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Synthesis and Antihypercholesterolemic Activity of α-Alkyl Substituted Indan-1-acetic acids

MANORANJAN ADAK* and JAYANTA KUMAR GUPTA†
Department of Biochemistry, National Medical College & Teaching Hospital
Birgunj, Nepal
E-mail: manoranjanadak@rediffmail.com

Non-methoxy and methoxy indan derivatives having alkyl groups at the α-carbon atom of acetic acid moiety were synthesized from their respective indan-1-acetic acids. The chemical structures of the synthesized compound were confirmed by spectral analysis. The synthesized compounds on screening for antihypercholesterolemic activity in male albino Charles Foster rats were used in this study. It has been observed that the pharmacological activity of the synthesized compounds decreases on increasing the α-alkyl chain.

Key Words: Synthesis, Antihypercholesterolemic agent, α-alkyl indanyl acetic acid.

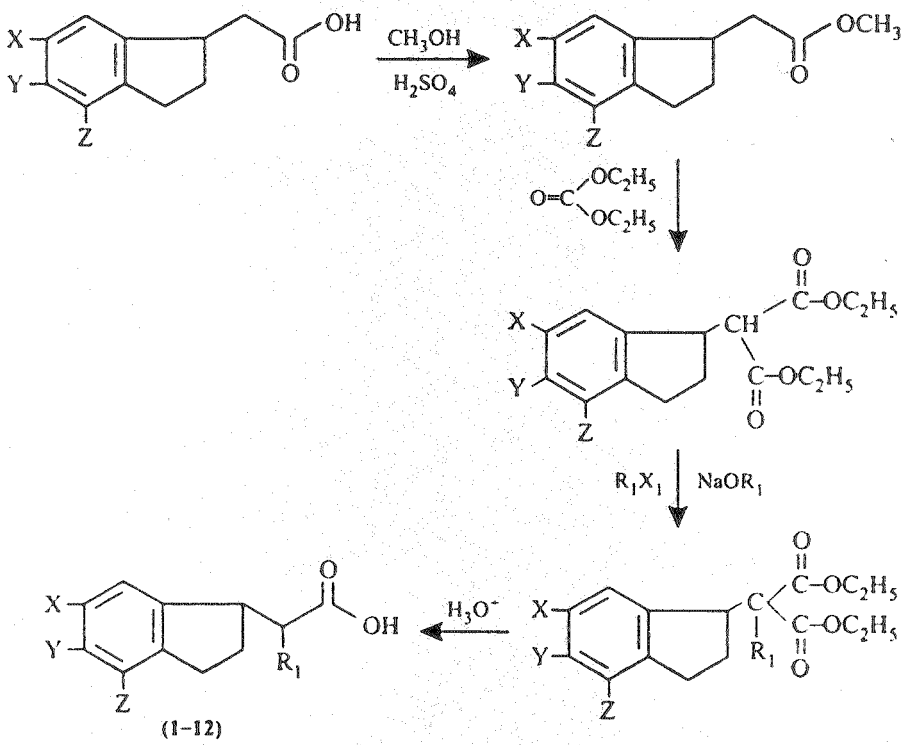
INTRODUCTION

A number of clinically useful non-steroidal antihyperlipidemic drugs are now in the market each having its own limitation for continuous administration in the treatment of patients suffering from hypercholesterolemia[1]. Several workers have reported a series of aryl alkanoic acids having non-steroidal antihyperlipidemic activity[2, 3]. Furthermore, some biphenyl acetic acids with methyl group in α-position were reported as antihyperlipidemic agents with low toxicity[4]. Indan acids which belong to the class of aryl alkanoic acids were reported to possess various biological activities[5, 6]. Simple and methoxy substituted indan acids were synthesized, screened for biological activity and extensively investigated in our laboratory in the field of oral hypoglycemic[7], anti-inflammatory[8, 9], prostaglandin biosynthesis inhibitory[10] and plant growth regulatory activities[11]. Lahiri *et al.*[12] reported a number of simple and methoxy substituted indan-1-acetic acids which exhibited varying degrees of cholesterol lowering activity but none of them was superior to standard drug clofibrate. Low toxicity and low ulcerogenicity of the indan acids were also reported[13]. We, therefore, undertook the synthesis of methoxy substituted α-alkyl indan-1-acetic acids with an expectation of better anti-hypercholesterolemic activity. The present communication deals with the synthesis of the α-alkyl indan-1-acetic acids starting from the corresponding indan-1-acetic acids[14]. Synthesis of the title compounds was carried out following the **Scheme-I** given below:

