

Studies in Antibacterials: — Synthesis of Hydroxy — Chloro chalkones. II

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Summary

With a view to study their antibacterial properties a number of chalkones have been prepared employing 2:3- and 2:4-dichlorobenzaldehydes and a number of substituted hydroxy catophenones. These have been characterised by preparation of their derivatives. The behaviour of some of these chalkones when submitted to Algar-Flynn reaction has also been studied and the results recorded.

In Part I of this series the antibacterial activity of various substituted chalkones was discussed and the synthesis of a few hydroxy chloro chalkones recorded. These chalkones were the products of condensation of 2:3- and 2:4-dichloro-benzaldehydes¹⁾²⁾³⁾ and ketones having a simple phenol or resorcinol nucleus. This work has now been extended by employing ketones having a phloroglucinol or hydroxyquinol nucleus and 2:3- and 2:4-dichlorobenzaldehyde as the aldehydic component.

Thus 2-hydroxy-4:6-dimethoxy acetophenone⁴⁾, 2-hydroxy-4:5-dimethoxy acetophenone⁵⁾ and 2:4:5-trimethoxy-acetophenone⁶⁾ have been condensed with 2:3 and 2:4-dichloro-benzaldehyde to yield the corresponding chalkones. These have been characterised by preparation of their 2:4-dinitrophenylhydrazones and acetyl derivatives (for the 2-hydroxy chalkones).

Further the chalkones carrying a free hydroxyl group in the 2'-position have been subjected to Algar-Flynn oxidation⁷⁾ when the correspond-

¹⁾ S. P. HIREMAT, N. GUDI, V. BADIGER and S. RAJAGOPAL, Arch. Pharm. **294** (1960).

²⁾ C. S. MARVEL, C. C. OVERBERGER, R. E. ALLEN, H. W. JOHNSTON, J. H. SAUNDERS and J. D. YOUNG, J. Amer. chem. Soc. **68**, 861 (1946).

³⁾ L. GINDRAUX, Helv. chim. Acta **12**, 921 (1929).

⁴⁾ P. FRIEDLÄNDER and L. C. SCHMELL, Berichte **30**, 2150 (1897).

⁵⁾ BARGELLINI and AURELI, Atti. Acad. Lincei, II [5] **20**, 118 (1911).

⁶⁾ J. REGRODSKI and J. TAMBOR, Berichte **43**, 1965 (1910).

⁷⁾ J. ALGAR and J. P. FLYNN, Proc. Roy. Irish. Acad., Sect B. **42** (1) (1934); cf. Cem. Abstr. **28**, 1126 (1934).

ing flavonol or benzalcoumaranones have been obtained depending on whether the 6'-position of the chalcone molecule is substituted or not. Thus 2'-hydroxy-4':6'-dimethoxy-2:3 (2:4)-dichloro-chalcones gave the benzalcoumaranones while their 4':5'-dimethoxy isomers yielded the flavonols. This is in agreement with the observation of GEISMANN

