627. *Purines, Pyrimidines, and Glyoxalines. Part VI.* Some 5-Aryl(or alkyl)sulphonyluracils.*

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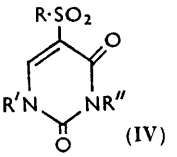
Several 5-aryl(or alkyl)sulphonyluracils (IV) have been prepared by the reaction of ammonia or primary amines with the α-aryl(or alkyl)sulphonyl-β-ethoxy-*N*-ethoxycarbonylacrylamides (II; R = X·SO_2, R′ = H or Me).

The synthesis of substituted uracils by reaction of ammonia or a primary amine with a linear acylurethane of type (II) has been shown [1] to be successful with the compounds (II; R = R′ = H; * and R = CN, R′ = H, Me). We now report an extension of this reaction to the synthesis of some 5-aryl(or alkyl)sulphonyluracils (IV) as part of our antimetabolite studies. Analogous 6-sulphonyluracils have recently been shown to inhibit lymphomas and the sarcoma 180 in mice.[2]

R·CH_2·CO·NR′·CO_2Et (I)

R·C(:CH·OEt)·CO·NR′·CO_2Et (II)



(IV)

p-MeC_6H_4·SO_2·C(:CH·NHR)·CO·NH·CO_2Et (III)

p-Tolylsulphonylacetylurethane (I; R = *p*-C_6H_4Me·SO_2, R′ = H), prepared by reaction of sodium toluene-*p*-sulphinate with chloroacetylurethane,[3] reacted slowly with an excess of ethyl orthoformate and acetic anhydride to give a good yield of the ethoxymethylene derivative (II; R = *p*-C_6H_4Me·SO_2, R′ = H). With aqueous ammonia, methylamine, or an alkaline solution of glycine this gave the corresponding *p*-tolylsulphonyluracil (IV; R = *p*-tolyl, R′ = H, Me, and CH_2·CO_2H, R″ = H). With aniline and phenylhydrazine in ethanol or benzene the ethoxymethylene derivative gave the linear aminomethylene compounds (III; R = Ph and Ph·NH respectively). These cyclised to the sulphonyluracils (IV; R = *p*-tolyl, R′ = Ph and Ph·NH, R″ = H) when boiled with water or treated with sodium hydroxide solution.

The arylsulphonyluracils (IV; R = Ph, R′ = H or Et, R″ = H; and R = *p*-NHAc·C_6H_4, R′ = R″ = H) were similarly prepared.

Ethylsulphonylacetylurethane (I; R = Et·SO_2, R′ = H) and the methyl derivative (I; R = Et·SO_2, R′ = Me) were prepared from ethylsulphonylacetic acid and urethane or *N*-methylurethane in the presence of phosphoryl chloride, and, when treated as above, gave the uracils (IV; R = Et, R′ = H, R″ = H or Me).

Experimental

β-*Ethoxy*-N-*ethoxycarbonyl*-α-p-*tolylsulphonylacrylamide*.—*p*-Tolylsulphonylacetylurethane (14·25 g.), ethyl orthoformate (12·9 g.), and acetic anhydride (14·5 ml.) were heated together at 120° for 1 hr., and at 130° for 1·5 hr. under an air-condenser and then without a condenser for 30 min. at 140°. When the solution was cooled a crystalline precipitate separated; this was filtered off and washed with ether. β-*Ethoxy*-N-*ethoxycarbonyl*-α-p-*tolylsulphonylacrylamide* (12·5 g.) separated from ethanol as needles, m. p. 126—128° (Found: C, 52·6; H, 5·35; N, 4·1. $C_{15}H_{19}O_6NS$ requires C, 52·8; H, 5·6; N, 4·1%).

5-p-*Tolylsulphonyluracil*.—The foregoing amide (0·3 g.) was warmed for 10—15 min. with 15N-aqueous ammonia (10 ml.) until a clear solution was obtained. The solution was evaporated to half-volume, cooled, and neutralised with hydrochloric acid, yielding a crystalline precipitate. 5-p-*Tolylsulphonyluracil* (0·27 g.) separated from ethanol as needles, m. p. >350° (Found: C, 49·55; H, 3·95; N, 10·4. $C_{11}H_{10}O_4N_2S$ requires C, 49·6; H, 3·7; N, 10·5%).

