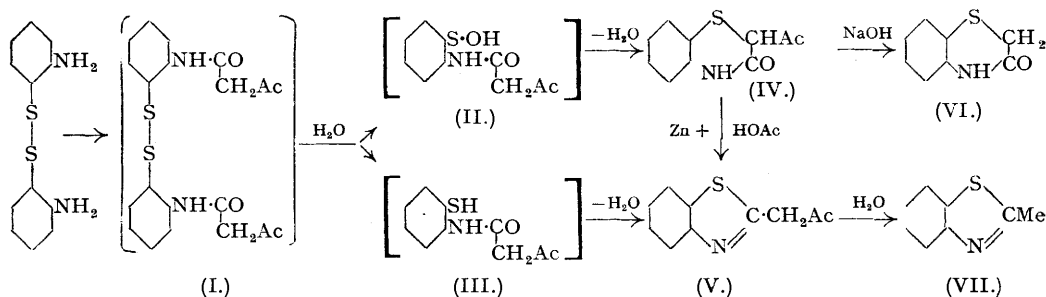
* The numbering of the benzthiazole system (A) here follows what is now the usual practice. In



earlier papers of this series (*J.*, 1939, 470, 473; 1942, 304; 1944, 11) the Richter numbering (B) was used.—EDITOR.

2 : 3-dihydrobenzthiazine (IV) (43%), together with water. The structure of the new compounds was established as follows.

The substance (IV), which crystallised from the chlorobenzene on cooling, and which *a priori* might be expected to be the bis-*N*-acetoacetyl derivative (I) of diaminodiphenyl disulphide, was shown to have a molecular weight of half that required for this structure. Since the possibility of dissociation of (IV) during the molecular-weight determination could not be excluded, and since analysis fails to differentiate between the thiazine and the disulphide structures, (IV) and (I), respectively, a chemical method was sought and found in the action of *N*-sodium hydroxide; for on dissolving in this reagent and being warmed, the whole material was rapidly converted into 3-keto-2 : 3-dihydrobenzthiazine (VI) and acetic acid, the latter being determined by titration. This is easily explained on the basis of the thiazine formula (IV) as hydrolysis, whereas the disulphide structure could give only half the amount of each of these (unless atmospheric oxygen was absorbed, and this was excluded by showing that the reaction is not affected by the absence of air, or by the presence of reducing agents); for the hydrolytic fission of disulphides leads to the formation of equimolecular quantities of thiols and sulphenic acids (see Gilman, "Organic Chemistry", 1942, 2nd Ed., Vol. II, p. 863) and only the sulphenic acid moiety is able to give 3-keto-2 : 3-dihydrobenzthiazine and acetic acid. Other properties of the substance (carbonyl activity, coupling of freshly prepared alkaline solutions with diazonium salts) are as readily understood on the basis of the formula (IV) as on the basis of the disulphide structure (I).



The structure of the other new product of the condensation, (V), presented little difficulty. It was soluble in both acids and alkalis, and the alkaline solution coupled with diazonium solutions; it showed carbonyl activity (2 : 4-dinitrophenylhydrazone) and gave an isonitroso-derivative; and its alkaline solution decomposed rapidly on heating to give 2-methylbenzthiazole. Finally, it was made in good yield from (IV) by reduction with zinc dust and acetic acid, which might be expected if (IV) is considered as a cyclic derivative of acetoacetanilide; the thiol (III) is a probable intermediate.

It is not difficult to postulate a reasonable mechanism for the formation of the three products of the acetoacetic ester condensation. It may be supposed that the bisacetoacetyl derivative (I) of the diamine is the first product, and that this is hydrolysed by traces of water, which may be present initially in the reagents, or may be formed by a Schiff's base type of side reaction. Such a neutral hydrolysis of the disulphide link is not usually considered to take place, but Schöberl and Eck (*Annalen*, 1936, 522, 97) have shown that it is probable that the reaction $-S-S- \rightleftharpoons -SH + -S\cdot OH$ is reversible, with equilibrium much on the side of the disulphide; provided that irreversibility is ensured, in their case by loss of hydrogen sulphide, the hydrolysis can go to completion. We picture the thiol (III) as being removed as soon as it is formed by ring closure to (V), while the sulphenic acid (II) is likewise converted into (IV). The water which is formed in each of these processes is available for further hydrolysis of the disulphide link, and the reaction becomes autocatalytic. Some of the thiazole (V) is hydrolysed during the reaction or during the subsequent steam distillation to methylbenzthiazole, so the combined yields of this and of (V) approach the theoretical of 50%, as does that of (IV).

