384. *The Condensation of* N-*Substituted Maleimides with Thioureas.*

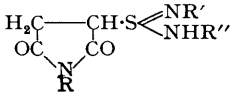
By D. H. Marrian.

N-Substituted maleimides condense readily with thiourea, *N*-phenylthiourea, and with thiocarbanilide. The products, which are additive in molecular formula, are shown to be probably thiazolidones of type (III).

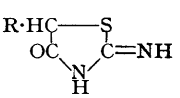
To further the investigation of the reactivity of maleimides towards free thiol groups (Friedmann, Marrian, and Simon-Reuss, *Brit. J. Pharmacol.*, 1949, **4**, 105; Marrian, this vol., p. 1515) it was decided to investigate whether these imides would react with the incipient thiol group of thioureas. Equimolar solutions of the reactants readily deposited the crystalline products in good yield, although in the case of the more insoluble phenyl-substituted thioureas it was sometimes necessary to carry out the reaction in boiling alcohol. All the six compounds obtained analysed as addition products and were neutral, thereby eliminating one of the possible structures (I), which is that of a mono-acid base. Furthermore, Raney-nickel desulphurisation in boiling alcohol did not give a substituted succinimide (cf. Marrian, *loc. cit.*).

A second possibility was that the reaction was analogous to that reported by Andreasch (*Monatsh.*, 1895, **16**, 789; 1897, **18**, 56), who showed that simple or substituted thioureas with unsaturated dicarboxylic acids or their anhydrides gave thiazolidones such as (II; R = $CH_2 \cdot CO_2H$) from maleic acid and thiourea, and (II; R = $CHMe \cdot CO_2H$) from citraconic acid or anhydride.* Compounds of structure (II) were originally prepared by Volhard (*Annalen*, 1873, **166**, 383) and Maly (*ibid.*, 1873, **168**, 133) by condensation of chloroacetic acid with thiourea, and their structure as thiazolidones or ψ-thiohydantoins was elucidated by Liebermann and Lange (*Ber.*, 1879, **12**, 1588). The unambiguous synthesis of (II; R = $CH_2 \cdot CO_2H$) from thiomalic acid and cyanamide (Andreasch, *loc. cit.*) completed the structural evidence for (II). This is an argument in favour of a structure such as (III) for the products from *N*-substituted maleimides and thioureas, and (III) is supported by the nature of the products of desulphurisation which are all substituted succindiamides (IV) formed by fission of (III) along the broken line. The six-membered-ring structure corresponding to (III) is less likely although the present work does not eliminate it.

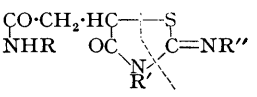
A third possibility, that the compounds might be substituted pyrimidines [cf. the reaction reported by Erlenmeyer and Heitz (*Helv. Chim. Acta*, 1942, **25**, 832) between cinnamic acid and thiourea], can be dismissed on the evidence of desulphurisation.



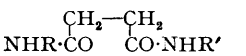
(I.)



(II.)



(III.)



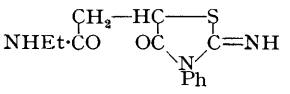
(IV.)

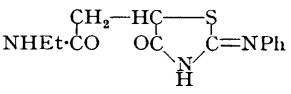
From aqueous-alcoholic solutions of *N*-ethylmaleimide and thiourea at room temperature was isolated 2-*iminothiazolid*-4-*one*-5-*acetoethylamide* (III; R = Et; R′ = R″ = H) which furnished, on treatment with Raney nickel, N-*ethylsuccindiamide* (IV; R = Et; R′ = H), also prepared by ammonolysis of *N*-ethylsuccinimide in alcohol. Similarly from *N*-ethylmaleimide and *N*-phenylthiourea was isolated 2-*imino*-3-*phenylthiazolid*-4-*one*-5-*acetoethylamide*

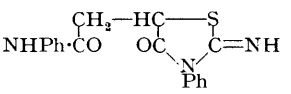
* Bougault and Chabrier (*Compt. rend.*, 1947, **224**, 656) have shown that benzoylacrylic acid and thiourea react analogously.