Table I

Name of the Compound	appearance	M. P.	Analysis
2'-Hydroxy-4':6'-dimethoxy-2:3-dichloro-chalkone	Yellow needles dil. alcohol	178—80°	Found 19.98% Cl $C_{17}H_{14}O_4Cl_2$ (353.1) req. 20.08% Cl
-Do-acetyl derivative	fine needles (ethanol)	138°	
-Do-2:4-dinitro-phenyl-hydrazone	orange-red needles (ethanol)	249—50°	
2'-Hydroxy-4':6'-dimethoxy-2:4-dichloro-chalkone	fine yellow needles (ethanol)	182—83°	Found 20.46% Cl $C_{17}H_{14}O_4Cl_2$ (353.1) req. 20.08% Cl
-Do-acetyl-derivative	fine needles (ethanol)	154—55°	
-Do-2:4-dinitro-phenyl-hydrazone	scarlet-red needles (ethanol)	225°	
2'-Hydroxy-4':5'-dimethoxy-2:3-dichloro-chalkone	yellow needles (abs. alcohol)	115°	Found 20.22% Cl $C_{17}H_{14}O_4Cl_2$ (353.1) req. 20.08 Cl
-Do-acetyl derivative	tiny needles (ethanol)	105°	
-Do-2:4-dinitro-phenyl-hydrazone	violet tiny crystals (ethanol)	158—60°	
2'-Hydroxy-4':5'-dimethoxy-2:4-dichloro-chalkone	yellow needles (aq. alcohol)	123—25°	Found 20.11% Cl $C_{17}H_{14}O_4Cl_2$ (353.1) req. 20.08% Cl
-Do-acetyl derivative	stout needles (ethanol)	128°	
-Do-2:4-dinitro-phenyl-hydrazone	scarlet needles (ethanol)	176°	
2':4':5'-Trimethoxy-2:3-dichloro-chalkone	bright-yellow needles (abs. alcohol)	170°	Found 19.48% Cl $C_{18}H_{16}O_4Cl_2$ (367.1) req. 19.32% Cl
-Do-2:4-dinitro-phenyl-hydrazone	red shining needles (ethanol)	226°	
2':4':5'-Trimethoxy-2:4-dichloro-chalkone	yellow needles (abs. alcohol)	173°	Found 19.22% Cl $C_{18}H_{16}O_4Cl_2$ (367.1) req. 19.32% Cl
-Do-2:4-dinitro-phenyl-hydrazone	bright-red needles (acetic acid)	252—53°	

and FUKUSHIMA⁸) who have established the predominant formation of benzalcoumaranones when chalkones carrying a substituent in the 6' position are subjected to oxidation with alkaline hydrogen peroxide.

These chalkones will be subjected to screening experiments in due course.

Experimental

General methods of preparation of Chalkones

To an alcoholic solution containing the appropriate acetophenone and aldehyde in equimolecular proportions were added a few drops of 50% sodium hydroxide and warmed. The mixture was shaken, corked tight and allowed to stand for 24 hours. The condensation product was worked up in the usual manner. The resulting chalkones were crystallised from appropriate solvents. The properties of the chalkones as well as of their derivatives like acetyl and 2:4-dinitro-phenylhydrazones and the halogen analysis of the parent chalkones are summarised in Table I.

Algar-Flynn oxidation of the various Chalkones

The appropriate chalkone (0.5 g.) dissolved in methyl alcohol (15 cc.) was treated with aqueous sodium hydroxide (50%, 2 cc) and cooled to 0°. Hydrogen peroxide (5 cc. 20 Vols.) was slowly added to it with shaking. The mixture was allowed to stand overnight in an ice-bath, then diluted with water and acidified with ice-cold dilute sulphuric acid

Table II

Name of the parent chalkone	Algar-Flynn reaction product			
	Name	M.P.	Structure and solvent of crystallisation	Analysis values
1. 2'-Hydroxy-4'-6'-dimethoxy-2:3-dichloro chalkone	2':3'-Dichloro-2-benzylidene 4:6-dimethoxy-coumaranone	90-92°	Pale yellow plates (dil. alcohol)	Found 20.34% Cl C ₁₇ H ₁₂ O ₄ Cl ₂ (351.0) req. 20.20% Cl
2. 2'-Hydroxy-4'-6'-dimethoxy-2:4-dichloro chalkone	2':4'-Dichloro-2-benzylidene-4:6-dimethoxy coumaranone	235°	Pale yellow plates (dil. alcohol).	Found 20.45% Cl C ₁₇ H ₁₂ O ₄ Cl ₂ (351.0) req. 20.20% Cl
3. 2'-Hydroxy-4':5-dimethoxy-2:4-dichloro chalkone	2':4'-Dichloro-6:7-dimethoxy flavonol	210°	Pale yellow plates (ethanol)	Found 19.22% Cl C ₁₇ H ₁₂ O ₅ Cl ₂ (367.0) req. 19.32% Cl

⁸) T. A. GEISMAN and D. K. FUKUSHIMA, J. Amer. chem. Soc. **70**, 1686 (1948).

when the flavonol or the benzalcoumaranone was obtained. The properties of the oxidation products obtained with the various chalcones as well as the halogen analysis values of the products are recorded in Table II.

Acetyl Derivatives

These were prepared by heating the appropriate chalcone with acetic anhydride and a few drops of pyridine.

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