SEARCH FOR PHYSIOLOGICALLY ACTIVE COMPOUNDS

Part XI. Structure-Fungistatic Activity Relationship among Substituted 1 : 2-Naphthoquinones

BY B. HARINATH BABU AND N. V. SUBBA RAO, F.A.SC.

(Department of Chemistry, Osmania University, Hyderabad-7)

Received June 10, 1967

ABSTRACT

A few halo, nitro and methoxy substituted 1 : 2-naphthoquinones with the substituents in both the benzenoid and the quinonoid rings have been synthesised and evaluated for their fungistatic properties. Among the quinonoid compounds tested 3 : 4-dichloro-1 : 2-naphthoquinones exhibited the highest activity.

INTRODUCTION

THE antibacterial, antifungal, and insecticidal properties of naphthoquinones have been reviewed by Baichwal and Khorana.[1] A survey of the literature revealed that they are mostly 1 : 4-naphthoquinones and only a few 1 : 2-naphthoquinones have been studied for their fungistatic activity. It was reported[2] earlier from this laboratory that the introduction of halo and nitro groups into a compound already known to be physiologically active, enhanced the toxicity of the compound. The present work has been undertaken to synthesise chloro, bromo, nitro and methoxy substituted 1 : 2-naphthoquinones with a view to study the structure—fungistatic activity relationship among them and compare their activity with that of 2 : 3-dichloro-1 : 4-naphthoquinone.

In the present investigation halogenation could be made use of in the preparation of halo naphthoquinones substituted in the quinonoid ring. 3-Chloro and 3-bromo-1 : 2-naphthoquinones[3] have been obtained by halogenation of 1 : 2-naphthoquinone and subsequent dehydrohalogenation of the resulting dihydro-dihalo-1 : 2-naphthoquinone. 1 : 2-Naphthoquinones with halogen in 4-position have been synthesised by treatment of 1 : 2-naphthoquinone-4-sulphonic acid suspended in halo acid with the corresponding potassium halate. 3 : 4-Dichloro and 3 : 4-dibromo-1 : 2-naphtho-

quinones could be prepared from 1-amino-2-naphthol by treatment with chlorine and bromine respectively when simultaneous oxidation and halogenation takes place.

For the synthesis of 1:2-naphthoquinones with the substituents in the benzenoid ring the cyclisation method of Sen and Sen[4] has been employed. By the condensation of the appropriate aldehyde with pyruvic acid and subsequent cyclisation 5-chloro, 7-chloro, 5:7-dichloro, 7-methoxy, 6 : 7-dimethoxy and 7-nitro-1:2-naphthoquinones have been prepared. 3-Chloro-7-nitro and 3-bromo-7-nitro-1:2-naphthoquinones have been prepared by direct halogenation.

The 1:2-naphthoquinones synthesised together with the analytical data are presented in Table I. Reduction of the radial growth of *Aspergillus niger* on synthetic medium has been employed for the determination of

TABLE I

Naphthoquinone	M.P. °C.	Analysis			
		Found		Calculated	
		C	H	C	H
7-Chloro-1:2-naphthoquinone ..	160	62·1	2·8	62·3	2·6
5:7-Dichloro-1:2-naphthoquinone..	180	53·2	2·0	52·9	1·8
6:7-Dichloro-1:2-naphthoquinone ..	188	53·1	1·8	52·9	1·8
6:7-Dimethoxy-1:2-naphthoquinone	180	66·4	4·8	66·1	4·6
3-Chloro-7-nitro-1:2-naphthoquinone	235	50·8	1·9	50·5	1·7
3-Bromo-7-nitro-1:2-naphthoquinone	256	42·5	1·5	42·6	1·4

fungistatic activity and the per cent. inhibition of growth by each of the substances is tabulated in Table II. The results of the fungistatic activity indicate that the introduction of a halo group specially into the quinonoid ring enhances the fungistatic activity whereas a similar substituent in the benzenoid ring has no pronounced effect. For example, 3-chloro-1:2-naphthoquinone and 3:4-dichloro-1:2-naphthoquinone have been found to be superior to 5-chloro or 7-chloro and 5:7-dichloro or 6:7-dichloro 1:2-

naphthoquinones respectively. The quinonoid substituted dihalo compounds 3 : 4-dichloro and 3 : 4-dibromo-1 : 2-naphtho quinones have greater activity than the corresponding mono-substituted 1 : 2-naphtoquinones and among themselves, chloro compounds exhibited better activity than the bromo derivatives. Similar conclusions were drawn by Schoene and co-workers[7] with respect to halo substituents in 1 : 4-naphthoquinones.

