24. *Some* 5-spiro*Thiazolidiones.*

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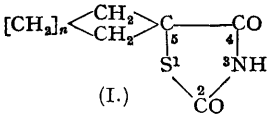
Syntheses *via* the 2-*imino-compounds*, of 5-spirocyclo*pentyl*- and 5-spirocyclo*hexyl*-2 : 4-*thiazolidiones*, of possible interest as hypnotics, are described.

5 : 5-Dialkyl-2 : 4-thiazolidiones, analogous to the well-known barbituric acid derivatives, were synthesised and examined pharmacologically by Erlenmeyer and Meyenburg (*Helv. Chim. Acta*, **1937**, **20**, 1389; **1938**, **21**, 1013) and Doran and Shonle (*J. Org. Chem.*, **1938**, **3**, 193). The classical preparative method, consisting of condensation of an α-halogenated acid or acid derivative with thiourea followed by acid hydrolysis of the resulting imino-compound, was employed in all cases (see also B.P. 503,478; U.S.P. 2,225,903; G.Ps. 670,684,

672,972; F.P. 827,150). The authors reported that the compounds examined exhibited marked sedative and anæsthetic activity, but Doran and Shonle (*loc. cit.*) found that intravenous injection of the sodium salts of the thiazolidiones led to tremors or convulsions and they concluded that members of this series are less satisfactory sedatives than the corresponding barbituric acids.


(I.)

In the hope of effecting appreciable modification of the physiological properties, spiro*thiazolidiones* of type (I) have now been synthesised by conventional methods which require no comment. The light absorption properties of these compounds and of their *N*-methyl ethers, determined in alcohol, are practically identical with those of 2 : 4-thiazolidione (Max. 2250A.; $\varepsilon = 5000$) and of its *N*-methyl ether (Max. 2265A.; $\varepsilon = 4500$).

The only one of these compounds to be tested adequately was 5-*spirocyclo*hexyl-2 : 4-thiazolidione (I; $n = 3$). A solution in dilute alkali when injected into mice produced narcosis and analgesia. The narcotic effect was of shorter duration than that obtained with ethyl*iso*amylbarbituric acid (Amytal) and the analgesic effect was less marked than with morphine. The *N*-methyl ethers were not sufficiently soluble in water to be tested in solution, but *N*-methyl-5-*spirocyclo*hexyl-2 : 4-thiazolidione produced narcosis when injected intraperitoneally in the liquid state. Attempts to induce sleep by rectal administration of the two diones and their *N*-methyl ethers dissolved in equal volumes of *tert.*-amyl alcohol were only partially successful.

Experimental.

(Light absorption data were determined in alcohol.)

1-*Bromo*cyclo*pentane*-1-*carboxylic Acid.*—A mixture of *cyclo*pentane-carboxylic acid (52 g.; method of Gilman and Kirby, *Org. Syntheses*, Coll. Vol. I (2nd Ed.), 361) and red phosphorus (0·5 g.) was heated on the steam-bath, bromine (160 g.) was added during 2 hours and heating was continued for a further 7 hours. After some hours the excess of bromine was removed by heating under reduced pressure and a pale brown crystalline mass of crude acid (70 g.) was obtained on cooling. A portion was sublimed at 100° (bath temp.)/10^{-4} mm. and on crystallisation from ligroin (b. p. 40—60°) gave 1-*bromo*cyclo*pentane*-1-*carboxylic acid* as leaflets, m. p. 70° (Found: C, 37·55; H, 4·9. $C_6H_9O_2Br$ requires C, 37·35; H, 4·7%). The *anilide*, prepared *via* the acid chloride, formed needles from aqueous alcohol, m. p. 89° (Found: C, 53·9; H, 5·35. $C_{13}H_{14}ONBr$ requires C, 53·75; H, 5·25%).