* Part V, *J.*, 1957, 2363.

[1] *J.*, 1955, 1834; 1956, 1877.
[2] Hakala, Law and Welch, *Proc. Ann. Assoc. Cancer Res.*, 1956, **2**, 113.
[3] Frerichs, *Arch. Pharm.*, 1899, **237**, 288.

1-*Phenyl*-5-p-*tolylsulphonyluracil*.—The acrylamide (0·17 g.) in benzene (5 ml.) was heated with aniline (0·5 g.) on a water-bath for 10 min. β-*Anilino*-α-p-*tolylsulphonyl*-N-*ethoxycarbonylacrylamide* (0·15 g.) separated on cooling and recrystallised from ethanol as pale yellow needles, m. p. 146—148° (Found: C, 58·75; H, 5·2; N, 7·2. $C_{19}H_{20}O_5N_2S$ requires C, 58·75; H, 5·3; N, 7·2%). A suspension of the anilino-derivative (0·15 g.) in water (20 ml.) was boiled under reflux for 50 min., then cooled. 1-*Phenyl*-5-p-*tolylsulphonyluracil* (0·12 g.) separated and crystallised from ethanol as prisms, m. p. 242° (Found: C, 59·8; H, 4·25; N, 8·0. $C_{17}H_{14}O_4N_2S$ requires C, 59·65; H, 4·1; N, 8·2%).

1-*Methyl*-5-p-*tolylsulphonyluracil*.—The acrylamide (1 g.) was boiled with 10% aqueous methylamine (10 ml.) for a few minutes. The cooled solution was neutralised with acetic acid, 1-*methyl*-5-p-*tolylsulphonyluracil* (0·75 g.) separating. From ethanol it formed prisms, m. p. 274—275° (Found: C, 51·2; H, 4·4; N, 9·85. $C_{12}H_{12}O_4N_2S$ requires C, 51·4; H, 4·3; N, 10·0%).

1-*Carboxymethyl*-5-p-*tolylsulphonyluracil*.—The acrylamide (0·5 g.) was heated with glycine (0·15 g.) in N-sodium hydroxide (5 ml.) on a water-bath for 30 min., to give a clear solution. This was cooled and acidified with hydrochloric acid. 1-*Carboxymethyl*-5-p-*tolylsulphonyluracil* (0·3 g.) separated after a few hours and recrystallised from water as needles, m. p. 310° (darkening at 275°) (Found: C, 48·0; H, 3·9; N, 8·5. $C_{13}H_{12}O_6N_2S$ requires C, 48·15; H, 3·75; N, 8·65%).

N-*Ethoxycarbonyl*-β-*phenylhydrazino*-α-p-*tolylsulphonylacrylamide*.—β-Ethoxy-*N*-ethoxycarbonyl-α-*p*-tolylsulphonylacrylamide (0·3 g.) in warm ethanol (10 ml.) was treated with a few drops of phenylhydrazine, and the solution kept at room temperature for a few hours, crystals separating. The β-*phenylhydrazino-derivative* (0·3 g.) formed pale yellow needles, m. p. 174° (decomp.), from ethanol (Found: C, 56·45; N, 5·2; N, 10·6. $C_{19}H_{21}O_5N_3S$ requires C, 56·55; H, 5·25; N, 10·4%).

1-*Anilino*-5-p-*tolylsulphonyluracil*.—The foregoing acrylamide (0·1 g.) was boiled with N-sodium hydroxide (5 ml.) for 5 min. A crystalline salt separated on cooling. The hot solution was neutralised with acetic acid and cooled to give 1-*anilino*-5-p-*tolylsulphonyluracil* (0·05 g.), plates, m. p. 250° (decomp.) (from ethanol) (Found: C, 57·2; H, 4·35; N, 11·9. $C_{17}H_{15}O_4N_3S$ requires C, 57·15; H, 4·25; N, 11·75%).

