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Synthesis of 5-Substitute-3-Aryl-2H,3H-Benzo/Naphtho-[1,2-f] [1,3,4]-Oxadiazepin-2-Thiones as Potential Tranquillizers and Anticonvulsants

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It has been reported that certain synthetic analgesics, sedatives, hypnotics, tranquillizers and anticonvulsants are associated with the presence of carboxamido (—HN—C(=O)—) and carboximido (—HN—C(=O)—NH—) groups in these drugs. Biosteric replacement of carboxamido group (—HN—C(=O)—) with thioamido (—HN—C(=S)—) function has successfully resulted in many more potent but relatively short acting and less toxic drugs with similar muscle relaxing properties. In the present study a series of compounds containing benz/nepth oxadiazepine systems has been synthesised through cyclisation with thiophosgene of substituted arylhydrazones obtained by condensation of 2-hydroxyarylaldehydes/ketones with substituted arylhydrazines. The synthesised compounds are cyclic thiocarbamates and may prove to be effective insecticides/pesticides also.

INTRODUCTION

A variety of diseases and ailments which afflicted man since the dawn of life on earth were mitigated by using herbal remedies. With the progress of science, the biologically active principles from these herbs were isolated in pure forms using purification techniques. The study of structures of these isolated biologically active principles stimulated the organic chemists to synthesise such compounds and their modified versions. On retaining the basic type of carbon skeleton in the modified versions, homologues were found to have similar, more effective, specific or even opposite activities. The resemblance of benzene to thiophene and pyridine in having similar physical and chemical properties was noticed by Hinsberg[1] who termed these as "ring equivalents" which were mutually interchangeable without much change in physico-chemical behaviour. This concept was further strengthened by Grim[2] into "Grim's Hydride Displacement Law".

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According to this law bio-isostersim occurs more frequently in divalent atoms or groups and similar steric disposition and valence angles lead to similarity in physical, chemical or even biological properties. Hence biosters are the compounds which possess the same number of electrons in the outer shell and should have similar electron density regions in molecules of analogous size and shape. Bio-isosterism can be achieved not only by the exchange of atoms or groups but one can tamper with the carbon skeleton of the parent compound by opening or closing the ring so as to produce derivatives which may still resemble the original compound in at least one of its steric configurations. This type of bio-isosterism has been extensively used in the synthesis of analgesics, antihistaminics, hypnotics, sedatives and anticonvulsants.

With rapid advance in our knowledge of drug designs, organic reaction mechanism and availability of better synthetic organic methods, it has become possible to synthesise better and more effective drugs with minimal chances of addiction, adverse toxicity and side effects. A survey of the literature showed that a limited number of 1,3-oxazin-2-ones/thiones had been reported and that the compounds did show anticonvulsant and sedative properties.

Encouraged by these antecedents, the synthesis of a new class of seven membered compounds (1,3,4-oxadiazepin-2-thiones) with a biosteric replacement of (—CH(R)—) with (—C(R)=N—) in the amino carbinols was attempted. In the present study 2-hydroxyaryl aldehydes/ketones were condensed with aryl-hydrazine to yield corresponding hydrazones that are subsequently subjected to cyclisation with thiophosgene to yield the desired oxadiazepin-2-thiones in good yields.

EXPERIMENTAL

IR spectra were run on Hitachi 270–50 spectrophotometer, mass spectra on MS-12 spectrometer and NMR on VARION A-60 spectrophotometer.

I. (a) Synthesis of 2,4-Dinitrophenyl Hydrazones

All the 2,4-dinitrophenyl hydrazones were synthesised by a similar procedure as reported in British Pharmacopoeia (1948 edition). However, preparation of 2-hydroxyacetophenone-(2,4-dinitrophenylhydrazone) has been outlined below as a representative case.

A solution of 2-hydroxyacetophenone (0.16 mL; 0.001 mole) in ethanol (25 mL) was treated with a solution of 2,4-dinitrophenylhydrazine (75 mL) obtained by dissolving (1.5 gm; 0.006 mole) 2,4-dinitrophenylhydrazine in 20 mL sulphuric acid (50 per cent v/v), diluting to 100 mL with distilled water and filtering. The reaction mixture was slowly refluxed with constant shaking for 2 h. Ethanol was distilled off from the reaction mixture which was then cooled and diluted to 200 mL with sulphuric acid (2 per cent v/v) and kept overnight at room temperature when an orange-coloured crystalline solid separated out which was collected under suction and washed with successive quantities (5.0 mL each) of ice-cold water until the washings were neutral. The crystalline solid so obtained after drying over $CaCl_2$ in a desiccator (m.p. 205°C, yield 88%) was pure enough

to proceed directly for cyclisation reactions. Other 2,4-dinitrophenylhydrazones were prepared by the same procedure.