Similar results were obtained in a brief investigation of the analogous series from ethyl benzoylacetate; 3-keto-2-benzoyl-2 : 3-dihydrobenzthiazine and 2-phenacylbenzthiazole were made in this way.

EXPERIMENTAL.

2 : 2'-Diaminodiphenyl Disulphide.—2 : 2'-Dinitrodiphenyl disulphide (100 g.; the sulphide made as described in *Org. Synth.*, Coll. Vol. I, p. 215, is satisfactory, provided that all inorganic sulphur be

removed by thorough washing with water) was added to a mixture of boiling alcohol (95%; 2 l.) and iron filings (200 g.), to which had been added concentrated hydrochloric acid (10 c.c.) 30 mins. previously. The mixture was heated under reflux for 16 hours in a water-bath in an apparatus fitted with efficient mechanical stirring, and was then filtered hot through a kieselguhr bed and concentrated to 600 c.c. On cooling, the diamine (60 g.; 76%) separated as yellow plates, m. p. 90—92°. One recrystallisation from alcohol (charcoal) gave material of better colour, m. p. 93—93.5°.

3-Keto-2-acetyl-2 : 3-dihydrobenzthiazine (IV).—The foregoing diamine (12.4 g.), dissolved in warm chlorobenzene (50 c.c.), was added during $\frac{1}{4}$ hr. to a boiling solution of ethyl acetoacetate (14.5 c.c.) in chlorobenzene (75 c.c.). The clear yellow liquid was distilled until wet chlorobenzene (80 c.c.) had been collected. To the residue was added further chlorobenzene (50 c.c.), and the same amount was distilled over. The process was repeated, no more water then appearing in the distillate. The residue was kept overnight, and the pale yellow prisms were collected and washed with light petroleum (b. p. 40—60°) (8.9 g., 43%); recrystallisation (charcoal) from alcohol or toluene gave large, colourless prisms, m. p. 164—164.5° (Found : C, 57.9; H, 4.35; N, 6.75; S, 16.1; *M*, Rast, 189. $C_{10}H_9O_2NS$ requires C, 57.95; H, 4.35; N, 6.75; S, 15.5%; *M*, 207). **2 : 4-Dinitrophenylhydrazones**, mustard-yellow micro-needles from toluene, m. p. 242—243° (decomp.) (Found : C, 49.9; H, 3.8. $C_{16}H_{13}O_6N_5S$ requires C, 49.6; H, 3.4%).

2-Acetylbenzthiazole (V).—(a) *From the ethyl acetoacetate condensation.* The filtrates from the foregoing experiment were subjected to steam distillation; after the chlorobenzene had distilled, the subsequent cloudy distillate had a smell like that of pyridine; about 600 c.c. of this were collected. The yellow oil remaining from the steam-distillation solidified on standing. After one crystallisation from alcohol it gave yellow plates (1.55 g.), m. p. 113—115°. Recrystallisation from alcohol gave colourless plates, m. p. 122° (Found : N, 7.55. $C_{10}H_9ONS$ requires N, 7.35%). The distillate was acidified (hydrochloric acid), whereupon the oily material passed into solution, leaving a little solid which was removed by filtration and identified as 2-acetylbenzthiazole (0.2 g.; total yield 26.7%). The filtrate was basified to Clayton-yellow with sodium hydroxide, and extracted with ether, and the ether removed by distillation, leaving 2-methylbenzthiazole (1.8 g.; 21.6%), identified as its picrate, m. p. 153—155° (lit. m. p. 152—153°).

