ACTA CHEMICA SCANDINAVICA 17 (1963) 1157–1159

Syntheses of Aucuparin and Methoxyaucuparin

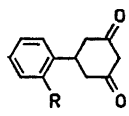
MARTIN NILSSON and TORBJÖRN NORIN

Organisk-kemiska Institutionen, Kungl. Tekniska Högskolan, Stockholm, Sweden

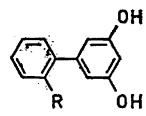
Dehydrogenation of 5-phenylcyclohexan-1,3-dione over palladised charcoal in boiling diphenyl ether gave 3,5-dihydroxybiphenyl. The dimethyl ether was lithiated in the 4-position and oxidised by the lithium salt of *t*-butylhydroperoxide to give a very good yield of 4-hydroxy-3,5-dimethoxybiphenyl identical with aucuparin. A similar reaction sequence starting with 5-(2-methoxyphenyl)-cyclohexan-1,3-dione gave methoxyaucuparin.

In the preceding paper [1] full details have been given of the structural elucidation of two phenolic heartwood constituents of mountain ash, *Sorbus aucuparia* (L.), *viz.* aucuparin and methoxyaucuparin, including the syntheses of their methyl ethers. The present paper deals with the syntheses of the two phenols.

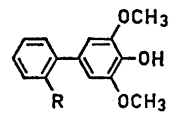
Dehydrogenation of 5-phenylcyclohexan-1,3-dione (1a) over palladised charcoal in boiling diphenylether gave a high yield of the previously unknown 3,5-dihydroxybiphenyl (2a), which was converted to its dimethyl ether. Lithiation (metalation) of resorcinol ethers is known to take place in the 2-position [2] and is therefore a practical way of introducing other substituents into this otherwise rather inaccessible position. Lithiation of 3,5-dimethoxybiphenyl was readily accomplished by butyl-lithium or phenyl-lithium. The lithium compound was oxidised by the lithium salt of *t*-butylhydroperoxide (*cf.* Ref.[3]), conveniently prepared from butyl-lithium and *t*-butylhydroperoxide, to give a very good yield of 4-hydroxy-3,5-dimethoxybiphenyl (3a) identical with aucuparin.



1



2



3

a, R = H; b, R = CH_3O

The use of lithium compounds in this reaction does not seem to lead to any inconvenient caging of the reaction mixture as encountered in the oxidation of Grignard reagents (*cf.* Ref.[3]).

A similar reaction sequence starting with 5-(2-methoxyphenyl)-cyclohexan-1,3-dione (1b) gave a good yield of 4-hydroxy-3,5,2′-trimethoxybiphenyl (3b) identical with methoxyaucuparin.

EXPERIMENTAL

Melting points, were taken on a Kofler micro hot stage.

3,5-Dihydroxybiphenyl (2a). 5-Phenylcyclohexan-1,3-dione (phenyldihydroresorcinol)[4] (1a) (10 g) and palladised charcoal (10 %, 2 g) were heated in diphenylether (100 g) in an atmosphere of nitrogen. At about 200° a vigorous evolution of hydrogen started and the mixture was then allowed to reflux for 3 h. After cooling and addition of ether the reaction mixture was filtered and the ether solution extracted with aqueous sodium hydroxide. The alkaline aqueous phase was washed with ether, acidified and re-extracted with ether. Evaporation of the dried ether solution gave a crude crystalline product, which was heated on a water bath under reduced pressure in order to evaporate most of the phenol formed during the reaction. The crystalline residue was chromatographed on silica gel (600 g). Methanol-chloroform (2 %) eluted some oily coloured material (0.3 g). Further elution with methanol-chloroform (4 %) gave *3,5-dihydroxybiphenyl* (2a) (9.0 g) which after purification by sublimation under reduced pressure had m.p. 160—162°. (Found: C 77.5; H 5.3. $C_{12}H_{10}O_2$ requires C 77.4; H 5.4 %). Methylation with dimethyl sulphate in the usual way gave *3,5-dimethoxybiphenyl* which after recrystallisation from methanol and sublimation under reduced pressure had m.p. 61—62°. (Found: C 78.5; H 6.5; OCH_3 29.1. $C_{12}H_8(OCH_3)_2$ requires C 78.5; H 6.6; OCH_3 29.0).

4-Hydroxy-3,5-dimethoxybiphenyl (aucuparin) (3a). A solution of butyl-lithium (10 mmole) in ether (20 ml) was slowly added to a dry, ice-cooled, ether solution (10 ml) of 3,5-dimethoxybiphenyl (2.14 g). When the mixture was left in a refrigerator for 2 days the lithium compound precipitated. The stirred ether slurry of the crystalline lithium compound was added with cooling (dry ice/acetone), to the lithium salt of *t*-butylhydroperoxide (10 mmole). The latter was prepared by addition of butyl-lithium (10 mmole) in ether to a stirred ether solution of *t*-butylhydroperoxide (10 mmole) with cooling (dry ice/acetone). The stirred reaction mixture was allowed to warm to room temperature and was then heated under reflux for 5 min. After cooling, it was poured into ice-cooled aqueous sulphuric acid (10 %). The ether phase was washed with water and extracted with aqueous sodium hydroxide (10 %). The sodium salt of the phenolic material precipitated but gradually dissolved when larger amounts of the sodium hydroxide solution were used. The alkaline phase was washed with ether, acidified and re-extracted with ether. The dried ether extract gave, after evaporation of the solvent, a crude crystalline product (1.55 g) which was chromatographed on silica gel (60 g). Chloroform-benzene (10 %) eluted *4-hydroxy-3,5-dimethoxybiphenyl* (3a), identical with aucuparin (m.p. and mixed m.p. 101—101.5°, identical infrared and ultraviolet spectra).

