Oxidative Cyclisation of Ketone Thiosemicarbazones. Part II.[1] Derivatives of Phenoxyacetone

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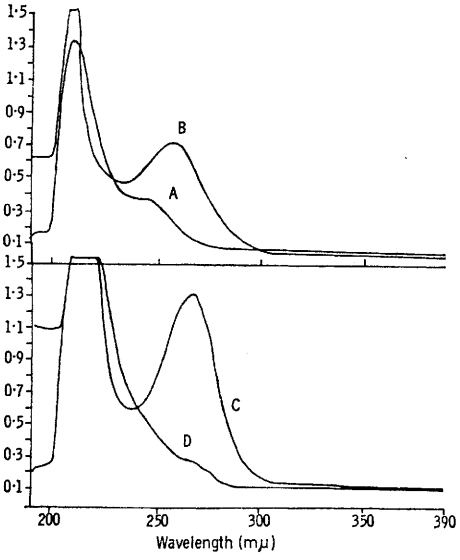
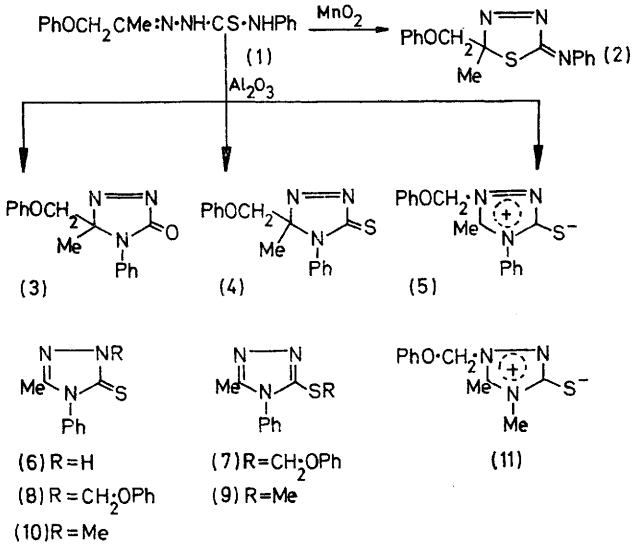
Oxidative cyclisation of phenoxyacetone (4-phenyl)thiosemicarbazone to 5-methyl-5-phenoxymethyl-4-phenyl-Δ^1-1,2,4-triazoline-3-thione was accompanied by a rearrangement giving 3-mercapto-5-methyl-1-phenoxymethyl-4-phenyl-1,2,4-triazolinium hydroxide inner salt. Proof of structure was afforded by synthesis of 3-methyl-1-phenoxymethyl-4-phenyl-Δ^2-1,2,4-triazoline-5-thione, 3-methyl-5-phenoxymethylthio-4-phenyl-1,2,4-triazole, and 2-methyl-2-phenoxymethyl-5-phenylimino-Δ^3-1,3,4-thiadiazoline.

OXIDATION of phenoxyacetone (4-phenyl)thiosemicarbazone (1) with manganese dioxide gave 2-methyl-2-phenoxymethyl-5-phenylimino-Δ^3-1,3,4-thiadiazoline (2), and atmospheric oxidation over basic alumina gave 5-methyl-5-phenoxymethyl-4-phenyl-Δ^1-1,2,4-triazoline-3-one (3), 5-methyl-5-phenoxymethyl-4-phenyl-Δ^1-1,2,4-triazoline-3-thione (4), and an isomer of the latter compound. This was colourless and polar (crystallisable from water), and its n.m.r. spectrum showed a low τ value for the methylene group (Table). Acid hydrolysis gave phenol and 3-methyl-4-phenyl-Δ^2-1,2,4-triazoline-5-thione (6).[2] Structures (7) and (8) were therefore considered for the rearrangement product, but alkylation of (6) with phenoxymethyl chloride (*a*) in aqueous sodium hydroxide and (*b*) in dimethylformamide with sodium hydride gave two other isomers. These were shown to be (7) and (8) respectively by comparison of their u.v. spectra with those of (9) and (10), the *S*- and *N*-methyl derivatives of (6) (Figure). 1,3-Dimethyl-4-phenyl-Δ^2-1,2,4-triazoline-5-thione (10) was made from 1,1,1-triethoxyethane and 2-methyl-(4-phenyl)thiosemicarbazide, and its preparation established the structure of the known[2] methyl derivative (9).



U.v. absorption spectra of A, (9); B, (10); C, (8); and D, (7) (10^{-4}M-solutions in methanol)

The rearrangement product from (1) was therefore assigned the meso-ionic structure (5), which is compatible with its spectroscopic and other properties.



The name 'endothiotriazoline' has been applied to compounds of this type.[3] A similar compound (11) was obtained from phenoxyacetone (4-methyl)thiosemicarbazone, but no reaction was observed with phenoxyacetone thiosemicarbazone.

