New Compounds

Synthesis of Alkylsalicylic Acids as Antimicrobial Agents

D. BUCKLEY* AND J. THOMAS

Department of Pharmacy, University of Sydney, Sydney, Australia

Received August 28, 1970

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.

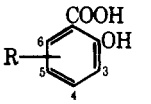
Experimental Section[2]

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.

(1) (a) F. Eichbaum, *Mem. Inst. Butantan, Sao Paulo*, **19**, 69 (1946). (b) A. K. Biswas and A. B. Roy, *Nature (London)*, **182**, 1299 (1958). (c) A. K. Biswas and A. B. Roy, *J. Proc. Inst. Chem., Calcutta*, **33** (2), 81 (1961). (d) A. K. Biswas and A. B. Roy, *Nature (London)*, **200**, 1203 (1963). (e) F. Eichbaum, H. Hauptmann, and H. Rothschild, *An. Ass. Brasil. Quim.*, **4**, 83 (1945).

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

(3) Huang-Minlon, *J. Amer. Chem. Soc.*, **68**, 2487 (1946).

(4) (a) G. G. S. Dutton, T. I. Briggs, B. R. Brown, and R. K. Powell, *Can. J. Chem.*, **31**, 837 (1953). (b) A. W. Ralston and S. T. Bauer, *J. Org. Chem.*, **5**, 165 (1940).

Search for Potential Oral Hypoglycemic Agents. Hydrindene Derivatives

A. U. DE* AND B. P. SAHA

Department of Pharmacy, Jadavpur University, Calcutta 32, India

Received September 23, 1970

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-

(1) A. Bänder, "Oral Hypoglycemic Agents Pharmacology and Therapeutics," G. D. Campbell, Ed., Academic Press, London and New York, 1969, p 29.

(2) S. C. Lahiri and B. Pathak, *J. Med. Chem.*, **8**, 131 (1965).

(3) S. C. Lahiri and N. C. De, *ibid.*, **11**, 900 (1968).

ported to possess appreciable hypoglycemic activity. Based on these observations, several indanamides like 1-*N*-alkylacetamidoindans[4] and 3-oxo-1-*N*-alkylacetamidoindans have been synthesized to evaluate their hypoglycemic activity. None of these compounds, however, possessed any hypoglycemic activity.

Experimental Section[5]

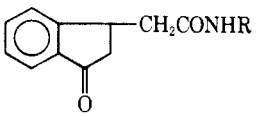
Methyl 3-Oxoindan-1-acetate.—3-Oxoindan-1-acetic acid[6] (27 g) was esterified with dry MeOH (90 ml) in the presence of dry HCl (6 g) by refluxing on a steam bath for 8 hr. The crude ester was crystd from EtOAc–petr ether (bp 40–60°) in 90% yield, mp 67–68°. *Anal.* ($C_{12}H_{12}O_3$) C, H.

3-Oxo-1-*N*-alkylacetamidoindan. A.—A mixt of methyl 3-oxoindan-1-acetate (1 mole) and the appropriate alkylamine (2 moles) was heated in a sealed tube on steam bath for 6 hr. The reaction mass was poured into H_2O, acidified with 2 *N* HCl, either filtered or extd (PhH), and washed (H_2O). The crude product was crystd from PhH–petr ether (bp 40–60°) as shining crystals.

b.—$SOCl_2$ (5 ml) was added dropwise to a mixt of 3-oxoindan-1-acetic acid[6] (3 g) and dry PhH (120 ml) with stirring till the evoln of HCl ceased. Approx 90 ml of PhH was distd off and the residual mass (3-oxoindan-1-acetyl chloride) was cooled in ice water. The cooled soln of 3-oxoindan-1-acetyl chloride (1 mole) was added dropwise under stirring to a soln of alkylamines (2.5 moles) in PhH (40 ml) with the simultaneous addn of 2 *N* NaOH to keep the mass alk. After stirring for 2 hr it was either filtered or extd (PhH), washed (H_2O), and purified by crystn from PhH–petr ether (bp 40–60°) as shining crystals (see Table I).

