Synthesis of 2-Arylimino-3-aryl-4-keto-tetrahydrothiazoles by Condensing Di-Arylthioureas with Monochloroacetic Acid

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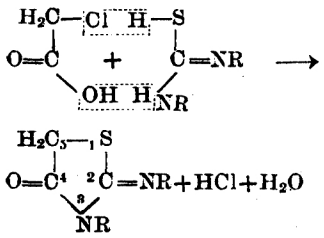
A number of sulfathiazoles have been known for their therapeutic properties and have been universally used as drugs. Amidothiazoles and their isomers were reported by Jacobson[1] and Jacobson and Ney.[2] Nitroso-compounds of thiazoles were synthesised previously by Hantzsch[3] and Hantzsch *et al.*[4] Goldberg and Kelley[5] synthesised 2-ω-aminoalkyl- and 2-ω-sulfanilamidoalkyl derivatives of thiazoles. Gregory and Wiggins[6] studied 2:4-dimethylthiazole derivatives and 2:4:5-trimethyl thiazole. Recently Alexander R. Surrey has prepared 3-alkyl (and aralkyl) -2-aryl-4-thiazolidones[7] and 3-alkylaminoalkyl-2-aryl-4-thiazolidones.[8]

The author has carried out the condensations of monochloroacetic acid with diphenylthiourea, di-*o*-tolylthiourea, di-*p*-tolylthiourea, di-α-naphthylthiourea, di-β-naphthylthiourea, di-*p*-anisylthiourea, and di-*p*-phenetylthiourea. The general method of preparation is analogous to the formation of 2-imino-4-keto-tetrahydrothiazole[9],[10], by condensing thiourea with monochloroacetic acid and subsequently dehydrating by heating with glacial acetic acid.



The synthesis has been accomplished on standard lines, thereby showing the constitution of the compounds. All these condensation products are solids of high melting points.

The formation of semicarbazones of the respective compounds gives evidence regarding the presence of a keto-group.

Experimental

2-Phenylimino-3-phenyl-4-keto-tetrahydrothiazole.—To a mixture of thiocarbanilide (22.8 g.), monochloroacetic acid (12.0 g.) and finely powdered anhydrous sodium acetate (12.3 g.) in a dry flask was added 50 cc. of absolute alcohol and the above boiled on a water-bath for 2 hours. Towards the end of the condensation, some of the product separated in leaflets. The major portion of the alcohol was distilled off and the contents of the flask were poured out into a porcelain dish to crystallise. The crystals were washed with cold water to remove excess of monochloroacetic acid. It was purified by recrystallising three times from hot absolute alcohol. Colorless laminae (23.76 g.), m. p. 176° (Found: N, 10.45. Calcd. for $C_{15}H_{12}N_2OS$: N, 10.44%).

Semicarbazone.—The above 2-phenylimino-3-phenyl-4-keto-tetrahydrothiazole (250 mg.) was dissolved in 95% alcohol (20 cc.) and to this semicarbazide hydrochloride (300 mg.) and anhydrous sodium acetate (500 mg.) were added. The whole mixture was refluxed for 15 minutes and poured into water. The crystals were collected and recrystallised from absolute alcohol in needles, m. p. 194° (Found : N, 21.58. Calcd. for $C_{16}H_{15}N_5OS$: N, 21.53%).

2-*o*-Tolylimino-3-*o*-tolyl-4-keto-tetrahydrothiazole.—A suspension of di-*o*-tolylthiourea (12.4 g.) in absolute alcohol (50 cc.) was heated under reflux with monochloroacetic acid (6.0 g.) and anhydrous sodium acetate (6.0 g.) for 2 hours. The condensation was effected, and the product was isolated as described above. The residue on crystallisation from absolute alcohol and drying in vacuum at 110° over phosphorus pentoxide yielded white needles (12.18 g.), m. p. 154–155° (Found : N, 9.44. Calcd. for $C_{17}H_{16}N_2OS$: N, 9.46%).

Semicarbazone.—2-*o*-Tolylimino-3-*o*-tolyl-4-keto-tetrahydrothiazole (260 mg.) was dissolved in 95% alcohol (20 cc.) and refluxed with semicarbazide hydrochloride (300 mg.) and anhydrous sodium acetate (300 mg.) for 20 minutes. On pouring the mixture into water (80 cc.) a precipitate was obtained, which was crystallised from absolute alcohol in leaflets, m. p. 182° (Found: N, 19.85; calcd. for $C_{18}H_{19}N_5OS$: N, 19.83%).

2-*p*-Tolylimino-3-*p*-tolyl-4-keto-tetrahydro-

(1) Jacobson, *Ber.*, **19**, 1067 (1886).
(2) Jacobson and Ney, *ibid.*, **22**, 904 (1889).
(3) Hantzsch, *Ann.*, **262**, 250 (1889).
(4) Hantzsch *et al.*, *ibid.*, **265**, 108 (1889).
(5) Goldberg and Kelley, *J. Chem. Soc.*, **1947**, 1372.
(6) Gregory and Wiggins, *ibid.*, **1947**, 1400.
(7) Alexander R. Surrey, *J. Am. Chem. Soc.*, **70**, 4262. (1948).
(8) Alexander R. Surrey, *ibid.*, **71**, 3354 (1949).
(9) P. N. Bhargava, *Proc. Ind. Sci. Cong. Chem. Sec. Abst.*, **1949**, 78.
(10) R. D. Desai, R. F. Hunter and L. G. Koppar, *Rec. trav. chim.*, **54**, 118 (1935).

thiazole.—A mixture of di-*p*-tolylthiourea (12.0g.), monochloroacetic acid (6.2 g.), anhydrous sodium acetate (6.0 g.) and absolute alcohol (45 cc.) was refluxed on a water-bath for 3 hours. The condensation was effected as above and the residual product was crystallised three times from absolute alcohol in cream colored feathery crystals (12.2 g.), m. p. 128° (Found : N, 9.49. Calcd. for $C_{17}H_{16}N_2OS$: N, 9.46%).