N.m.r. spectra (τ values excluding signals for aromatic protons)

Compound	Me	CH_2
(2)	8·03	5·58 (δ_{ab} 0·02 p.p.m., J_{ab} 10·5 Hz)
(4)	8·31	5·55 (δ_{ab} 0·62 p.p.m., J_{ab} 10·5 Hz)
(5)	7·52	3·97
(7)	7·21	4·23
(8)	7·85	3·88
(9)	7·68, 7·35	
(10)	7·83, 6·18	
(11)	7·31, 6·43	4·0

Determined with a Varian A60 instrument for solutions in deuteriochloroform, with tetramethylsilane as internal standard.

The rearrangement presumably occurs through a [1,2] shift to an electron-deficient centre during the

[1] Part I, J. K. Landquist, *J. Chem. Soc.* (*C*), 1970, 63.
[2] J. D. Kendall, G. F. Duffin, and H. R. J. Waddington, B.P. 766,380.
[3] W. Baker and W. D. Ollis, *Quart. Rev.*, 1957, **11**, 15; G. W. Evans and B. Milligan, *Austral. J. Chem.*, 1967, **20**, 1779.

oxidation of the intermediate triazolidine; the triazoline (4) was not rearranged to (5) by treatment with alumina.

EXPERIMENTAL

Phenoxyacetone (4-*Phenyl*)*thiosemicarbazone*.—(4-Phenyl)-thiosemicarbazide (8·35 g.), ethanol (100 c.c.), and phenoxyacetone (7·5 g.) were boiled under reflux for 3 hr., and the solution was concentrated to *ca.* 30 c.c. The *phenylthiosemicarbazone*, which crystallised when scratched, had m.p. 120—121° (from ethanol) (Found: C, 63·8; H, 5·9; N, 13·9. $C_{16}H_{17}N_3OS$ requires C, 64·2; H, 5·7; N, 14·0%). The following were prepared similarly: *phenoxyacetone thiosemicarbazone*, m.p. 137° (from ethanol) (Found: C, 53·9; H, 5·9; N, 18·8. $C_{10}H_{13}N_3OS$ requires C, 53·8; H, 5·8; N, 18·8%); *phenoxyacetone* (4-*methyl*)*thiosemicarbazone*, m.p. 120—121° (from ethanol) (Found: C, 55·5; H, 6·7; N, 18·0. $C_{11}H_{15}N_3OS$ requires C, 55·7; H, 6·3; N, 17·7%).

2-*Methyl*-2-*phenoxymethyl*-5-*phenylimino*-Δ^3-1,3,4-*thiadiazoline*.—Phenoxyacetone (4-phenyl)thiosemicarbazone (3 g.) dissolved in chloroform (75 c.c.) was stirred with manganese dioxide (50 g.) for 40 min. at room temperature. The manganese dioxide was filtered off and washed with chloroform, and the filtrate and washings were evaporated. The residual oil (2·7 g.) (carbylamine odour) was purified by chromatography on silica (chloroform) and the thiadiazoline which slowly crystallised after removal of the solvent was drained on a tile; m.p. 75—76°. Attempted recrystallisation converted it into an oil (Found: C, 64·6; H, 4·9; N, 14·0. $C_{16}H_{15}N_3OS$ requires C, 64·65; H, 5·0; N, 14·1%).

Cyclisation of Phenoxyacetone (4-*Phenyl*)*thiosemicarbazone on Alumina*.—The (phenyl)thiosemicarbazone (21 g.) dissolved in chloroform (1 l.) was stirred for 3 days with basic alumina (500 g.). The alumina was filtered off and washed with chloroform until the washings were colourless. The chloroform was evaporated off and the residue (11 g.) gave 5-*methyl*-5-*phenoxymethyl*-4-*phenyl*-Δ^1-1,2,4-*triazoline*-3-*thione* (5·6 g.) as red-orange blades, m.p. 167—168° (from ethanol) (Found: C, 64·7; H, 5·0; N, 14·2. $C_{16}H_{15}N_3OS$ requires C, 64·65; H, 5·0; N, 14·1%). Evaporation of the mother liquor and fractional crystallisation from ethanol gave 5-*methyl*-5-*phenoxymethyl*-4-*phenyl*-Δ^2-1,2,4-*triazoline*-3-*one* (*ca.* 2 g.) as large orange tablets, m.p. 110—112°, $\nu_{max.}$ 1750s cm.$^{-1}$ (Found: C, 68·0; H, 5·3; N, 14·8. $C_{16}H_{15}N_3O_2$ requires C, 68·3; H, 5·35; N, 14·95%). The alumina was extracted with ethanol (Soxhlet) and the extract was concentrated to give 3-*mercapto*-5-*methyl*-1-*phenoxymethyl*-4-*phenyl*-1,2,4-*triazolinium hydroxide inner salt* as laminae, m.p. 195—196° (from ethanol) (Found: C, 64·4; H, 5·2; N, 14·2; S, 11·0. $C_{16}H_{15}N_3OS$ requires C, 64·65; H, 5·0; N, 14·1; S, 10·9%) *m/e* 297 (M^+). Prolonged extraction of the alumina with ethanol gave 3-methyl-4-phenyl-Δ^2-1,2,4-triazoline-5-thione (1 g.), m.p. 215—218°, *m/e* 191 (M^+), i.r. spectrum identical with that of an authentic sample.