(b) Synthesis of Phenyl Hydrazones

The corresponding phenylhydrazones were synthesised by a procedure as reported by Vogel. The synthesis of 2-hydroxyacetophenone-phenylhydrazone has been outlined below as a representative case.

Phenylhydrazine (2.0 mL, 0.018 mole) and 2-hydroxyacetophenone (2.2 mL, 0.018 mole) were refluxed in ethanol (30 mL) for 10–15 min, and chilled in ice for 1 h when a cream-coloured crystalline product separated out.

The latter was collected under suction and recrystallized from 90% ethanol-water mixture to give fine cream-coloured crystals (m.p. 97°C, yield 97%). Other phenylhydrazones were prepared by the same method.

II. Cyclisation of Hydrazones with Thiophosgene

The following procedure was adopted for the cyclisation of substituted arylhydrazones with thiophosgene to give 5-substituted-3-aryl-2H, 3H-benzo/naphtho-[1,2-f][1,3,4]-oxadiazapin-2-thiones.

2-Hydroxyacetophenone-(2,4-dinitrophenyl hydrazone) (0.745 g, 0.002 mole) in dry chloroform (10 mL) and triethylamine (0.56 mL, 0.004 mole) were placed in a 25 mL conical flask fitted with two-way head having a guard tube filled with anhydrous $CaCl_2$ and a micro-graduated dropping funnel and were chilled in an ice-bath for $\frac{1}{2}$ h. A solution of thiophosgene (0.12 mL, 0.002 mole) in dry chloroform was added dropwise with constant stirring from the dropping funnel. The flask was then taken out of the ice-bath, disconnected and fitted with another guard tube filled with anhydrous $CaCl_2$ to avoid moisture entry into the flask and kept at room temperature for 10 h. The contents were washed with distilled water to remove triethylamine hydrochloride formed, dried over anhydrous sodium sulphate and filtered. The solvent was evaporated off and the thick mass left was crystallised from 1 : 1 benzene-petroleum ether mixture to give a brown crystalline product of 5-methyl-3-(2′,4′-dinitrophenyl)-2H,3H-benzo-[1,2-f][1,3,4]-oxadiazepine-2-thiones (m.p. 208°C, yield 82%). Other cyclised products were also synthesised in the same way as described above and are reported in Table-1.

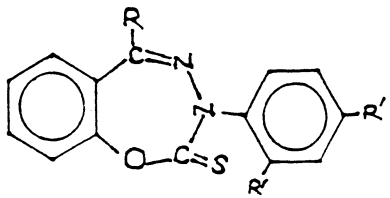
RESULTS AND DISCUSSION

Six parent hydrazones were synthesised in quantitative yields by reaction of 2-hydroxyacetophenone, 2-hydroxybenzaldehyde and 2-hydroxynaphthaldehyde with phenylhydrazine and 2,4-dinitrophenylhydrazine. The characteristics of these hydrazones are in agreement with those already reported in literature.

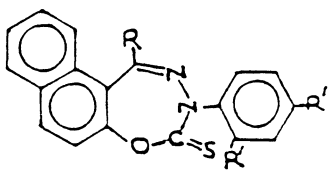
Base catalysed cyclisation of these hydrazones with thiophosgene was attempted to yield stable 5-substituted 3-aryl-2H,3H-benzo/naphtho [1,2-f] [1,3,4]-oxadiazepine-2-thiones (Table-1.)

The IR spectra of these compounds lack —OH and —NH absorption bands implying that cyclisation of aryl hydrazones with thiophosgene has taken place.