(b) *From 3-keto-2-acetyl-2 : 3-dihydrobenzthiazine (IV).* To the thiazine (5.2 g.) in boiling acetic acid (150 c.c.) was added zinc dust (8 g.) during 10 mins. After refluxing for a further $\frac{1}{4}$ hour, the solution was filtered and cooled, and water was added, precipitating 2-acetylbenzthiazole (II) as colourless plates (4.2 g., 87.5%), m. p. 122°.

It decolourised bromine in carbon tetrachloride solution; its solutions in cold 2*N*-sodium hydroxide gave yellow azo-compounds with diazonium solutions; on boiling the alkaline solution, an oil, with a pyridine-like smell, separated after a few minutes, and was extracted with ether, dried over sodium hydroxide, and the ether removed. Addition of alcoholic picric acid to an alcoholic solution of the residue gave the picrate of 2-methylbenzthiazole, m. p. 153—155°. 2-Acetylbenzthiazole was soluble in hot 2*N*-hydrochloric acid; on cooling, the hydrochloride separated as colourless needles, m. p. 200° (from 2*N*-hydrochloric acid or from alcohol). Treatment of a suspension of the hydrochloride in dilute hydrochloric acid with sodium nitrite solution until a permanent starch-iodine reaction was obtained gave pale yellow isonitroso-2-acetylbenzthiazole, long yellow needles, m. p. 152—152.5° (from alcohol) (Found : C, 54.7; H, 3.6. $C_{10}H_9O_2N_2S$ requires C, 54.55; H, 3.6%).

Action of Alkali on 3-Keto-2-acetyl-2 : 3-dihydrobenzthiazine (IV).—The thiazine (2.08 g.) was dissolved in boiling *N*-sodium hydroxide (20 c.c.). After about 3 mins. there separated long needles of 3-keto-2 : 3-dihydrobenzthiazine (VI); after a further $\frac{1}{4}$ hour at 100°, the suspension was cooled and *N*-hydrochloric acid (30 c.c.) was added; the solution was filtered through a weighed IG3 sintered-glass Gooch funnel. The ketodihydrothiazine (VI) was washed with water, dried at 100°, and weighed; 1.66 g. (100%); m. p. 179° (not depressed by mixture with an authentic specimen) (Found : N, 8.4; S, 19.4. Calc. for C_8H_7ONS : N, 8.5; S, 19.4%). The yield was not lowered by conducting the reaction in an atmosphere of nitrogen or by the presence of sodium sulphide in the alkaline solution.

A further portion of the thiazine (2.08 g.) was treated with 0.975*N*-sodium hydroxide (20 c.c.) in the same way; the cooled alkaline suspension was filtered, and the residue washed well with water. Titration of the filtrate, using phenolphthalein, with hydrochloric acid (10 c.c. of 0.929*N*) shows, by difference, a weak acid content of 1.02 mols. per mol. of thiazine. Similar results were obtained when the hydrolysis was conducted in an atmosphere of nitrogen.

(IV) (2.0 g.) was recovered unchanged (1.5 g.) when its solution in alcohol (20 c.c.) was heated under reflux with 2*N*-hydrochloric acid (5 c.c.) for 6 hours.

3-Keto-2-benzoyl-2 : 3-dihydrobenzthiazine.—This was made from ethyl benzoylacetate (42.4 g.) and diaminodiphenyl disulphide (24.8 g.) in chlorobenzene (250 c.c.) as described for (IV); it formed large lemon-yellow prisms, m. p. 188° (Found : C, 66.55; H, 4.0; N, 5.05; *M*, Rast, 242. $C_{15}H_{11}O_2NS$ requires C, 66.9; H, 4.1; N, 5.2%; *M*, 269). It formed yellow solutions in hot *N*-sodium hydroxide which faded on boiling with quantitative formation of the thiazine (VI); acidification of the filtrate gave benzoic acid (m. p. and mixed m. p.). **2-Phenacylbenzthiazole**, made by zinc dust reduction of the foregoing compound in acetic acid, formed needles from benzene, m. p. 150° (Found : N, 5.6. $C_{15}H_{11}ONS$ requires N, 5.55%).