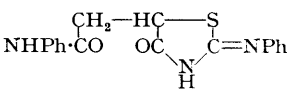
(III; R = Et; R′ = Ph; R″ = H), and from thiocarbanilide, 2-*anilo*-3-*phenylthiazolid*-4-*one*-5-*acetoethylamide* (III; R = Et; R′ = R″ = Ph), both of which gave N-*phenyl*-N′-*ethylsuccindiamide* (IV; R = Et; R′ = Ph) on desulphurisation. The structure of the latter diamide was proved by synthesis from maleic acid monoethylamide by catalytic hydrogenation to N-*ethylsuccinamic acid*, which with thionyl chloride and aniline gave (IV; R = Et; R′ = Ph). The series from *N*-phenylmaleimide differed in only one respect: the compounds formed by the imide with thiourea and *N*-phenylthiourea gave the same desulphurised product, the known *N*-phenylsuccindiamide (IV; R = Ph; R′ = H) (Menschutkin, *Annalen*, 1872, **162**, 182), whilst that from thiocarbanilide gave the known succindianilide (IV; R = R′ = Ph) (*idem*, *ibid.*, p. 187). The products are therefore 2-*iminothiazolid*-4-*one*-5-*acetanilide* (III; R = Ph; R′ = R″ = H) from *N*-phenylmaleimide and thiourea, 2-*anilothiazolid*-4-*one*-5-*acetanilide* (III; R = R″ = Ph; R′ = H) from *N*-phenylmaleimide and *N*-phenylthiourea, and 2-*anilo*-3-*phenylthiazolid*-4-*one*-5-*acetanilide* (III; R = R′ = R″ = Ph) from *N*-phenylmaleimide and thiocarbanilide.

The Raney-nickel treatment is seen to lead to breakdown of the molecule further than the dethio-stage. In the case of (III; R = Et; R′ = R″ = H), ammonia (identified as the picrate) was isolated from the effluent gases.


(V*a*.)


(V*b*.)


(VI*a*.)


(VI*b*.)

A point of interest arises in the products from both imides and *N*-phenylthiourea. In both cases, two formulations are possible (V*a* and *b*) from *N*-ethylmaleimide and (VI*a* and *b*) from *N*-phenylmaleimide. In each case only one isomer was isolated, (V*a*) in quantitative crude yield, and (VI*b*) in 69% crude yield. The melting points of the crude products were not raised by recrystallisation, so that mixtures were, in all probability, not formed.

Experimental.

2-*Iminothiazolid*-4-*one*-5-*acetoethylamide*.—*N*-Ethylmaleimide (5 g.) in alcohol (40 c.c.) and water (80 c.c.) was added to thiourea (3·04 g.) in alcohol (20 c.c.) and water (40 c.c.), and the mixture kept overnight at room temperature. Scratching caused crystallisation of the *product* (5·58 g., 69·5%), m. p. 195—196°. For analysis, the material was recrystallised from water, giving colourless prisms, m. p. unchanged (Found, in material dried at 80°: C, 41·3; H, 5·8; N, 20·5. $C_7H_{11}O_2N_3S$ requires C, 41·8; H, 5·5; N, 20·9%). The low value for carbon and the high value for hydrogen are due doubtless to the extremely hydroscopic nature of the dried material, which readily forms the *monohydrate* (Found: C, 38·6; H, 6·0; loss at 120°, 7·7. $C_7H_{11}O_2N_3S,H_2O$ requires C, 38·4; H, 6·0; H_2O, 8·2%).