TABLE I

3-OXO-1-*N*-ALKYLACETAMIDOINDANS



R	Mp, °C	Empirical formula[c]
Me[a]	144–146	$C_{12}H_{13}O_2N$
Et[b]	120–121	$C_{13}H_{15}O_2N$
n-Pr[b]	116–118	$C_{14}H_{17}O_2N$
n-Bu[b]	97–98	$C_{15}H_{19}O_2N$

[a] Prepd from ester. [b] Prepd from acid chloride. [c] *Anal.* C, H, N.

Acknowledgment.—The authors' thanks are due to Bristol Laboratories, Syracuse, N. Y., for the hypoglycemic test report.

(4) A. U. De and B. Pathak, *J. Med. Chem.*, **13**, 152 (1970).
(5) Analytical results were within ±0.4% of the theoretical values. All melting points are uncorrected.
(6) R. H. Manske, *J. Amer. Chem. Soc.*, **53**, 1104 (1931).

Anti-*Trichinella spiralis* Activity of Some 1-Carbamoyl-3-methyl-2-pyrazolin-4,5-dione 4-Arylhydrazones

H. G. GARG

Department of Chemistry, University of Roorkee, Roorkee, India

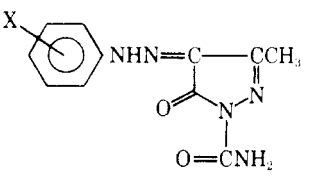
Received September 8, 1970

Heterocyclic compounds containing a carbamoyl group have been reported to possess various activities[1] due to their ability to inhibit acetylcholinesterase, probably by the transfer of a carbamoyl group to an active site of the enzyme. This report includes the potencies against *Trichinella spiralis* of several 1-carbamoyl-3-methyl-2-pyrazolin-4,5-dione 4-arylhydrazones which were described earlier in connection with our work on potential antidiabetics.[2]

The compounds were prepared as described previously[2,3] and were tested in mice and have shown the order of decreasing potency listed in Table I.

TABLE I

ANTI-*Trichinella* ACTIVITY[a]



No.	X	Mp, °C	Mean worm count Control	Drug	% reduction[a]
1	2-Cl-4-NO_2	210[b]	396	326	17.7
2	2,5-Cl_2	258–259[c]	396	388	2.0
3	2-Cl-6-Me	226[c]	396	394	0.5
4	4-NO_2	257–258[c]	495	536	0
5	2,6-Cl_2	200[c]	396	403	0

[a] Drug administration was po in Charles River Mice. Compound effectiveness was calcd as a percentage reduction based on the following formula. % reduction = 100 − [(Mean of medicated group worm count)/(mean of unmedicated control group worm count)]. [b] Ref 2. [c] Ref 3.

Acknowledgment.—The author is thankful to Dr. Maxwell Gordon (SK and F Laboratories, Philadelphia, Pa.) for making testing data available and to Professor W. U. Malik, Head of the Chemistry Department, for encouragement.

(2) H. G. Garg and S. N. Mehra, *J. Indian Chem. Soc.*, **38**, 325 (1961).
(3) H. G. Garg and P. P. Singh, *J. Chem. Soc. C*, 1141 (1969).

Modified Syntheses of 2,4,5-Trihydroxyphenylalanine, 2,4,5-Trihydroxyphenethylamine, and Analogs[1]

FRED G. H. LEE,* DONALD E. DICKSON,

Regis Chemical Company, Chicago, Illinois 60610

AND ALBERT A. MANIAN

Psychopharmacology Research Branch, National Institute of Mental Health, Chevy Chase, Maryland 20015

Received October 12, 1970

We are reporting new and more rewarding syntheses of 2,4,5-trihydroxyphenylalanine (I) (6-hydroxydopa),[2]

(1) This investigation was supported by the Psychopharmacology Research Branch, National Institute of Mental Health, Contract No. HSM-42-70-41.
(2) H. H. Ong, C. R. Creveling, and J. W. Daly, *J. Med. Chem.*, **12**, 458 (1969).