TABLE II

Fungistatic Activity of 1 : 2-*Naphthoquinones*

1 : 2-Naphthoquinone, substituent =	% Inhibition	
	10 p.p.m.	100 p.p.m.
3-Chloro- ...	20	87
3-Bromo- ...	13	47
4-Chloro- ...	7	33
4-Bromo- ...	7	27
5-Chloro- ...	7	33
7-Chloro- ...	7	27
7-Methoxy- ...	0	13
7-Nitro- ...	0	13
3 : 4-Dichloro- ...	33	100
3 : 4-Dibromo- ...	13	67
5 : 7-Dichloro- ...	0	33
6 : 7-Dichloro- ...	7	33
3-Chloro-7-nitro- ...	13	47
3-Bromo-7-nitro- ...	13	33
Unsubstituted ..	13	47
Blank ..	0	0

EXPERIMENTAL

3-Chloro, 3-bromo, 3 : 4-dichloro and 3 : 4-dibromo-1 : 2-naphthoquinones were prepared according to the known procedures.[3, 5]

4-Chloro-1 : 2-naphthoquinone.—A solution of sodium salt of 1 : 2-naphthoquinone-4-sulphonic acid (2 g.) in water (150 ml.) and concentrated hydrochloric acid (15 ml.) was heated on a water-bath and while stirring potassium chlorate (2 g.) was added slowly in two hours. The mixture was refluxed for an additional three hours and cooled. The solid on crystallisation from benzene yielded brown needles, m.p. 135° C. (Lit.[3], 136° C).

4-Bromo-1 : 2-naphthoquinone.—According to the procedure described above, 4-bromo-1 : 2-naphthoquinone was prepared from the sodium salt of 1 : 2-naphthoquinone-4-sulphonic acid (2 g.) in water (150 ml.) and hydrobromic acid (15 ml.) and potassium bromate (2 g.). Recrystallisation from benzene afforded red needles, m.p. 150° C. (Lit.[6], 150° C.).

1 : 2-Naphthoquinones substituted in the benzene ring.—The general procedure employed as reported by Sen and Sen[4] was as follows:

Suitably substituted benzaldehyde (0·1 mole) was condensed with pyruvic acid (0·1 mole) in the presence of alcoholic potassium hydroxide in the cold. The resulting potassium salt of benzylidine pyruvic acid was purified and cyclised to the corresponding 1 : 2-naphthoquinone by heating at about 200° C. with acetic anhydride and fused sodium acetate. 5-Chloro, 7-chloro, 5 : 7-dichloro, 7-methoxy, 6 : 7-dimethoxy and 7-nitro-1 : 2-naphthoquinones were prepared according to this procedure and the analytical data recorded in Table I.

3-Chloro-7-nitro-1 : 2-naphthoquinones.—Chlorination of 7-nitro-1 : 2-naphthoquinone according to the procedure followed for the simple 3-chloro-1 : 2-naphthoquinone[3] afforded the chloroquinone, m.p. 235° C.

3-Bromo-7-nitro-1 : 2-naphthoquinone.—Bromination of 7-nitro-1 : 2-naphthoquinone as described above gave the bromo quinone, m.p. 256° C.

REFERENCES

1. Baichwal, R. S. and Khorana, M. L. — *J. Sci. and Ind. Res.*, 1952, **11 A**, 197.
2. Babu Rao, K. and Subba Rao, N. V. — *Ibid.*, 1958, **17 B**, 225.

3. Fieser, L. F. and Dunn, J. T. *J. Am. Chem. Soc.*, 1937, **59**, 1016.

4. Sen, R. N. and Sen, B. K. *J. Ind. Chem. Soc.*, 1934, **11**, 411.

5. Zincke, Th. .. *Ber.*, 1886, **19**, 2493.

6. Fries, K. and Schmmelschmidt, K. *Ann.*, 1930, **484**, 245.

7. Schoene, D. L., Tate, H. D. and Brasfield, T. W. *Agr. Chemicals*, 1949, **4**, 25