911. *The Synthesis of 3-Alkyl-1-arylsulphonyl-hydantoins and -2-thiohydantoins.*

By G. Holan and E. Samuel.

N^1-Alkyl-N^2-arylsulphonyl ureas with ethyl chloroacetate give 3-alkyl-1-arylsulphonylhydantoins whose structures are confirmed by independent synthesis of a 1-arylsulphonylhydantoin, followed by alkylation at the 3-position. An N^1-aryl-N^2-arylsulphonylurea could not be cyclised.

With ethyl chloroacetate an N^1-alkyl-N^2-arylsulphonylthiourea gave a thiazolidone, the thiourea reacting in its iso-form. The desired 3-alkyl-1-arylsulphonyl-2-thiohydantoin was obtained, together with the S-alkyl derivative, by treating the 1-arylsulphonyl-2-thiohydantoin with an alkyl iodide.

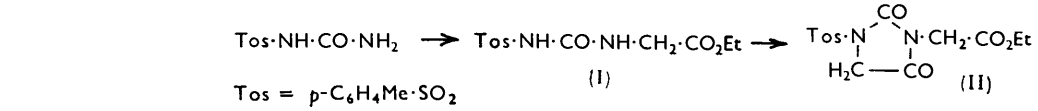
Desulphurisation of an *S*-alkyl-2-thiohydantoin with chloroacetic acid yielded the unsubstituted 1-arylsulphonylhydantoin. Sulphurisation of a 3-alkyl-1-arylsulphonylhydantoin with phosphorus pentasulphide afforded the 4-thiohydantoin.

The use of N^1-alkyl-N^2-arylsulphonylureas in oral control of diabetes is well known. In the present work we have attempted to build this structure into hydantoins and thiohydantoins, which were reported to affect the blood-sugar level of mammals.[1] The chosen compounds were the 3-alkyl-1-arylsulphonyl-hydantoins and -2-thiohydantoins.

1,3-Dialkyl(or aryl-alkyl)-hydantoins or -2-thiohydantoins are conventionally synthesized by cyclisation of an *N*-alkyl- or *N*-aryl-glycine with an alkyl isocyanate or isothiocyanate. Therefore in our work we would have required the arylsulphonyl isocyanates and isothiocyanates. Such isocyanates have been prepared,[2] but with difficulty, and their reaction with alkylglycines was accompanied by polymerization. Attempts to prepare arylsulphonyl isothiocyanates were unsuccessful.

The reverse reaction, in which an alkyl isothiocyanate was treated with an arylsulphonylglycine, afforded the arylsulphonylglycine alkylamide and the 1,4-diarylsulphonyl-2,5-dioxopiperazine, indicating that an alkyl isothiocyanate does not react with a substituted sulphonamido-group.

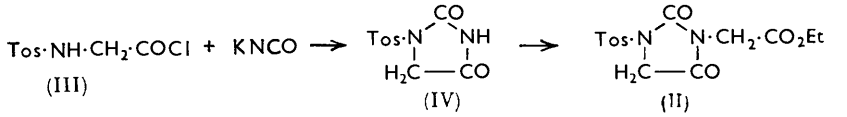
After this preliminary work the simplest approach appeared to be cyclisation of N^1-alkyl-N^2-arylsulphonylureas with ethyl chloroacetate. Aspelund[3] cyclised N^1-methyl-N^2-phenylurea with chloroacetyl chloride or ethyl chloroacetate to the 3-methyl-4-oxo-2-phenylimino-oxazolidine and 3-methyl-1-phenylhydantoin by means of sodium in ethanol. The N^2-nitrogen of the N^1-alkyl-N^2-arylsulphonylureas is more acidic than that in the dialkyl- or alkylaryl-ureas owing to the electron-withdrawing effect of the sulphonyl group; thus their condensation with ethyl chloroacetate proceeded in aqueous ethanol or, preferably, dimethylformamide in presence of potassium carbonate as a condensing agent. We thus prepared 3-butyl-1-toluene-*p*-sulphonyl- and 1-*p*-chlorobenzenesulphonyl-3-propylhydantoin, but we failed to obtain 3-phenyl-1-toluene-*p*-sulphonylhydantoin.