5-*Phenylsulphonyluracil* (with R. N. Warrener).—5-Phenylsulphonylacetylurethane [3] (1·11 g.), ethyl orthoformate (1·06 g.), and acetic anhydride (1·17 g.) were heated together at 120° for 1·5 hr., 120—130° for 1 hr., and 170° for 30 min. The cooled solution gave crystals (0·4 g.) which were filtered off, washed with ether, and used directly. The compound was warmed with aqueous ammonia until a clear solution was obtained. This was acidified to precipitate 5-*phenylsulphonyluracil* (0·2 g.) which crystallised from a large volume of ethanol as pale yellow rhombs, m. p. 350° (softened from 322°) (Found: C, 47·8; H, 3·4; N, 11·0. $C_{10}H_8O_4N_2S$ requires C, 47·6; H, 3·2; N, 11·1%).

1-*Ethyl*-5-*phenylsulphonyluracil*.—The foregoing acrylamide (0·2 g.) was warmed with aqueous ethylamine until a clear solution was obtained. This was cooled and acidified to precipitate 1-*ethyl*-5-*phenylsulphonyluracil*, (0·2 g.), very pale yellow prisms, m. p. 222° (from alcohol) (Found: C, 51·6; H, 4·65; N, 9·75. $C_{12}H_{12}O_4N_2S$ requires C, 51·4; H, 4·3; N, 10·0%).

5-p-*Acetamidobenzenesulphonyluracil*.—A solution of sodium *p*-acetamidobenzenesulphinate [4] (5 g.) and *N*-chloroacetylurethane (3·72 g.) in 95% ethanol was boiled under reflux for 3 hr., evaporated to half-volume, filtered, and cooled, to precipitate p-*acetamidobenzenesulphonylacetylurethane* (4·83 g.), needles, m. p. 192—194° (from ethanol or water) (Found: C, 47·1; H, 5·1; N, 8·45. $C_{13}H_{16}O_6N_2S$ requires C, 47·55; H, 4·9; N, 8·55%). Reaction in dry ethanol and in presence of a little sodium hydroxide gave *ethyl* p-*acetamidobenzenesulphonylacetate*, plates (from ethanol), m. p. 120° (Found: C, 50·5; H, 5·3; N, 4·9. $C_{12}H_{15}O_5NS$ requires C, 50·5; H, 5·3; N, 4·9%). The foregoing urethane (2 g.), ethyl orthoformate (2·72 g.), and acetic anhydride (4·1 g.) were heated together under a condenser at 135—140° for 1·5 hr. and then at 140° without a condenser. The solution was evaporated *in vacuo* and the residue warmed with aqueous ammonia for 30 min. The filtered solution was acidified and the precipitate crystallised from water, to give 5-p-*acetamidobenzenesulphonyluracil monohydrate* (0·5 g.) as needles, m. p. 326° (decomp.) (Found: C, 43·85; H, 3·9; N, 12·75. $C_{12}H_{11}O_5N_3S,H_2O$ requires C, 44·05; H, 4·05; N, 12·85%). The uracil (0·1 g.) was refluxed with 10N-hydrochloric acid for 1 hr. The solution

[4] *Org. Synth.*, 1921, **1**, 8.

was cooled to precipitate 5-p-*aminobenzenesulphonyluracil* (0·05 g.), needles (from water), m. p. >360° (Found : C, 45·1; H, 3·5; N, 15·0. $C_{10}H_9O_4N_3S$ requires C, 44·95; H, 3·4; N, 15·75%).

N-*Ethylsulphonylacetylurethane*.—(*a*) Ethylsulphonylacetic acid [6] (29·5 g.), urethane (17·3 g.), and phosphoryl chloride (7·4 ml.) were heated together on a water-bath for 20 min. The residue was warmed with methanol (50 ml.) until one phase was obtained. Cooling to −30° caused crystallisation of ethyl allophanate (3 g.), needles (from methanol), m. p. 186—188° which after sublimation at 100°/0·5 mm. had m. p. and mixed m. p. 190° [6] (Found : N, 21·0. Calc. for $C_4H_9O_3N_2$: N, 21·0%). The methanolic filtrate was adjusted to pH 6 with 2N-sodium hydroxide and kept at 0° overnight, affording a precipitate of N-*ethylsulphonylacetylurethane* (4·8 g.), needles (from water), m. p. 108° (Found : C, 37·8; H, 5·9; N, 6·35. $C_7H_{13}O_5NS$ requires C, 37·7; H, 5·9; N, 6·3%). (*b*) The same product was obtained in higher yield, but contaminated with traces of ethyl allophanate in the following way : Ethylsulphonylacetic acid (17 g.), urethane (10 g.), and phosphoryl chloride (4 ml.) were heated together at 100—115° (internal) for 20 min. Further portions of urethane (5 g.) and phosphoryl chloride (2 ml.) were added, and the reactants kept at the above temperature for another 20 min. The solution was cooled and mixed with ether (50 ml.) and ice-water (50 ml.). The crystals (12·0 g.) which separated were collected and washed with cold water (3 × 20 ml.). The acylurethane (8·3 g.) crystallised from water as needles, m. p. 103—105°. The material contained traces of ethyl allophanate but was good enough for most purposes.

