231. *Syntheses of Certain Thiazolopyrimidines (4 : 5 : 6 : 9-Tetrahydro-1-thia-7 : 9-diazaindanes).*

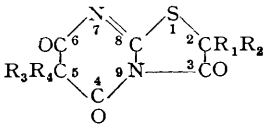
By P. J. Heald and T. K. Walker.

N-α-Carboxyacyl derivatives of 2-amino-5 : 5-dimethyl-4-thiazolone have been synthesised. When they are heated at temperatures somewhat below their melting points they lose water to give 3 : 4 : 6-triketo-4 : 5 : 6 : 9-tetrahydro-1-thia-7 : 9-diazaindanes (triketo-tetrahydrothiazolo-[3 : 2-*a*]pyrimidines). The yield is increased when the heating is conducted *in vacuo*.

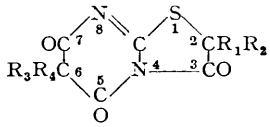
Consideration of the types of physiological activity promoted in certain molecules by the presence therein of the system ·CO·CR_1R_2·CO· (cf. Robinson, Suthers, and Walker, *Biochem. J.*, 1932, **26**, 1890) suggested that antibiotic properties might be associated with molecules of type (I*a* ≡ I*b*), and this communication describes syntheses of three compounds considered to be of this type in which, in all cases, $R_1 = R_2 = Me$ and $R_3 = H$, while in the several cases R_4 is Pr^n, Bu^n, and *n*-amyl.

α-Bromo*iso*butyric acid was condensed with thiourea in absolute ethyl alcohol to yield 2-amino-5 : 5-dimethyl-4-thiazolone. Attempts to condense this with ethyl malonate under

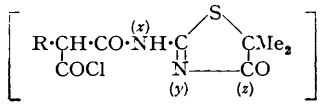
various conditions were without success. In place of this ester the more reactive alkyl-substituted malonyl chlorides were then tried in the hope that ring closure would be effected



(I*a*.)



(I*b*.)



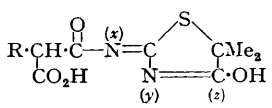
(II.)

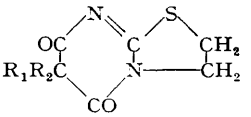
through the intermediary formation of the hypothetical type (II). It would be reasonable to suppose that in such a structure cyclisation could be effected by migration of the hydrogen atom at (*x*) to the ring nitrogen atom (*y*), followed by elimination of hydrogen chloride. This would parallel the well-known tautomerism of the amidines (cf. Shriner and Neumann, *Chem. Rev.*, 1944, **35**, 378; Pyman, *J.*, 1923, **123**, 361, 3359) and would be facile or otherwise according to the degree of basicity of the ring nitrogen atom (*y*). The findings of Dains and his co-workers indicate that such a migration can occur (*J. Amer. Chem. Soc.*, 1933, **55**, 3859; 1935, **57**, 21; 1936, **58**, 2544; *Chem. Abs.*, 1938, **32**, 3396). However, when *n*-propyl-, *n*-butyl-, and *n*-amylmalonyl chloride were brought into contact with 2-amino-5 : 5-dimethyl-4-thiazolone in anhydrous pyridine or in dioxan, only one acid chloride group reacted in each case, the expected cyclisation did not occur, and the ultimate product in each instance contained a free carboxyl group. On analysis, all these products proved to be of type (II; R = Pr, Bu, or amyl) in which COCl had been replaced by CO_2H. The *n*-butyl compound had an equivalence of 2 and yielded a di-*p*-bromophenacyl ester, owing to enolisation. On these grounds it is presumed that the three acidic products are, respectively, 2-(α-carboxy-*n*-valerylamido)-, 2-(α-carboxy-*n*-hexoylamido)-, and 2-(α-carboxy-*n*-heptoylamido)-5 : 5-dimethyl-4-thiazolone. When each of these substances was heated carefully at 10—20° below its m. p., in every instance water was formed and a colourless crystalline solid sublimed. Later, better yields were more quickly obtained by conducting the heating at 0·005 mm. pressure. From their analyses and properties we consider these dehydration products to be 3 : 4 : 6-triketo-2 : 2-dimethyl-5-*n*-alkyl-4 : 5 : 6 : 9-tetrahydro-1-thia-7 : 9-diazaindanes (I*a*) {=3 : 5 : 7-triketo-2 : 2-dimethyl-6-*n*-alkyl-2 : 3 : 6 : 7-tetrahydro-5-thiazolo[3 : 2-*a*]pyrimidines (I*b*)}, the *n*-alkyl group being propyl, butyl, and amyl, respectively.