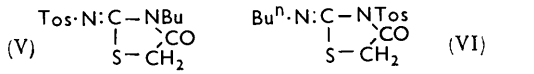
Treating toluene-*p*-sulphonylurea with ethyl chloroacetate gave 3-ethoxycarbonylmethyl-1-toluene-*p*-sulphonylhydantoin (II) and the urea (I), and no 1-toluene-*p*-sulphonylhydantoin was isolated. Therefore the reaction involves further condensation of the urea (I) with ethyl chloroacetate.

[1] Isshiki, *Pharmacol. Jap.*, 1932, **15**, No. 1, Breviaria 4.
[2] Franz, personal communication.
[3] Aspelund, *Finska Kemistsamfundets Medd.*, 1940, **49**, 49.

The hydantoin (II) was also used for the proof of the substitution pattern of the hydantoins in our reaction. This was carried out by unambiguous synthesis of the 1-toluene-*p*-sulphonylhydantoin (IV) from toluene-*p*-sulphonylglycine chloride (III) and potassium isocyanate, and conversion of this by ethyl chloroacetate into the hydantoin (II).

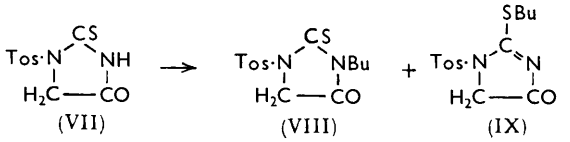


We expected that cyclisation of the N^1-alkyl-N^2-arylsulphonylthioureas with ethyl chloroacetate would yield the thiazolidones and not the 2-thiohydantoins, as thioureas generally react in their iso-form. The thiazolidone obtained by this cyclisation of N^1-butyl-N^2-toluene-*p*-sulphonylthiourea yielded on acid hydrolysis N^1-butyl-N^2-toluene-*p*-sulphonylurea, but this is not a definitive proof of structure as the same hydrolysis product would be obtained from the two isomers (V) and (VI) that could be formed in the cyclisation. Although no final proof is available, structure (V) is the more probable as the initial isomerisation of the substituted thiourea in the cyclisation would be expected to proceed by transfer of the more labile hydrogen from the sulphonamido-group to sulphur.



On failure of the chloroacetate cyclisation to yield the required 3-alkyl-1-arylsulphonyl-2-thiohydantoins several other methods of synthesis were attempted. Reaction of butyl isothiocyanate with toluene-*p*-sulphonylglycine under various conditions yielded either *N*-butyl-*N*-toluene-*p*-sulphonylacetamide or 2,5-dioxo-1,4-di-*p*-toluenesulphonylpiperazine by condensation of two molecules of the substituted glycine. On treatment of butyl isothiocyanate with the ester or acyl chloride of the arylsulphonylglycine only the starting materials were recovered. The reverse cyclisation of butylglycine with the arylsulphonyl isothiocyanate could not be carried out as attempts to prepare the isothiocyanate, or to treat it *in situ* with the butyl compound, were unsuccessful.

3-Butyl-1-toluene-*p*-sulphonyl-2-thiohydantoin (VIII) was finally prepared by reaction of 1-toluene-*p*-sulphonyl-2-thiohydantoin (VII) with butyl iodide: this gave also the *S*-alkyl derivative (IX) owing to a shift of the hydrogen from the 3-position of the thiohydantoin to sulphur. The structure of the *S*-alkyl isomer was determined by its ease of desulphurisation with chloroacetic acid to 1-toluene-*p*-sulphonylhydantoin (IV): the 3-alkylated derivative (VIII) could not be desulphurised.



3-Butyl-1-toluene-*p*-sulphonyl-4-thiohydantoin was obtained by sulphurisation of 3-butyl-1-toluene-*p*-sulphonylhydantoin with phosphorus pentasulphide. Elemental analysis confirmed the product as an isomer of the thiohydantoins (VIII) and (IX), its infrared spectrum was different, and mixed melting points were depressed.