5-spirocyclo*Pentyl*-2-*imino*-4-*thiazolidone.*—A mixture of thiourea (18 g., 1·5 mol.), anhydrous sodium acetate (20 g.), the crude bromo-acid (30 g.) described above, and dioxan (350 c.c.) was refluxed for 8—9 hours. After filtering, the hot solution was evaporated and the residue was treated with saturated bicarbonate. The brown flocculent precipitate was separated and washed, and sublimation of a portion at 100—110° (bath temp.)/10^{-4} mm., followed by crystallisation from aqueous alcohol, yielded the *imino-compound* as leaflets, decomp. *ca.* 230° (Found: C, 49·4; H, 5·8. $C_7H_{10}ON_2S$ requires C, 49·4; H, 5·9%).

5-spirocyclo*Pentyl*-2 : 4-*thiazolidione* (I; $n = 2$).—The bulk of the above crude imino-compound was refluxed with 2N-hydrochloric acid (250 c.c.) for 4—5 hours, the solution was decolorised (charcoal) and on cooling long needles of 5-spirocyclo*pentyl*-2 : 4-*thiazolidione* (11·5 g.) were obtained which, after crystallisation from aqueous alcohol, had m. p. 111—112° (Found: C, 49·1; H, 4·9. $C_7H_9O_2NS$ requires C, 49·1; H, 5·3%). Light absorption: Maximum, 2275A.; $\varepsilon = 4000$. The N-*methyl ether*, prepared by heating the dione (4 g.) with methyl iodide (6 g.) and 2N-sodium hydroxide (12·5 c.c.) in methanol (20 c.c.) in a sealed tube at *ca.* 50° for 42 hours, was purified by sublimation at 40—60° (bath temp.)/ 10^{-4} mm. and crystallisation from ligroin (b. p. 60—80°), and formed prisms (2·7 g.), m. p. 53° (Found: C, 51·9; H, 5·9. $C_8H_{11}O_2NS$ requires C, 51·85; H, 6·0%). Light absorption: Maximum, 2280A.; $\varepsilon = 3500$.

5-spirocyclo*Hexyl*-2-*imino*-4-*thiazolidone.*—Attempts to condense ethyl 1-bromo*cyclo*hexane-1-carboxylate with thiourea under a variety of conditions were unsuccessful. When the acid chloride was employed (cf. Doran and Shonle, *loc. cit.*) only the *thioureide* of 1-*bromo*cyclo*hexane*-1-*carboxylic acid* could be isolated. It crystallised from methanol in plates, m. p. 184° (Found: N, 10·55. $C_8H_{13}ON_2BrS$ requires N, 10·55%).

A mixture of thiourea (3 g.; 1·5 mol.), anhydrous sodium acetate (3 g.), 1-bromo*cyclo*hexane-1-carboxylic acid (5·3 g.; Fourneau *et al.*, *Chem. Abstracts*, 1922, **16**, 240) and dioxan (90 c.c.) was refluxed for 7 hours. The hot solution was filtered and the crystalline powder which separated on cooling was recrystallised from aqueous alcohol and hot water giving the *imino-compound* (1·8 g.) as prismatic needles, m. p. 254—256° (slight decomp.) (Found: C, 52·3; H, 6·6; N, 15·55. $C_8H_{12}ON_2S$ requires C, 52·15; H, 6·55; N, 15·2%).

5-spirocyclo*Hexyl*-2 : 4-*thiazolidione* (I; $n = 3$).—A similar experiment to that described above, using bromo-acid (26 g.), in which the crude imino-compound was hydrolysed by refluxing with 2N-hydrochloric acid (250 c.c.) for 2 hours, gave the *thiazolidione* (11·4 g.), crystallising from aqueous alcohol or water as long needles, m. p. 125—126° (Found: C, 51·6, 51·7; H, 6·2, 5·95. $C_8H_{11}O_2NS$ requires C, 51·85; H, 6·0%). Light absorption: Maximum, 2250A.; $\varepsilon = 4500$. The N-*methyl ether*, prepared in 70% yield as described for the *cyclo*pentyl analogue, formed rhombic prisms from ligroin (b. p. 60—80°), with m. p. 55° (Found: C, 54·15; H, 6·6. $C_9H_{13}O_2NS$ requires C, 54·25; H, 6·6%). Light absorption: Maximum, 2280A.; $\varepsilon = 4000$.

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