†Department of Pharmaceutical Technology, Division of Medicinal Chemistry, Jadavpur University, Kolkata-700 032, India, E-mail: jkgjpt@yahoo.co.in

EXPERIMENTAL

Melting points of synthesized compounds were determined in open capillaries in an ADCO melting point apparatus and are uncorrected; preheated baths were used for compounds which melted with decomposition. Identity and purity of the compounds were ascertained by elemental microanalysis and spectral analysis. UV, IR and NMR spectral data were recorded on a Hitachi 200-20 UV-Vis spectrophotometer, a Perkin–Elmer Infracord 297 spectrophotometer and a Jeol-JNM-FX-100 FT-NMR spectrometer, respectively. Spectral data of all the compounds gave characteristic bands[15, 16]. Elemental microanalysis of all compounds conformed well with their proposed structure.



where, X = Y = Z = H, X = Z = H, Y = OCH_3, X = Y = OCH_3, Z = H,
R_1 = CH_3 · C_2H_5 · C_3H_7 · C_4H_9 and X_1 = Br, I

Scheme I

The key intermediate, indan-1-acetic acid (1) was synthesized by the general method of cyclodehydration with polyophosphoric acid of the corresponding β-phenylglutaric acids and subsequent reduction of the resulting indan-3-keto-1-acetic acids by the Clammensen method as reported earlier[17].

2-Methyl-2-(indan-1-yl) acetic acid (1): Sodium alkoxide solution was prepared by adding absolute methanol (50 mL) with metallic sodium (0.8 g) under mild reflux. 5.7 g (0.03 mol) of indan-1-yl-methyl acetate (b.p. = 118–120°C at 1.2 mm of Hg, n^{29} = 1.5136) dissolved in absolute methanol (50 mL) was added dropwise to this alkoxide solution over a period of 1 h under mild reflux and reflux was continued for 6 h. The mixture of diethyl carbonate (3.5 g, 0.03 mole) and absolute methanol (50 mL) was then added to the refluxing solution over a period of 1 h with stirring; the entire mixture was then refluxed for another 6 h. 4.3 g (0.03 mole) of

methyl iodide dissolved in absolute methanol (50 mL) was added dropwise over a period of 3 h under mild reflux with stirring and refluxing was then continued for another 24 h. The reaction mixture was then cooled to room temperature and triturated with H_2O. The solvent was distilled off and the residual ester was extracted thoroughly with benzene (3 × 200mL). Benzene layer was washed with successive quantities of H_2O, 0.2 M HCl, dil. $NaHCO_3$ (100 mL) solution and finally washed free of alkalinity. Acid free benzene layer was then dried over anhydrous sodium sulphate. On the subsequent day, benzene was distilled off and the crude ester was acidified with ice cold 6 N HCl (50 mL) and then refluxed for 12 h. This acidified ester solution was diluted by adding distilled water (100 mL), boiled for 1 h and kept in freeze overnight. The precipitated acid was filtered and recrystallized from aqueous EtOH using decolourising charcoal. Yield 4.3 g (75%), m.p. = 59–60°C. (Found: C, 75.63; H, 7.42%; $C_{12}H_{14}O_2$ requires: C, 75.79; H, 7.3%); λ_{max} (CH_3OH) at 260 nm; ν_{max} (nujol) OH of COOH at 3392 cm^{-1}, —CH_2—CH_2— at 2940 cm^{-1} and C=O of COOH at 1625 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 2.40 (2H, m, 2′-CH_2); 2.80 (2H, quin, 3′-CH_2); 4.73 (1H, t, 1′-CH) and 7.20 (4H, s, ArH).

2-Ethyl-2-(indan-1-yl)-acetic acid (2): A solution of indanyl methyl acetate (5.7 g, 0.03 mol) was dissolved in absolute ethanol (50 mL). To this solution sodium alkoxide (50 mL) solution was added, with stirring, under mild reflux condition. Ethyl bromide (3.3 g, 0.03 mole) as an alkylating agent in absolute ethanol (50 mL) was added to the ester solution over a period of 4 h under reflux with stirring and reflux continued for 24 h. Extraction and purification were done as per earlier procedure. Yield 4.2 g (68%), m.p. = 61–62°C. (Found: C, 76.61; H, 7.32%; $C_{13}H_{16}O_2$ requires: C, 76.40; H, 7.84%); λ_{max} (CH_3OH) at 261.5 nm; ν_{max} (nujol) OH of COOH at 3388 cm^{-1}, —CH_2—CH_2— at 2940 cm^{-1} and C=O of COOH at 1622 cm^{-1}.