5-(2-Methoxyphenyl)-cyclohexan-1,3-dione (1b) was prepared following the procedure given for the synthesis of the *p*-analogue [5]; Ethyl *o*-methoxybenzylidenemalonate [6] (28.0 g) and ethyl acetoacetate (13.0 g) were added to a solution of sodium ethoxide from 4.6 g sodium in ethanol (100 ml). The reaction mixture was refluxed for 12 h. The solvent was evaporated and the residue kept at about 130° under reduced pressure for about 3 h. The dry hard mass was allowed to cool, ice-water was added and the solution acidified. Extraction with ether and evaporation of the dried ether extract gave a yellowish oil which solidified on standing. Recrystallisation from ethyl acetate gave *diethyl 2-(2-methoxyphenyl)-4,6-dioxocyclohexan-1,3-dicarboxylate* (12.3 g) as prisms with m.p. 133—134°. (Found: C 62.6; H 6.3. $C_{19}H_{22}O_7$ requires C 63.0; H 6.1).

The ester (10 g) was hydrolysed by refluxing for 1 h with aqueous sodium hydroxide (10 %, 200 ml). The warm reaction mixture was acidified with dilute sulphuric acid and kept at 100° until evolution of carbon dioxide ceased. *5-(2-Methoxyphenyl)-cyclohexan-1,3-dione* (1b) (7.0 g) crystallised on cooling. The recrystallised (ethyl acetate) and subli-

med product had m.p. 147—148°. (Found: C 71.5; H 6.4. $C_{13}H_{14}O_3$ requires C 71.5; H 6.5).

The oily residue from the evaporated mother liquors of the ester was also hydrolysed and decarboxylated as described above. The oily diketone thus obtained was chromatographed on silica gel. Ethanol-chloroform (3 %) eluted additional amounts of 5-(2-methoxyphenyl)-cyclohexan-1,3-dione (1b), bringing the total yield to 70 %.

4-Hydroxy-3,5,2'-trimethoxybiphenyl (methoxyaucuparin) (3b). 5-(2-Methoxyphenyl)-cyclohexan-1,3-dione (1b) was dehydrogenated similarly to 3,5-dihydroxybiphenyl (2a). *3,5-Dihydroxy-2'-methoxybiphenyl* (2b) was obtained in 82 % yield and had, after sublimation under reduced pressure, m.p. 139—140°. (Found: C 72.2; H 5.6; OCH_3 14.3. $C_{12}H_9O_2(OCH_3)$ requires C 72.2; H 5.6; OCH_3 14.3).

Methylation with dimethyl sulphate gave the oily *3,5,2'-trimethoxybiphenyl*, which was purified by percolation through a silica gel column (in benzene solution), followed by distillation under reduced pressure. The product would not crystallise. (Found: C 74.0; H 6.4; OCH_3 37.8. $C_{12}H_7(OCH_3)_3$ requires C 73.8; H 6.6; OCH_3 38.1).

The lithiation of 3,5,2'-trimethoxybiphenyl and the oxidation of the corresponding lithium compound with the lithium salt of *t*-butylhydroperoxide was carried out as described above. *4-Hydroxy-3,5,2'-trimethoxybiphenyl* (3b) was obtained in 53 % yield and found to be identical with methoxyaucuparin. (M.p. and mixed m.p. 120—121°, identical infrared and ultraviolet spectra).

Acknowledgements. We thank Professor H. Erdtman for his interest in this work. Thanks are also due to the *Swedish Technical Research Council* for a fellowship to one of us (T.N.) and to Dr. A. Morrison for linguistic advice.

REFERENCES

1. Erdtman, H., Eriksson, G., Norin, T. and Forsén, S. *Acta Chem. Scand.* **17** (1963) 1151.
2. Gilman, H. and Morten, Jr., J. W. *Org. Reactions* **8** (1954) 258.
3. Lawesson, S.-O. and Yang, N. C. *J. Am. Chem. Soc.* **81** (1959) 4230.
4. Vorländer, D. *Ber.* **27** (1894) 2053. *Cf.* also Knoevenagel, E. *Ber.* **27** (1894) 2337, and Rosenmund, K.W., Herzberg, H. and Schütt, H. *Chem. Ber.* **87** (1954) 1258.
5. Papadakis, P. E., Hall, L. M. and Augustine, R. L. *J. Org. Chem.* **23** (1958) 123.
6. Hey, D. H. and Nagdy, K. A. *J. Chem. Soc.* **1953** 1894.

Received January 14, 1963.