5-*Ethylsulphonyluracil*.—The urethane (3·1 g.), ethyl orthoformate (2·5 g.), and acetic anhydride (3·4 g.) were heated together at 125—135° (internal) for 1 hr., then cooled. The same amounts of orthoformate and anhydride were added and heating was continued for a further 45 min. After removal of the solvent *in vacuo* a pale yellow oil (3·8 g.) remained. This was heated with water (30 ml.) and 15N-ammonia (5 ml.) to 70°, giving a clear solution. Acetic acid precipitated 5-*ethylsulphonyluracil* (1·7 g.) which recrystallised from water as prisms, m. p. 282° (Found : C, 35·3; H, 4·1; N, 13·8. $C_6H_8O_4N_2S$ requires C, 35·3; H, 3·95; N, 13·7%). A further quantity (0·3 g.) was obtained by evaporation of the mother-liquors and trituration of the residue with 1 : 1 methanol–water (10 ml.).

N-*Ethylsulphonylacetyl*-N-*methylurethane*.—Ethylsulphonylacetic acid (18 g.), *N*-methylurethane (12 g.), and phosphoryl chloride (4·5 ml.) were heated to 95° during 20 min., and kept thereat for 1 hr. Evolution of hydrogen chloride was then complete. The supernatant liquid was decanted from a thick syrup and cooled to give crystals which were filtered off and washed with 20% aqueous methanol (25 ml.). N-*Ethylsulphonylacetyl*-N-*methylurethane* (13·7 g.) sublimed at 80—100°/0·1 mm. as plates, m. p. 89° (Found : C, 40·8; H, 6·4; N, 5·7. $C_8H_{15}O_5NS$ requires C, 40·5; H, 6·4; N, 5·9%). More of it (1·4 g.) was obtained by extraction of the original syrup and the filtrates with chloroform.

β-*Ethoxy*-N-*ethoxycarbonyl*-α-*ethylsulphonyl*-N-*methylacrylamide*.—*N*-Ethylsulphonylacetyl-*N*-methylurethane (3·5 g.), ethyl orthoformate (2·7 ml.), and acetic anhydride (3·1 ml.) were heated together at 130° for 1 hr. The residue was heated six times at the same temperature for 30 min. with one-third each of the former quantities of orthoformate and anhydride. The solution was cooled, filtered from a little unchanged urethane, and distilled to give β-*ethoxy*-N-*ethoxycarbonyl*-α-*ethylsulphonyl*-N-*methylacrylamide* (2 g.), b. p. 160°/0·3 mm. (Found : C, 44·9; H, 6·7; N, 4·5. $C_{11}H_{19}O_6NS$ requires C, 45·0; H, 6·5; N, 4·8%).

5-*Ethylsulphonyl*-3-*methyluracil*.—The foregoing acrylamide (1·1 g.) was warmed with 15N-ammonia (10 ml.) until it had dissolved. The solution was evaporated to remove ammonia, cooled, and acidified with acetic acid to give a solid precipitate. 5-*Ethylsulphonyl*-3-*methyluracil* crystallised from water as needles, m. p. 223° (Found : C, 38·4; H, 4·7; N, 12·9. $C_7H_{10}O_4N_2S$ requires C, 38·5; H, 4·6; N, 12·8%).

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[5] Klason, *Bull. Soc. chim. France*, 1875, **23**, 447; cf. Pomerantz and Connor, *J. Amer. Chem. Soc.*, 1939, **61**, 3139.
[6] Diels. *Ber.*, 1903, **36**, 745.