2-*n*-Propyl-2-(indan-1-yl)-acetic acid (3): A solution of indanyl methyl acetate (5.7 g, 0.03 mol) in 95% *n*-propanol (50 mL) was added slowly to alkoxide solution under mild reflux with constant stirring; *n*-propyl bromide (3.3 g, 0.03 mol) as an alkylating agent was added to the ester solution over a period of 5 h under mild reflux with slow stirring. After completion of addition the whole mixture was refluxed continuously for 24 h with stirring. The entire extraction and recrystallization were then followed as described earlier to provide the pure product. Yield 4.2 g (60%); m.p. 62.5–63.5°C. (Found: C, 77.40; H, 8.02%; $C_{14}H_{18}O_2$ requires: C, 77.06; H, 8.26%); λ_{max} (CH_3OH) at 263 NMR; ν_{max} (KBr) OH of COOH at 3386 cm^{-1}, —CH_2—CH_2— at 2941 cm^{-1} and C=O of COOH at 1620 cm^{-1}.

2-*n*-Butyl-2-(indan-1-yl)-acetic acid (4): The corresponding ester (5.7 g, 0.03 mol) in 95% *n*-butanol (50 mL) was added to alkoxide solution under mild reflux with constant stirring. The alkylating agent, *n*-butyliodide (5.5 g, 0.03 mol) was taken in 95% *n*-butanol (50 mL) and the mixture was added very slowly over a period of 6 h with stirring. The resulting compound was extracted as per earlier method and recrystallized from alcohol-water (1 : 4) mixture. Yield, 4 g (56%); m.p. 63–64°C. (Found: C, 77.09; H, 8.91%; $C_{15}H_{20}O_2$ requires: C, 77.58; H, 8.62%); λ_{max} (H_2O) at 264 nm, ν_{max} (KBr) OH of COOH at 3382 cm^{-1}, —CH_2—CH_2— at 2941 cm^{-1} and C=O of COOH at 1615 cm^{-1}.

2-Methyl-2-(6′-methoxy indan-1-yl)-acetic acid (5): 6′-Methoxy indan-1-yl-methyl acetate (b.p. 156–158°C at 2 mm of Hg, n^{29} = 1.5173), 6.6 g (0.03 mol)

was dissolved in absolute methanol (50 mL) by warming. To this warm solution sodium alkoxide (50 mL) solution was added over a period of 1 h under mild reflux and reflux was allowed for 6 h. A mixture of diethyl carbonate (3.5 g, 0.03 mol) in methanol (50 mL) and methyl iodide (4.3 g, 0.03 mol) in methanol (50 mL) were added dropwise over a period of 3 h with mild reflux and stirring. When the addition was complete, the solution was heated under reflux with constant stirring for 1 d. The resulting mixture was partitioned between benzene (150 mL) and water (150 mL). After separation of phase, the aqueous layer was reextracted with benzene (3 × 150 mL) and the combined organic extracts were washed successively with 0.2 M HCl (200 mL) and water (200 mL) and saturated sodium bicarbonate solution (3 × 150 mL). The benzene solution was dried over anhydrous sodium sulphate, filtered and distilled. The crude product was crystallized from aqueous-ethanol. Yield, 4.9 g (70%); m.p. = 85–87°C. Found: C, 70.50; H, 7.51%; $C_{13}H_{16}O_3$ requires: C, 70.90; H, 7.31%; λ_{max} (H_2O) at 275 nm; ν_{max} (nujol) OH of COOH at 3400 cm^{-1}; —CH_2—CH_2— at 2950 cm^{-1}; C=O of COOH at 1725 cm^{-1} and OCH_3 at 1181 cm^{-1}. ^1H NMR ($CDCl_3$, δ); 2.52 (2H, m, 2′-CH_2); 2.94 (2H, quin, 3′-CH_2); 4.75 (1H, t, 1′-CH); 3.68 (3H, s, 6′-OCH_3); 6.75 (1H, s, 7′-ArH); 6.80(1H, d, 5′-ArH) and 7.20 (1H, d, 4′-ArH).

