New Compounds

Synthesis of Alkylsalicylic Acids as Antimicrobial Agents

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This series of compounds has been prepared in order that the effects of the nature and position of the alkyl groups on the antimicrobial activity of alkylsalicylic acids may be examined. The stimulus for this investigation was the reported antimicrobial activity of anacardic acid and its salts.[1] The Wolff–Kishner reduction of *m*-methoxy-*n*-dodecanoylbenzene was accompanied by demethylation of the ether group. *p*-Acylphenols, particularly of the higher homologs, were reduced with more difficulty than the ortho isomers and some starting material was invariably recovered. Since this occurred when pure dodecanoylphenol hydrazone was reduced, it must result from ketone regeneration rather than incomplete hydrazone formation.

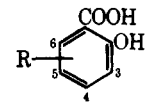
Experimental Section[2]

Acylphenols.—Ph ester was added portionwise to a mixt of anhyd $AlCl_3$ (1.1 moles) and dry CS_2 (100 ml) maintained at 70° and then the mixt was refluxed (1–2 hr). The CS_2 was distd off, the temp of the residue was maintained at 135° for 3 hr, and then HCl (150 ml, 5 *N*) followed by H_2O (200 ml) was added cautiously with stirring. A mixt of *o*- and *p*-acylphenols was isolated by Et_2O extraction. The isomeric acylphenols were sepd by chromatography on silica gel columns (200–300 mesh, activated at 100°, 10 g for each 1 g of crude reaction product) using $CHCl_3$. Fractions of the eluate were examined by tlc (silica gel G–$CHCl_3$) and bulked on the basis of this. The products were purified and derivs prepd. All corresponded with lit. values where available.

Alkylphenols were prepared by the Wolff–Kishner reduction of acylphenols. The Huang-Minlon[3] method was efficient with *o*- and *p*-acetylphenol, *o*-*n*-dodecanoylphenol, *o*-*n*-tetradecanoylphenol, and *o*-*n*-octadecanoylphenol. *p*-*n*-Octanoylphenol was reduced by preparing the hydrazone in ethanol prior to reduction. Reduction of *p*-*n*-dodecanoylphenol by this method gave a mixture of starting material and product. These were separated by the chromatographic method described above.

Alkylsalicylic Acids.—A mixture of alkylphenol (1.0 mole) and anhyd K_2CO_3 (2.0 moles) was subjected to CO_2 at 52.7 kg/cm² at 180° for 8 hr with continuous shaking. The mixt was washed (Et_2O), the residue was acidified (HCl), and the product was isolated by extn (Et_2O). Final purification was accomplished by short-path distn at 190° (0.5 mm). The orientations of the alkylsalicylic acids were deduced from the acylphenols[4] and were confirmed by nmr (Varian Associates A60A) spectra. Data relevant to alkylsalicylic acids are given in Table I.

TABLE I
ALKYLSALICYLIC ACIDS



R	Amount of alkylphenol, mole (yield, %)	Mp, °C	Formula[a]
3-CH_3	0.045 (28)	161–162	$C_8H_8O_3$
4-CH_3	0.051 (60)	176	$C_8H_8O_3$
5-CH_3	0.045 (67)	149–150	$C_8H_8O_3$
3-C_2H_5	0.05 (22)	112–113	$C_9H_{10}O_3$
5-C_2H_5	0.05 (68)	116–117	$C_9H_{10}O_3$
3-*n*-C_6H_{13}	0.02 (5)	80–81	$C_{13}H_{18}O_3$
3-*n*-C_7H_{15}	0.016 (13)	80–81	$C_{14}H_{20}O_3$
3-*n*-C_8H_{17}	0.04 (60)	77–78	$C_{15}H_{22}O_3$
5-*n*-C_8H_{17}	0.02 (54)	72–73	$C_{15}H_{22}O_3$
3-*n*-$C_{12}H_{25}$	0.005 (30)	86–87	$C_{19}H_{30}O_3$
5-*n*-$C_{12}H_{25}$	0.0066 (30)	88–89	$C_{19}H_{30}O_3$
4-*n*-$C_{12}H_{25}$	0.0114 (48)	93–94	$C_{19}H_{30}O_3$
3-*n*-$C_{14}H_{29}$	0.17 (19)	91–92	$C_{21}H_{34}O_3$
3-*n*-$C_{18}H_{37}$	0.02 (6)	94–95	$C_{25}H_{42}O_3$

[a] All compounds showed a correct analysis for C, H (C.S.I.R.O., Melbourne, Australia).

***m*-Methoxy-*n*-dodecanoylbenzene.**—An Et_2O sol of *m*-$C_{11}H_{23}MgBr$ was contained in a flask fitted with a dropping funnel, a Soxhlet, and a N_2 inlet port. *m*-Methoxybenzamide was contained in the Soxhlet. The reaction mixt was refluxed until all the amide had been transferred to it (80 hr). It was worked up in the usual manner and the crude product was chromatographed on silica gel (100–200 mesh, activated at 110°). Elution with petroleum produced two compounds *n*-$C_{22}H_{46}$ and *n*-$C_{11}H_{24}$. Further elution with $CHCl_3$ yielded the ketone (nmr and ir were consistent).

***m*-*n*-Dodecylphenol.**—The hydrazone of *m*-methoxy-*n*-dodecanoylbenzene was prepared and isolated. This was then reduced by Huang-Minlon modification of the Wolff–Kishner reaction, the crude product was worked up in the usual manner and then chromatographed (silica gel, 100–200 mesh activated at 110°). Elution with petr ether–$CHCl_3$ (10%) gave *m*-methoxy-*n*-dodecylbenzene (2.4 g) while elution with $CHCl_3$ produced *m*-*n*-dodecylphenol (5.13 g). Nmr, ir, and analyses were consistent.

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(2) Melting points were determined on a Kofler micro hot stage and are uncorrected.

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Search for Potential Oral Hypoglycemic Agents. Hydrindene Derivatives

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Among various ring systems, the hydrindene ring has already led to an effective oral hypoglycemic agent like glyhexamide.[1] Several hydrindene derivatives like indenopyrroles[2] and indanamines[3] have also been re-

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