TABLE-1



S. No	Substituent		Chemical name	Physical characteristics			IR spectral data (cm^{-1})						PMR spectral data		
	R	R′		Nature	m.p. (°C)	(%) Yield	ν(C=N)	Aromatic stretching	ν(C=S)	ν(C–N)	ν(C–O)	Aromatic ring absorptions	Aromatic protons	—CH_3	Benzylic proton
1.	H	H	3-Phenyl-2H,3H-benzo-[1,2-f][1,3,4]-oxadiazepine-2-thiones	Greyish crystals	146	89	1682	1610	1362, 1140, 1060	1304	1224	880, 700, 685	7.9–6.7 9-H(m)	—	merged with aromatic protons 1-H
2.	H	NO_2	3-(2′,4′-Dinitrophenyl)-2H,3H-benzo-[1,2-f][1,3,4]-oxadiazepine-2-thione	Dark brown crystals	263	74	1610	1580, 1495	1375, 1140, 1050	1345	1240	800, 725, 650	—	—	—
3.	CH_3	H	5-Methyl-3-phenyl-2H, 3H-benzo-[1,2-f][1,3,4]-oxadiazepine-2-thione	Dark brown crystals	124	82	1650	1485, 1495	1360, 1120, 1040	1280	1235	810, 680	7.7–6.9 9-H(m)	2.35 3-H(S)	—

S. No	Substituent		Chemical name	Physical characteristics			IR spectral data (cm^{-1})						PMR spectral data		
	R	R′		Nature	m.p. (°C)	(%) Yield	ν(C=N)	Aromatic stretching	ν(C=S)	ν(C–N)	ν(C–O)	Aromatic ring absorptions	Aromatic protons	—CH_3	Benzylic proton
4.	CH_3	NO_2	5-Methyl-3-(2′,4′-dinitrophenyl)-2H, 3H-benzo-[1,2-f][1,3,4]-oxadiazepine-2-thiones	Brown crystals	206	78	1645	1600, 1580	1350, 1150, 1040	1325	1218	835, 710	7.9–7.0 7-H(m)	1.65 3-H(S)	—
															
5.	H	H	3-Phenyl-2H, 3H-naphtho-[1,2-f][1,3,4]-oxadiazepine-2-thiones	White crystals	169	86	1640	1580	1345, 1140, 1040	1342	1260, 1180	800, 730, 700	8.2–6.9 11-H(m)	—	merged with aromatic protons 1-H
6.	H	NO_2	3-(2′,4′-Dinitrophenyl) -2H,3H-naphtho-[1,2-f] [1,3,4]-oxadiazepine-2-thiones	Brownish crystals	279	77	1670	1580	1340, 1170, 1040	1332	1258, 1190	806, 730, 620	8.2–7.2 11-H(m)	—	merged with aromatic protons 1-H

