A FACILE SYNTHETIC ROUTE TO THE ^{14}C-LABELED ENANTIOMERS OF MK-196, A NEW URICOSURIC DIURETIC, AND ITS MAJOR METABOLITE

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SUMMARY

The enantiomers of MK-196, (6,7-dichloro-2-methyl-1-oxo-2-phenyl-5-indanyloxy)-acetic acid, and the 2-(4-hydroxyphenyl) derivative, the major metabolite of MK-196, were resolved by classical methods using α-methylbenzylamine salts, and converted to the corresponding, enantiomerically pure (indanyloxy)acetic acids-α-^{14}C by facile ether cleavage with pyridine hydrochloride to the 5-indanols, selective O-re-alkylation with methyl bromoacetate-2-^{14}C and subsequent saponification.

Key Words: MK-196, URICOSURIC DIURETIC, MAJOR METABOLITE, ^{14}C-LABELED ENANTIOMERS.

The (aryloxy)acetic acid diuretics, e.g., ethacrynic acid, evolved from the classic mercurial agents, mersalyl and merbaphen.[1] Recently, this diuretic class reached a new level of interest with the development of a series of (1-oxo-5-indanyloxy)acetic acids which possess both uricosuric (i.e., uric acid excreting) and salidiuretic properties. One series member, MK-196[2], 1, is currently undergoing extensive clinical evaluation.

During metabolism studies in monkeys,[3] in chimpanzees[4] and in man,[5] 1 was converted primarily to the 2-(4-hydroxyphenyl) derivative. In subsequent metabolism studies, the enantiomers of 1 displayed qualitative differences in their pharmacokinetic parameters.[6] To quantitate this data it was required that both enantiomers of 1 and the corresponding 2-(4-hydroxyphenyl) metabolites[2] be ^{14}C-labeled. The resolutions of radiolabeled 1 and 2, although feasible, would have been inefficient since resolution yields for these racemates are in the 30-60% range.

During the course of investigating synthetic routes to (1-oxoindanyloxy)acetic acid diuretics it was observed that the pyridine hydrochloride scission of the 5-methyl ether to provide the 5-indanol served equally well to cleave the (6,7-dichloro-5-indanyloxy)-acetic acids (Scheme I; 1, 2 ⟶ 3, 4) to the same indanols. Although this reaction has not been thoroughly investigated, cursory experiments indicate that it is specific

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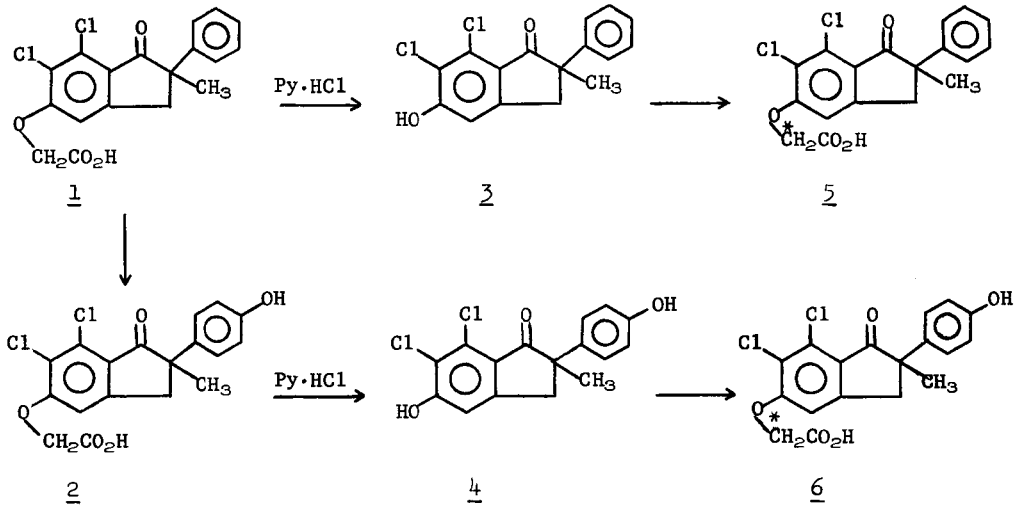
to the 6,7-dichloro-substituted compounds, since similar compounds, e.g., the 6-chloro, 7-chloro and 6,7-dimethyl substituted compounds were refractory to this cleavage.

Therefore, to conserve ^{14}C-labeled substrates, both 1 and 2 were resolved with chiral α-methylbenzylamine salts, converted to the corresponding carboxylic acids, cleaved to the precursor 5-indanols with pyridine hydrochloride and then re-alkylated with a ^{14}C-labeled haloacetic acid ester.

Although several suitable routes for the conversion of phenols to phenoxyacetic acids were available[7], we have found that alkylation of the 5-indanol with a haloacetic acid ester in a dipolar aprotic solvent (such as dimethylformamide) in the presence of potassium carbonate at ~ 55°C followed by a "same pot" hydrolysis of the ester with aqueous sodium hydroxide provided high yields of chemically and isotopically pure (indanyloxy)acetic acids.

The precursor of the MK-196 metabolite, 1-oxo-2-(4-hydroxyphenyl)-2-methyl-6,7-dichloro-5-indanol is a bis-phenolic compound. We had observed a difference of more than four pKa units (5.52 and 9.95) between the two hydroxy groups and this predicted the selective carbomethoxyalkylation of the desired 5-hydroxy group with retention of the 2-(4-hydroxyphenyl) substituent. When careful stoichiometry was observed, this prediction was experimentally confirmed.