2-*Imino*-3-*phenylthiazolid*-4-*one*-5-*acetoethylamide*.—*N*-Ethylmaleimide (125 mg.) and *N*-phenylthiourea (152 mg.) in alcohol (4 c.c.) were warmed until dissolution was complete, whereupon a yellow colour developed; after 3 days, the crystalline solid was filtered off and washed with alcohol [quantitative yield, m. p. 237° (decomp.) after sintering at 235°]. After one recrystallisation from dioxan and one from a large volume of water (90 mg. in 200 c.c.) the *amide* formed colourless prisms, m. p. 235° (decomp.) (Found, in material dried at 80°: C, 56·1; H, 5·4; N, 14·6. $C_{13}H_{15}O_2N_3S$ requires C, 56·3; H, 5·4; N, 15·2%).

2-*Anilo*-3-*phenylthiazolid*-4-*one*-5-*acetoethylamide*.—*N*-Ethylmaleimide (125 mg.), thiocarbanilide (228 mg.), and alcohol (8 c.c.) were heated under reflux for 2 hours and then kept overnight. Scratching yielded colourless prisms which were filtered off and washed with alcohol: yield, 160 mg. (46·7%); m. p. 204—205° (decomp.). Recrystallised from alcohol, from which it separates slowly in colourless prisms, the *product* had m. p. 209—210° (decomp.) (Found, in material dried at 80°: C, 64·4; H, 5·4; N, 12·5. $C_{19}H_{19}O_2N_3S$ requires C, 64·6; H, 5·4; N, 11·9%).

2-*Iminothiazolid*-4-*one*-5-*acetanilide*.—*N*-Phenylmaleimide (176 mg.), thiourea (76 mg.), and alcohol (10 c.c.) were warmed on the steam-bath until the initial yellow colour had almost disappeared. When the mixture was cooled, a colourless crystalline powder was deposited (180 mg., 71·5%), m. p. 223—223·5° (decomp.) (depending on the rate of heating). The *anilide* crystallised from alcohol (20 c.c.) in colourless prisms, m. p. 220—221° (decomp.) (Found, in material dried at 80°: C, 52·8; H, 4·5; N, 17·5. $C_{11}H_{11}O_2N_3S$ requires C, 53·0; H, 4·4; N, 16·9%).

2-*Anilothiazolid*-4-*one*-5-*acetanilide*.—*N*-Phenylmaleimide (1·76 g.), *N*-phenylthiourea (1·52 g.), and alcohol (40 c.c.) were heated under reflux for 2 hours and then set aside overnight. The colourless crystalline precipitate was filtered off and washed with alcohol, giving 2·26 g. (69%) of colourless prisms, m. p. 216·5—217·5° (decomp.). Recrystallisation from alcohol did not change the m. p. (Found, in material dried at 80°: C, 62·6; H, 4·5; N, 12·9. $C_{17}H_{15}O_2N_3S$ requires C, 62·8; H, 4·6; N, 12·9%).

2-*Anilo*-3-*phenylthiazolid*-4-*one*-5-*acetanilide*.—*N*-Phenylmaleimide (0·88 g.), thiocarbanilide (1·14 g.), and alcohol (30 c.c.) were heated under reflux for 2 hours and then allowed to cool. Scratching

readily caused crystallisation of the ***anilide*** in almost colourless prisms (1·05 g., 52%), m. p. 206—208° (decomp.). A second crop (0·28 g.), m. p. 203—205° (decomp.), was obtained by evaporation of the mother-liquors. Two recrystallisations from alcohol gave colourless matted needles, m. p. 209—210° (decomp.) (Found, in material dried at 80° : C, 68·8; H, 5·0; N, 9·8. $C_{23}H_{19}O_2N_3S$ requires C, 68·8; H, 4·7; N, 10·5%).

Desulphurisation Experiments.—The addition product (1·0 g.), Raney nickel (" 15 c.c."), and alcohol (*ca.* 40 c.c.) were heated under reflux for some 20 hours, the nickel was extracted for about the same time with hot alcohol, and the extract filtered and evaporated to incipient crystallisation.