In a similar manner, phenoxyacetone (4-methyl)thiosemicarbazone (6 g.) in chloroform (300 c.c.), stirred with alumina (150 g.) for 17 days, afforded 3-*mercapto*-4,5-*dimethyl*-1-*phenoxymethyl*-1,2,4-*triazolinium hydroxide inner salt* (1·3 g.), m.p. 162—163° (from ethanol) (Found: C, 56·2; H, 5·5; N, 18·2; S, 13·7. $C_{11}H_{13}N_3OS$ requires C, 56·2; H, 5·5; N, 17·9; S, 13·6%). No other cyclised product was isolated.

Phenoxymethylation of 3-*Methyl*-4-*phenyl*-Δ^2-1,2,4-*triazoline*-5-*thione*.—(*a*) The thione (1·9 g.), dissolved in 0·2N-sodium hydroxide (50 c.c.), was stirred vigorously and treated with phenoxymethyl chloride (2·2 g.); more sodium hydroxide was added as required to maintain pH at 10—11. After 2 hr. the gummy product was collected, washed with water, and crystallised from aqueous ethanol. Further crystallisation from benzene afforded 3-*methyl*-5-*phenoxymethylthio*-4-*phenyl*-1,2,4-*triazole* (0·6 g.), m.p. 149—150° (Found: C, 64·8; H, 5·1; N, 14·0; S, 10·9. $C_{16}H_{15}N_3OS$ requires C, 64·65; H, 5·0; N, 14·1; S, 10·8%), *m/e* 297 (M^+), $\lambda_{max.}$ *ca.* 215 (ε *ca.* 8000) and 242 infl. (*ca.* 2300) mμ.

(*b*) The thione (1·9 g.) in dry dimethylformamide (25 c.c.) was stirred with sodium hydride (50% dispersion in oil; 0·48 g.). After 5 min. phenoxymethyl chloride (2·2 g.) was added (exothermic) and the mixture was stirred and heated at 90—100° for 1 hr., filtered from sodium chloride, and evaporated to dryness under reduced pressure. The residue was crystallised from ethanol and then from benzene to give 3-*methyl*-1-*phenoxymethyl*-4-*phenyl*-Δ^2-1,2,4-*triazoline*-5-*thione* (0·4 g.), m.p. 135—136° (Found: C, 64·9; H, 4·9; N, 13·9; S, 10·8%), $\lambda_{max.}$ 205 (ε 19,100) and 268 (12,300) mμ.

1,3-*Dimethyl*-4-*phenyl*-Δ^2-1,2,4-*triazoline*-5-*thione*.—2-Methyl-(4-phenyl)thiosemicarbazide (0·9 g.) and 1,1,1-triethoxyethane (3 c.c.) were boiled under reflux for 1 hr. and the excess of ester was evaporated off under reduced pressure at 90—100°. The residue eventually crystallised, and gave the *triazoline* (0·7 g.), m.p. 72° [from cyclohexane or light petroleum (b.p. 60—80°)] (Found: C, 58·5; H, 5·4; N, 20·0. $C_{10}H_{11}N_3S$ requires C, 58·5; H, 5·35; N, 20·5%), $\nu_{max.}$ *ca.* 1200s cm.$^{-1}$, $\lambda_{max.}$ 207 (ε 7300) and 258 (5100) mμ.

3-Methyl-5-methylthio-4-phenyl-1,2,4-triazole, m.p. 119°, prepared by methylating 3-methyl-4-phenyl-Δ^2-1,2,4-triazoline-5-thione in aqueous alkali had $\lambda_{max.}$ 218 (ε *ca.* 7300) and 243infl (*ca.* 3100) mμ.

Hydrolysis of 3-*Mercapto*-5-*methyl*-1-*phenoxymethyl*-4-*phenyl*-1,2,4-*triazolinium Hydroxide Inner Salt*.—The 'endothiotriazoline' (0·4 g.) and 2N-hydrochloric acid (25 c.c.) were boiled under reflux. The clear solution first formed became turbid and the odour of phenol became apparent. After 0·5 hr. the solution was decanted from a resinous precipitate and was set aside to crystallise. The crystals (*ca.* 100 mg.) gave needles, m.p. 217—218° (from water), identified as 3-methyl-4-phenyl-Δ^2-1,2,4-triazoline-5-thione by i.r. spectroscopy and mixed m.p. with an authentic sample (m.p. 221—222°).

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