These structures are assumed because it is not obvious in what position in the thiazolone ring, other than at the nitrogen atom, condensation with the carboxyl group could have occurred. It might be argued that an alternative possibility would be the migration of the hydrogen atom at (*x*) to the ring carbonyl group (*z*), followed by elimination of water from the condensation of the resulting enol group with the carboxyl group; but such a migration would involve the setting up of a system (III) of three conjugated double bonds which, lying in one plane, would prevent the approach of the carboxyl group to the enol group at (*z*). That such would be the case was demonstrated by the use of Fischer models. On the other hand, by the use of these models the possibility of ring closure at (*y*) was definitely established.

Moreover, our case for ring closure at the nitrogen atom receives support from the work of Bogert and Masters (*J. Amer. Chem. Soc.*, 1942, **64**, 2709, 2712), who synthesised a series of analogous substances (type IV), by condensation of 2-aminothiazoline with substituted ethyl

(III.)





(IV.)

malonates. Finally, the allocation of structures of type (I) is supported by the fact that all three substances were stable to dilute hydrochloric acid but were readily disrupted by warm dilute aqueous sodium hydroxide, to give the original three thiazolones (type II, in which COCl is replaced by CO_2H) from which they had been prepared (analysis, mixed m.p.s). Incidentally, use of the Fischer models showed that in (II) the *gem*-dimethyl group should by steric hindrance prevent condensation of the adjacent carbonyl group with 2 : 4-dinitrophenylhydrazine and other ketonic reagents, and this deduction was verified.

The 6-*n*-butyl compound of type (I) was tested for bacteriostatic activity against *Escherichia coli*, *Mycobacterium phlei*, *Staphylococcus albus*, *Pseudomonas pyocyanea*, and *Chromobacterium prodigiosum* severally in nutrient broth. It showed a slight activity towards the first three organisms, whose growth it suppressed at a concentration of 1 in 2000 (w/v).

Experimental.

(M. p.s are corrected.)

2-(α-*Carboxy*-n-*valerylamido*)-5 : 5-*dimethyl*-4-*thiazolone*.—Condensation of α-bromo*iso*butyric acid with thiourea gave 2-amino-5 : 5-dimethyl-4-thiazolone, m. p. 241—242° (Reid, *J. Amer. Chem. Soc.*, 1930, **52**, 2137; Doran and Schonle, *J. Org. Chem.*, 1938, **3**, 193). This (5 g.) was dissolved in boiling anhydrous dioxan (100 ml.), and a solution of *n*-propylmalonyl chloride (6·5 g.) in anhydrous dioxan (20 ml.) was added. After 1 hour's heating under reflux, a precipitate of the hydrochloride of some of the parent thiazolone was removed and the reaction mixture was poured on a mixture of crushed ice (350 g.) and concentrated hydrochloric acid (100 ml.). The viscous oil which separated was washed with water and with ether (20 ml.) and, on cooling, solidified. Three recrystallizations from aqueous ethyl alcohol gave the colourless thiazolone (2·2 g.), m. p. 203—204° (decomp.). A further quantity (1·2 g.) was deposited from the mother-liquors of the reaction mixture after 3 weeks' standing (Found : N, 10·2, 10·1. $C_{11}H_{16}O_4N_2S$ requires N, 10·1%). Use of dried pyridine in place of anhydrous dioxan in the above condensation usually gave lower yields.

The compound was soluble in dilute sodium hydroxide and was reprecipitated unchanged on acidification of the solution. It failed to react with 2 : 4-dinitrophenylhydrazine, hydroxylamine, semicarbazide, or 3 : 5-dinitrobenzoyl bromide, and also failed to yield a picrate or to form a compound with *s*-trinitrobenzene.

Effect of heat on the thiazolone. 1·0 G. of the thiazolone was heated in a small flask at 180° in an oil-bath. After 8 hours, traces of liquid had collected on the upper part of the neck of the flask, and, below, a colourless crystalline sublimate (0·5 g.) had settled on the glass. The liquid was water (neutral reaction, and restoration of colour to anhydrous copper sulphate). The sublimate, after recrystallization, had m. p. 213—214°. In a similar experiment the heating was carried out at 185°/0·001 mm., and in 2 hours the yield of sublimate was 0·4 g. from 0·5 g. of the original thiazolone. The new substance, 3 : 4 : 6-*triketo*-2 : 2-*dimethyl*-5-n-*propyl*-4 : 5 : 6 : 9-*tetrahydro*-1-*thia*-7 : 9-*diazaindane*, was insoluble in water or benzene, slightly soluble in ether, chloroform, or carbon tetrachloride, and more freely in methyl alcohol, ethyl alcohol, or acetone (Found : C, 52·4; H, 5·2; N, 11·4. $C_{11}H_{14}O_3N_2S$ requires C, 52·1; H, 5·5; N, 11·4%). It was insoluble in dilute hydrochloric acid, but dissolved in dilute aqueous sodium hydroxide and subsequent acidification precipitated a substance which, after crystallization from ethyl alcohol, had m. p. 203—204° (Found : N, 10·0%), and was identical (mixed m. p. and properties) with the original thiazolone.