(*a*) 2-Iminothiazolid-4-one-5-acetoethylamide gave colourless plates (110 mg.), m. p. 175·5—177°, and a further 130 mg. of slightly lower-melting material. Recrystallised from alcohol, *N-ethylsuccindiamide* formed colourless prisms, m. p. 175·5—176·5° (Found, in material dried at 80° : C, 50·3; H, 8·4; N, 18·4. $C_6H_{12}O_2N_2$ requires C, 50·0; H, 8·3; N, 19·4%), identified by the following synthesis. *N*-Ethylsuccinimide (2·5 c.c.; Menschutkin, *Annalen*, 1876, **182**, 90) and alcoholic ammonia solution (50 c.c., saturated at 0°) were heated in a stoppered bottle at 105° overnight. The solution was evaporated *in vacuo*, and the residue recrystallised twice from alcohol to m. p. 174—175°, undepressed on admixture with the desulphurised product described above. The yield was low.

In one such degradation, a stream of nitrogen was blown through the reaction mixture, and the effluent gases passed through an alcoholic solution of picric acid. A precipitate formed which decomposed on heating at 269—284° alone or admixed with an authentic sample of ammonium picrate.

(*b*) 2-Imino-3-phenylthiazolid-4-one-5-acetoethylamide gave *N-phenyl-N′-ethylsuccindiamide* (365 mg.) in colourless needles, m. p. 170—171°, unchanged by recrystallisation from alcohol. 2-Anilo-3-phenylthiazolid-4-one-5-acetoethylamide gave 220 mg. of the same product (Found, in material dried at 80° : C, 65·7; H, 7·3; N, 12·4. $C_{12}H_{16}O_2N_2$ requires C, 65·5; H, 7·3; N, 12·7%). It was identified by the following synthesis.

Maleic acid monoethylamide (14·3 g.) was hydrogenated in 95% alcohol (125 c.c.) at atmospheric pressure over platinum oxide (uptake, 2340 c.c. in 2½ hours, inclusive of reduction of the catalyst). The filtered solution was boiled under reflux with charcoal, filtered, and evaporated *in vacuo*. The residue crystallised (15·2 g., inclusive of some oil; quantitative crude yield). The solid was pressed dry on a porous plate and recrystallised from ethyl acetate, giving *N-ethylsuccinamic acid* as colourless needles (8·4 g.), m. p. 93·5—95·5°; two further recrystallisations from the same solvent raised the m. p. to 95—96° (Found, in material dried at room temperature : C, 49·7; H, 7·5; N, 9·7; equiv., 143. $C_6H_{11}O_3N$ requires C, 49·7; H, 7·6; N, 9·6%; equiv., 145).

N-Ethylsuccinamic acid (1·45 g.) was dissolved in aniline (5 c.c.), cooled in a water-bath, and treated dropwise with thionyl chloride (0·75 c.c.) with manual shaking. The reaction flask was loosely stoppered and left at room temperature for 2 hours. The reaction mixture was dissolved in 5N-hydrochloric acid, and the solution extracted continuously with ether overnight. *N*-Phenyl-*N′*-ethylsuccindiamide separated from the ethereal extract on cooling (0·32 g.; m. p. 147—154°). Recrystallisation from water gave colourless needles, m. p. 171—171·5°. Evaporation of the ethereal mother-liquors gave a further 0·72 g. of impure material.

(*c*) 2-Iminothiazolid-4-one-5-acetanilide gave colourless prisms (0·31 g.), m. p. 175·5—176°, raised to 177—179° by two recrystallisations from alcohol, whilst 2-anilothiazolid-4-one-5-acetanilide gave 210 mg. of the same compound, which was identified as *N*-phenylsuccindiamide by mixed m. p. and by analysis (Found, in material dried at 80°; C, 62·6; H, 6·5; N, 14·5. Calc. for $C_{10}H_{12}O_2N_2$: C, 62·5; H, 6·2; N, 14·6%).

(*d*) 2-Anilo-3-phenylthiazolid-4-one-5-acetanilide gave succindianilide (300 mg.), m. p. 195—196° (raised to 223—224° by recrystallisation from alcoholic potassium hydroxide), identified by mixed m. p. with an authentic specimen, m. p. 224—225°.

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