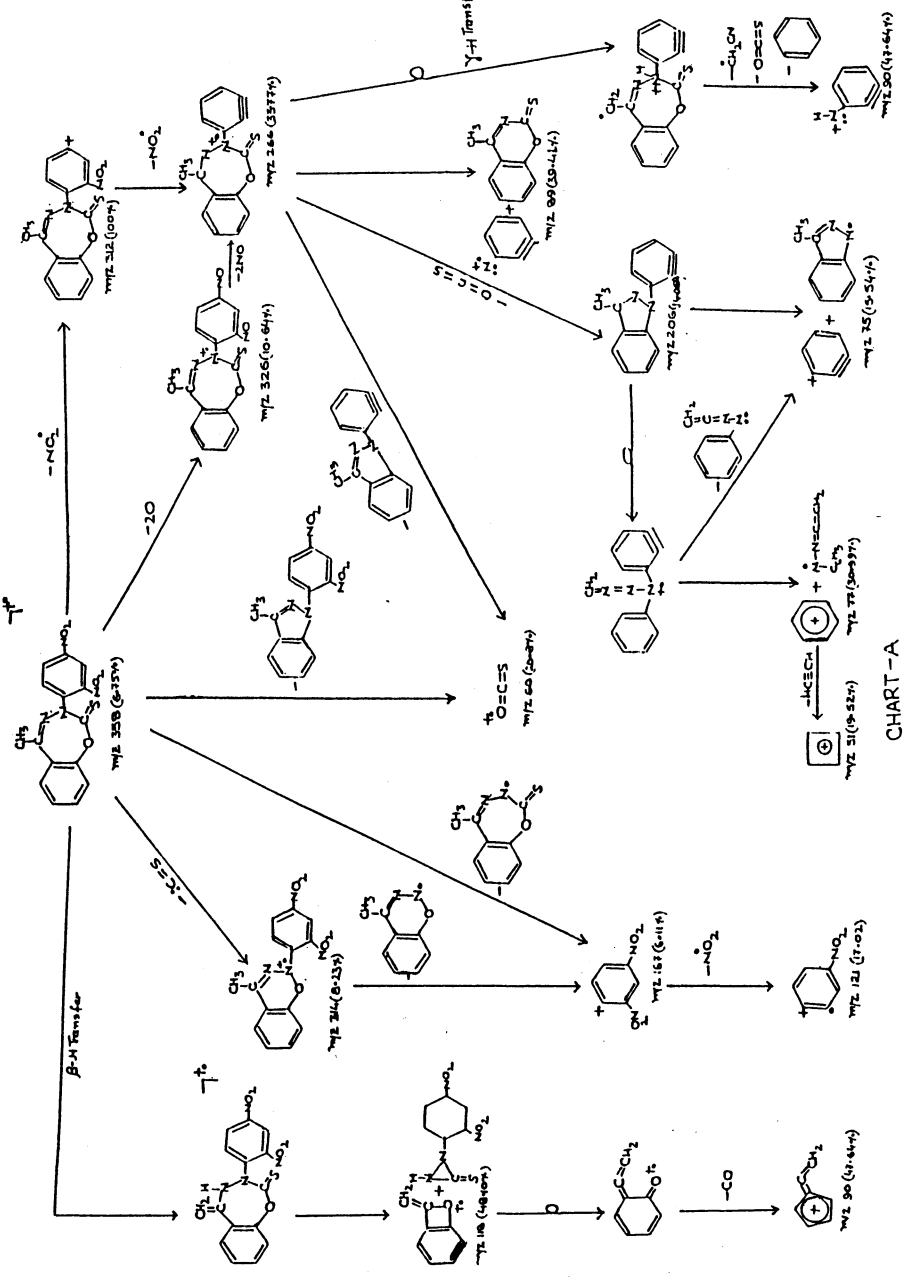


CHART-A

There is a lot of interaction between C—N, C—O and C=S stretching absorptions in the region 1400–1000 cm^{-1}. However, a careful study made it possible to identify a few absorption bands. The C—O stretching absorptions of moderate intensity have been noted at 1260–1195 cm^{-1}. The C—N stretching absorption bands appeared at a relatively higher grequency 1338–1300 cm^{-1} due to increased conjugation in the cycloadduct. Azomethinic function (—C=N—) absorption appeared in the region 1690–1618 cm^{-1}, thione function (—C=S) at 1165–1044 cm^{-1} and aromatic ring absorption in the region 898–670 cm^{-1}. All the IR absorption bands were consistent with the structure assigned to these cycloadducts (Table-1).

The PMR spectra lack the signals dur to —OH and —NH protons implying that cyclisation of arylhydrazones with thiophosgene had taken place. The signal due to aromatic protons appeared at δ 8.2–6.7. The benzylic proton merged with aromatic proton signal signifying anisotropic deshielding due to conjugation and ring current effect. The presence of oxygen in the ring which is further attached to the thione group also contributed to deshieding to some extent. The 3H(S) proton at δ 2.35–1.65 was due to $—CH_3$ protons (Table-1).

The mass spectrum of 5-methyl-3-(2′,4′-dinitrophenylhydrazone)-2H,3H-benz-[1,2-f][1,3,4]-oxadiazepine-2-thione had molecular ion peak at m/z 358 (6.75%) in agreement with the molecular formula assigned to this compound. The molecular ion was fragmented in a variety of ways which was mechanistically rationalised and explained (Chart A) to give different ionic species or ionic radicals like $[C_{15}H_{10}N_4O_3S]^{\bullet+}$ m/z-326 (10.64%); $[C_{15}H_{10}N_3O_3S]^{+}$ m/z-312 (100%); $[C_{15}H_{10}N_2OS]^{+}$ m/z-266 (33.77%); $[C_8H_6O]^{\bullet+}$ m/z-188 (48.10%); $[C_6H_3N]^{\bullet+}$ m/z-89 (33.41%) and $[C_4H_3]^{+}$ m/z-51 (19.52%) which clearly established the structure.

The biological aspects of these products will be investigated by the Central Drug Research Institute, Lucknow (India) to work out the insecticidal, pesticidal, tranquillizing and anticonvulsant activities.

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