SCHEME I



EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Non-radioactive intermediates were analyzed for the elements carbon and hydrogen and the analytical results obtained are within 0.4% of the theoretical values. The melting points of the (+) and (-) optical isomers of 1 are identical as are those of their metabolites; the specific rotations are equal and opposite in sign. Analytical TLC was carried out on 5 X 20 cm glass plates precoated with silica gel 60 F-254 (E. Merck, Darmstadt, Germany). Radioactive zones were determined by autoradiography. Radioactivity was determined with a Packard Tri-Carb Model 3320 liquid scintillation spectrometer, using 0.4% Omnifluor® in toluene/ethanol (7:3) as scintillator medium. Purity and specific activity of the methyl bromoacetate-2-^{14}C was taken as stated by the supplier.

Optical purity was determined on a Varian SC-300 superconducting NMR spectrometer using the chiral shift reagent, tris [(3-heptafluorobutyryl)-d-camphorato]europium (III) [Eu(hfbc)$_3$]. The 2-methyl substituent was used as the analytical signal. Under comparable conditions, a separation of 15 Hz was observed for the enantiomeric 2-methyls in the racemate.

Detailed experimental procedures are given for only one isomer; the isomer of opposite rotation in each case was obtained by converting the partially resolved isomer in the filtrate of the chiral salt to the oxyacetic acid then, using the chiral base of opposite rotation, forming the salt and recrystallizing it to optical purity.

(-)[6,7-Dichloro-2-(4-hydroxyphenyl)-2-methyl-1-oxo-5-indanyloxy]acetic acid. [(-) 2]. To a warm solution of 50 g, (0.131 mole) of the racemic compound 2 in 2-propanol (750 mL) was added d-(+)-α-methylbenzyl amine (15.9 g, 0.131 mole). After allowing the reaction mixture to age overnight, the crystals were filtered, rinsed with 2-propanol and dried to give 40 g of the partially resolved salt (mp, 230-2°C). The salt was dissolved in warm water (400 mL) with sufficient 10N sodium hydroxide to effect solution, then filtered into vigorously stirred, cold dilute hydrochloric acid. The partially resolved acid was reconverted to the salt in 2-propanol (750 mL), aged overnight, filtered and dried to give 26 g of optically pure salt (mp, 238°C) which provided 20.5 g (82%) of pure (-) 2 (mp, 253°C). $[\alpha]_D^{25}$ = -108° (C = 1, acetone).

(-)-6,7-Dichloro-5-hydroxy-2-methyl-2-phenyl-1-indanone. [(-) 3]. Pyridine hydrochloride (20 g) was fused in an oil bath at 190°C. To it was added, with stirring (-)-(6,7-dichloro-2-methyl-1-oxo-2-phenyl-5-indanyloxy)acetic acid (2.0 g, 5.5 mmoles). The reaction mixture was heated at 180-190°C for 1 1/2 h and poured into crushed ice-water to precipitate 1.55 g (92%) of (-) 3 (mp, 216-9°C) $[\alpha]_D^{25}$ = -57.5° (C ▫ 2, acetone).

(-)-6,7-Dichloro-5-hydroxy-2-(4-hydroxyphenyl)-2-methyl-1-indanone. [(-) 4]. To a stirred, fused sample of pyridine hydrochloride (6 g) was added (-) 2 (530 mg, 1.39 mmoles). The reaction mixture was heated at 175-185°C for 3/4 h then poured into crushed ice-water. The crude product was recrystallized from EtOAc-BuCl to give 320 mg (71%) of (-) 4, (mp, 210-6°C).

(-) (6,7-Dichloro-2-methyl-1-oxo-2-phenyl-5-indanyloxy)acetic acid -α-^{14}C. [(-) 5]. A mixture of (-) 3 (589 mg, 1.92 mmoles) K_2CO_3 (331 mg, 2.4 mmoles), methyl bromoacetate -2-^{14}C (49 mg, 6 mCi)[8] and unlabeled methyl bromoacetate (328 mg, 2.14 mmoles) in dimethylformamide (5 mL) was heated at 55-60°C for 2 h with vigorous stirring in an inert atmosphere. To the reaction mixture was added H_2O (5 mL) and 10N NaOH (0.7 mL) and heating was continued for 2 h at 90°C. The aqueous DMF solution was poured into cold dilute HCl, extracted with Et_2O which was washed with water and brine then dried over $MgSO_4$. The ether was evaporated in a stream of N_2 and the residue crystallized from toluene (10 mL) to give 458 mg (65%) of (-) 5 with a S.A. of 3.24 μCi/mg (mp, 164°C).

(-)-[6,7-Dichloro-2-(4-hydroxyphenyl)-2-methyl-1-oxo-5-indanyloxy]acetic acid -α-^{14}C. [(-) 6]. A mixture of (-) 4 (300 mg, 0.93 mmole), K_2CO_3 (133 mg, 0.96 mmoles) methyl bromoacetate-2^{14}C (49 mg, 6 mCi) and unlabeled methyl bromoacetate (111 mg, 0.73 mmoles; 0.98 mmoles total ester) in DMF (3 mL) was heated at 55-60°C with stirring for 3/4 h then treated with H_2O (4 mL) and 10N NaOH (0.25 mL), heated at 90°C for 1 h and poured into cold dilute HCl. The aqueous mixture was extracted with Et_2O, washed with water, dried over $MgSO_4$ and the Et_2O evaporated with a stream of N_2. Two recrystallizations from AcOH (8 mL and 5 mL) gave 89 mg (25%) of (-) 6 at an S. A. of 7.9 μCi/mg (mp, 251-3°C).

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