Semicarbazone.—A mixture of 2-*p*-tolylimino-3-*p*-tolyl-4-keto-tetrahydrothiazole (270 mg.), semicarbazide hydrochloride (300 mg.), anhydrous sodium acetate (500 mg.) and 95% alcohol (20 cc.) was refluxed for 15 minutes and then poured into water (60 cc.). The precipitate was crystallised two times from absolute alcohol in needles, m. p. 152° (Found: N, 19.78. Calcd. for $C_{18}H_{19}N_5OS$: N, 19.83%).

2-α-naphthylimino-3-α-naphthyl-4-keto-tetrahydrothiazole.—A mixture of di-α-naphthylthiourea (6.8 g.), monochloroacetic acid (3.0 g.), anhydrous sodium acetate (4.0 g.) and absolute alcohol (50 cc.) was heated on a steam-bath under reflux for 3 hours. The reaction was effected as above and the residue after washing free from acid was crystallised four times from absolute alcohol in grey leaflets (6.25 g.), m. p. 172–173° (Found : N, 7.63. Calcd. for $C_{23}H_{16}N_2OS$: N, 7.6%).

Semicarbazone.—The above compound (300mg.) was treated with 95% alcohol (20 cc.), semicarbazide hydrochlorjde (280 mg.) and anhydrous sodium acetate (450 mg.) and refluxed for 15 minutes. The mixture was poured into water (60 cc.) and the precipitate crystallised two times from absolute alcohol in leaflets, m. p. 186° (Found : N, 16.45. Calcd for $C_{24}H_{19}N_3OS$: N, 16.47%).

2-β-Naphthylimino-3-β-naphthyl-4-keto-tetrahydrothiazole.—Di-β-naphthylthiourea (7.0 g.) was suspended in absolute alcohol (50 cc.) and refluxed with monochloroacetic acid (3.0 g.) and finely powdered anhydrous sodium acetate (5.0 g.) for 3 hours on a steam-bath. The condensation was effected as above and the product after washing free from acid was crystallised three times from absolute alcohol in dark red needles (6.28 g.), m.p. 192–193° (Found : N, 7.56. Calcd. for $C_{23}H_{16}N_2OS$: N, 7.6%).

Semicarbazone.—A mixture of the above compound (320 mg.), 95% alcohol (20 cc.), semicarbazide hydrochloride (290 mg.) and finely powdered anhydrous sodium acetate (420 mg.) was refluxed for 15 minutes. The mixture was poured into water and the precipitate crystallised from absolute alcohol in brown needles, m. p. 208° (Found: N, 16.5. Calcd. for $C_{24}H_{19}N_5OS$: N, 16.47%).

2-*p*-Anisylimino-3-*p*-anisyl-4-keto-tetrahydrothiazole.—A suspension of di-*p*-anisylthiourea (5.5 g.) in absolute alcohol (40 cc) was treated with monochloroacetic acid (3.0 g.) and finely powdered anhydrous sodium acetate (4.0 g.) and refluxed for 3 hours on a steam-bath. The product after condensation was filtered rapidly while hot. The solvent was recovered by distillation and the residue crystallised three times from absolute alcohol in black needles (5.16 g.), m. p. 107–108° (Found: N, 8.56. Calcd. for $C_{17}H_{16}N_2O_3S$: N, 8.53%).

Semicarbazone.—The above compound (320mg.), 95% alcohol (20 cc.), semicarbazide hydrochloride (300 mg.) and finely powdered anhydrous sodium acetate (400 mg.) were refluxed for 20 minutes. The mixture was poured into water and the preciptate crystallised from absolute alcohol in dark brown needles, m. p. 120° (Found : N, 18.26. Calcd. for $C_{18}H_{19}N_5O_3S$: N, 18.18%).

2-*p*-Phenetylimino-3-*p*-phenetyl-4-keto-tetrahydrothiazole.—Di-*p*-phenetylthiourea (7.0 g.) was dissolved in absolute alcohol (50 cc.) and refluxed with monochloroacetic acid (3.0 g.) and anhydrous sodium acetate (4.0 g.) for 4 hours on a steam-bath. The resulting product after condensation was crystallised from absolute alcohol in brown needles (6.6 g.), m. p. 105–106° (Found : N, 7.84. Calcd. for $C_{19}H_{20}N_2O_3S$: N, 7.86%).

Semicarbazone.—A mixture of 2-*p*-phenetylimino-3-*p*-phenetyl-4-keto-tetrahydrothiazole (350 mg.) in 95% alcohol (22 cc.), semicarbazide hydrochloride (260 mg.) and finely powdered anhydrous sodium acetate (450 mg.) was refluxed on a steam-bath for 25 minutes. It was then poured into water and the precipitate crystallised from absolute alcohol in dark brown leaflets, m. p. 140° (Found: N, 16.98. Calcd. for $C_{26}H_{23}N_5O_3S$: N, 16.95%).

Summary

(1) 2-Arylimino-3-aryl-4-keto-tetrahydrothiazoles were prepared by condensation of di-arylthioureas with monochloroacetic acid in the presence of anhydrous sodium acetate and absolute alcohol.

(2) The formation of semicarbazones of 2-arylimino-3-aryl-4-keto-tetrahydrothiazoles has revealed the presence of a keto-group.

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