2-(α-*Carboxy*-n-*hexoylamido*)-5 : 5-*dimethyl*-4-*thiazolone*.—This was prepared by condensation of *n*-butylmalonyl chloride (3 g.) with 2-amino-5 : 5-dimethyl-4-thiazolone (2 g.) in anhydrous dioxan, according to the procedure adopted for the lower homologue. The precipitated viscid reaction mass solidified after it had been washed with water and with ether. Four crystallizations from ethyl alcohol afforded colourless needles (2 g.), m. p. 205—206° (decomp.) [Found : C, 50·6; H, 6·2; N, 10·0; S, 9·8%; *M* (Rast), 283. $C_{12}H_{18}O_4N_2S$ requires C, 50·0; H, 6·3; N, 9·8; S, 11·2%; *M*, 286]. This *thiazolone* was soluble in dilute aqueous sodium hydroxide and was reprecipitated unchanged on acidification of the solution. A p-*bromophenacyl* ester, prepared by the method of Judefind and Reid (*J. Amer. Chem. Soc.*, 1920, **42**, 1043), had m. p. 162—163° (Found : Br, 22·9. $C_{28}H_{28}O_6N_2Br_2S$ requires Br, 23·5%). Electrometric titration showed that the thiazolone exercised an equivalence of 2.

Effect of heat on the thiazolone. The thiazolone (1·0 g.) was heated at 180° under a pressure of 0·001—0·005 mm. Water was liberated and a solid (0·9 g.) sublimed, having m. p. 210—211° not raised by recrystallization from chlorobenzene (Found : C, 53·6; H, 6·0; N, 10·8. $C_{12}H_{16}O_3N_2S$ requires C, 53·7; H, 6·0; N, 10·4%). This 3 : 4 : 6-*triketo*-2 : 2-*dimethyl*-5-n-*butyl*-4 : 5 : 6 : 9-*tetrahydro*-1-*thia*-7 : 9-*diazaindane* had properties similar to those of its lower homologue, and on treatment with aqueous sodium hydroxide and subsequent acidification of the solution it yielded the original thiazolone, m. p. 205—206°, undepressed by admixture with the authentic preparation (Found : N, 9·9%).

2-(α-*Carboxy*-n-*heptoylamido*)-5 : 5-*dimethyl*-4-*thiazolone*.—To a solution of 2-amino-5 : 5-dimethyl-4-thiazolone (10 g.) in boiling anhydrous dioxan (300 ml.) was added *n*-amylmalonyl chloride (5·5 g.) in anhydrous dioxan (100 ml.). A white precipitate formed immediately. Heating was continued for 1 hour, the suspension was then filtered hot, and the filtrate poured on a mixture of crushed ice (800 g.) and concentrated hydrochloric acid (200 ml.). The aqueous emulsion was kept at 0° and after 12 hours yielded a solid (4·5 g.) which, washed and recrystallized 3 times from aqueous ethyl alcohol, formed colourless plates, m. p. 176·5°. After 2 weeks the reaction mother-liquors had deposited a further 2 g. of the same product (Found : N, 9·3. $C_{13}H_{20}O_4N_2S$ requires N, 9·3%). The properties of this *thiazolone* were similar to those of its analogues.

Effect of heat on the thiazolone. 3 : 4 : 6-*Triketo*-2 : 2-*dimethyl*-5-n-*amyl* 4 : 5 : 6 : 9-*tetrahydro*-1-*thia*-7 : 9-*diazaindane* collected as a sublimate (0·8 g.) when the thiazolone (1·0 g.) was heated at 160° for 4 hours at 0·001—0·005 mm. The m. p. was 155—156°, unchanged after recrystallization from chlorobenzene (Found : C, 55·0; H, 6·4; N, 10·1. $C_{13}H_{18}O_3N_2S$ requires C, 55·3; H, 6·1; N, 9·9%). The compound had properties similar to those of its lower homologues, and on treatment first with dilute aqueous sodium hydroxide and then with hydrochloric acid there was regenerated the parent thiazolone, m. p. 176·5°, undepressed by admixture with the authentic preparation.

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