Experimental

Cyclisation with Ethyl Chloroacetate.—To a stirred solution of the urea or thiourea (0·04 mole), in dimethylformamide (200 ml.), anhydrous potassium carbonate (0·04 mole) was added and the suspension heated to 80°. At this temperature ethyl chloroacetate (0·04 mole) in dimethylformamide (50 ml.) was added during 1 hr. After a further 1·5 hr. at 80° the mixture was cooled in ice, filtered, and concentrated under a vacuum. The first crop of hydantoin or

thiazolidone was filtered off. Treatment of the filtrate with dilute alkali gave a second crop. These materials were combined and recrystallised. The following were thus obtained.

3-*Butyl*-1-*toluene*-p-*sulphonylhydantoin* (35%; from *N'*-butyl-N^2-toluene-*p*-sulphonylurea [4]), needles (from ethanol), m. p. 153° (Found: C, 54·7; H, 5·9; S, 10·3. $C_{14}H_{18}N_2O_4S$ requires C, 54·2; H, 5·8; S, 10·3%).

1-p-*Chlorobenzenesulphonyl*-3-*propylhydantoin* (from N^1-*p*-chlorobenzenesulphonyl-N^2-propylurea [5]; 25%), needles (from methanol), m. p. 179° (Found: C, 45·9; H, 4·3; S, 10·0. $C_{12}H_{13}ClN_2O_4S$ requires C, 45·55; H, 4·1; S, 10·1%).

3-*Ethoxycarbonylmethyl*-1-*toluene*-p-*sulphonylhydantoin* (10%; from toluene-*p*-sulphonylurea [6]) (crystallised from methanol), m. p. 197° (Found: C, 49·3; H, 4·9; S, 9·4. $C_{14}H_{16}N_2O_6S$ requires C, 49·4; H, 4·7; S, 9·4%). Dilution with water of the dimethylformamide filtrate from the above experiment precipitated toluene-*p*-sulphonamide (80%). Acidification of the filtrate from this precipitate yielded *ethyl* N^2-*toluene*-p-*sulphonylureidoacetate* which recrystallised from aqueous ethanol as plates (4%), m. p. 168° (Found: C, 48·3; H, 5·5; S, 11·2. $C_{12}H_{16}N_2O_5S$ requires C, 48·0; H, 5·4; S, 10·7%).

The hydantoin was also obtained from 1-toluene-*p*-sulphonylhydantoin and ethyl chloroacetate by the method used for the cyclisations.

1-*Butyl*-2-*toluene*-p-*sulphonylimino*-3-*thiazolid*-5-*one*.—This *product* (obtained by the usual cyclisation from 3-butyl-1-toluene-*p*-sulphonylthiourea [7]) formed a buff-coloured powder (from methanol) (65%), m. p. 168° (Found: C, 51·4; H, 5·5; S, 19·05. $C_{14}H_{18}N_2O_3S_2$ requires C, 51·5; H, 5·6; S, 19·05%).

1-*Toluene*-p-*sulphonylhydantoin*.—Potassium cyanate (0·12 mole) and toluene-*p*-sulphonylglycine chloride [8] (0·04 mole) were dissolved in glacial acetic acid. An exothermic reaction raised the temperature to 60°. The solution was then refluxed for 15 min. After cooling, a small amount of resin was filtered off and the filtrate was neutralised with sodium carbonate solution. The *hydantoin* precipitated was recrystallised from methanol, forming needles (5%), m. p. 226° (Found: C, 47·0; H, 4·0; S, 12·7. $C_{10}H_{10}N_2O_4S$ requires C, 47·3; H, 4·0; S, 12·6%).

1-*Toluene*-p-*sulphonylhydantoin*.—2-Butylthio-1-toluene-*p*-sulphonyl-2-imidazolin-4-one (0·01 mole) and chloroacetic acid (0·1 mole) were refluxed in water (2 ml.) for 3 hr. The precipitated 1-toluene-*p*-sulphonylhydantoin recrystallised from methanol and was identified by a mixed m. p. and its infrared spectrum.

2,5-*Dioxo*-1,4-*ditoluene*-p-*sulphonylpiperazine*.—Toluene-*p*-sulphonylglycine [9] (0·06 mole) and butyl isothiocyanate [10] (0·06 mole) were refluxed in toluene (400 ml.) with triethylamine, the water formed being removed azeotropically. After 5 hours' refluxing the toluene was evaporated. The residue, which was insoluble in both acid and alkali, recrystallised from aqueous acetone and was identified as the piperazine, m. p. 293° (lit., 225°,[11] 275° [12]) (Found: C, 51·3; H, 4·4; S, 15·1. Calc. for $C_{18}H_{18}N_2O_6S_2$: C, 51·2; H, 4·3; S, 15·2%).

N-*Butyl*-N-*toluene*-p-*sulphonamidoacetamide*.[13]—Toluene-*p*-sulphonylglycine (0·02 mole) and butyl isothiocyanate with a trace of triethylamine were heated at 100° for 10 hr. Methanol was then added and a small amount of the above dioxopiperazine was filtered off. The filtrate was diluted with water. An oil was deposited which solidified and recrystallised from aqueous ethanol and ethyl acetate–light petroleum (b. p. 40—60°). This *amide* (30%), m. p. 93° (Found: C, 55·3; H, 6·8; S, 11·4. Calc. for $C_{13}H_{20}N_2O_3S$: C, 54·9; H, 7·1; S, 11·3%), was insoluble in acid or sodium carbonate but was soluble in sodium hydroxide. Its hydrolysis products were identified as toluene-*p*-sulphonylglycine and butylamine by paper chromatography.

3-*Butyl*-1-*toluene*-p-*sulphonyl*-2-*thiohydantoin* *and* 2-*Butylthio*-1-*toluene*-p-*sulphonyl*-2-*imidazolin*-4-*one*.—1-Toluene-*p*-sulphonyl-2-thiohydantoin (0·02 mole), potassium carbonate (0·01 mole), and butyl iodide (0·02 mole) were heated at 75—80° for 0·5 hr., then cooled and poured into water (200 ml.), and the yellow precipitate was filtered off. This was treated with hot benzene and the insoluble starting material removed. Cooling of the benzene filtrate gave

[4] Commercially available as " Orinase " or " Tolbutamide."
[5] Commercially available as " Chlorpropamide " or " Diabinese."
[6] Martin, U.S.P. 2,411,661/1946.
[7] Petersen, *Chem. Ber.*, 1950, **83**, 551.
[8] Swan, *Austral. J. Sci. Res.*, 1952, *A*, **5**, No. 4, 732.
[9] Fisher and Bergman, *Annalen*, 1913, **398**, 117.
[10] Schmidt and Schnegg, G.P. 14,755/1956.
[11] Wallin, *Acta Univ. Lundensis*, 1892, **28**, 2.
[12] Enger, *Z. physiol. Chem.*, 1930, **191**, 117.
[13] Rushig, Korger, Aumüller, Wagner, and Weyer, *Medizin und Chemie*, 1958, **6**, 61.

the S-*butyl derivative* (60%) as plates, m. p. 127° (from methanol), with an odour of butanethiol (Found: C, 51·45; H, 5·7; S, 19·5. $C_{14}H_{18}N_2O_3S_2$ requires C, 51·5; H, 5·6; S, 19·6%).

The filtrate was chromatographed on alumina, and the 3-*butylthiohydantoin* eluted with benzene and recrystallised from methanol as a yellowish powder (12%), m. p. 106° (Found: C, 51·6; H, 5·85; S, 19·6. $C_{14}H_{18}N_2O_3S_2$ requires C, 51·5; H, 5·6; S, 19·6%).

The *S*-alkyl derivative was desulphurised with chloroacetic acid to 1-toluene-*p*-sulphonylhydantoin. The 3-alkyl derivative gave toluene-*p*-sulphonylglycine on alkaline hydrolysis.

3-*Butyl*-1-*toluene*-p-*sulphonyl*-4-*thiohydantoin*.—3-Butyl-1-toluene-*p*-sulphonylhydantoin (0·07 mole) and phosphorus pentasulphide (0·05 mole) were refluxed for 1 hr. in tetralin (20 ml.). On cooling, crystals were formed which, recrystallised from methanol, gave the 4-*thiohydantoin* as white needles (20%), m. p. 167° (Found: C, 51·9; H, 5·6; S, 19·9. $C_{14}H_{18}N_2O_3S_2$ requires C, 51·5; H, 5·6; S, 19·6%).

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