2-Ethyl-2-(6′-methoxy indan-1-yl) acetic acid (6): The methoxy ester (6.6 g, 0.03 mole) was dissolved in dry ethanol (50 mL); to it was added stepwise a sodium alkoxide (50 mL) solution and diethyl carbonate (3.5 g, 0.03 mol). The reaction was refluxed with stirring for 6 h. Ethyl bromide (3.3 g, 0.03 mol) was used as an alkylating agent and the same procedure was followed as described earlier. Purification as well as crystallization was done from alcohol-water. Yield 5 g (66%); m.p. = 88–88.5°C. (Found: C, 71.54; H, 7.36%; $C_{14}H_{18}O_3$ requires: C, 71.79; H, 7.69%); λ_{max} (H_2O) at 277 nm; ν_{max} (nujol) OH of COOH at 3401 cm^{-1}; —CH_2—CH_2— at 2951 cm^{-1}; C=O of COOH at 1723 cm^{-1} and OCH_3 at 1191 cm^{-1}.

2-*n*-Propyl-2-(6′-methoxy indan-1-yl) acetic acid (7): It was synthesized from the corresponding ester (5.7 g, 0.03 mol) by adding diethyl carbonate and *n*-propyl iodide (5 g, 0.03 mol) as an alkylating agent under reflux with stirring and the same reaction procedures was followed as described for compound **3**. Yield 5 g (63%); m.p. = 89–90°C. (Found: C, 77–19; H, 8.31%; $C_{15}H_{20}O_3$ requires: C, 77.58; H, 8.06%); λ_{max} (CH_3OH) at 277 nm, ν_{max} (nujol) OH of COOH at 2228 cm^{-1}, —CH_2—CH_2— at 2950 cm^{-1}; C=O of COOH at 1720 cm^{-1} and OCH_3 at 1183 cm^{-1}.

2-*n*-Butyl-2-(6′-methoxy indan-1-yl) acetic acid (8): Compound **8** was prepared from the respective ester with *n*-butyl iodide (5.5 g, 0.03 mol) used as an alkylating agent under continuous refluxing for 24 h with stirring as per the reaction procedure compound **4**. Yield 4.8 g (57%), m.p. = 90–91°C. (Found C, 72.18%; H, 8.09%; $C_{16}H_{22}O_3$ requires: C, 73.28%; H, 8.39%); λ_{max} (CH_3OH) at 278 nm; ν_{max} (nujol) OH of COOH at 3333 cm^{-1}; —CH_2—CH_2— at 2950 cm^{-1}, C=O of COOH at 1715 cm^{-1} and OCH_3 at 1185 cm^{-1}.

2-Methyl-2-(5′,6′-dimethoxy indan-1-yl) acetic acids (9): (7.5 g, 0.03 mole) of 5′,6′-dimethoxy indan-1-yl methyl acetate (b.p. = 163–164°C at 0.8 mm of Hg, n^{29} = 1.5280) was reacted in equimolar ratio with diethyl carbonate and methyl iodide under reflux and was worked up as per procedure of compound **5** to give the desired compound **9**. Yield 5.0 g (67%); m.p. = 180–181°C. (Found: C, 68.04; H, 7.61%; $C_{14}H_{18}O_4$ requires: C, 68.18; H, 7.57%); λ_{max} (H_2O) at 280 nm; ν_{max} (KBr)

OH of COOH at 3445 cm^{-1}; —CH_2—CH_2— at 2955 cm^{-1}; C=O of COOH at 1710 cm^{-1} and OCH_3 at 1182 cm^{-1}. ^1H NMR ($CDCl_3$, β); 2.45 (2H, m, 2′-CH_2); 2.88 (2H quin 3′-CH_2); 4.75(1H, t, 1′-CH); 3.65 (3H, s, 6′-OCH_3); 3.75 (3H, s, 5′-OCH_3); 6.66 (1H, s, 7′-ArH) and 7.20 (1H, d, 4′-ArH). M^+ of methyl ester at 264, 250, 238, 223, 190.

2-Ethyl-2-(5′,6′-dimethoxy indan-1-yl) acetic acid (10): A mixture of corresponding ester (7.5 g, 0.03 mol), ethyl iodide (3.3 g, 0.03 mol) was refluxed for 24 h and was worked up as reaction procedure described under compound **6**. Yield 5.2 g (66%); m.p. = 181.5–182.5°C. (Found: C, 68.40; H, 7.60%; $C_{15}H_{20}O_4$ requires: C, 68.18; H, 7.57%); λ_{max} (H_2O) at 280 nm; ν_{max} (KBr) OH of COOH at 3444 cm^{-1}; —CH_2—CH_2— at 2954 cm^{-1}; C=O of COOH at 1712 cm^{-1}; and OCH_3 at 1180 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 2.50 (2H, m, 2′-CH_2); 2.89 (2H, quin, 3′-CH_2); 4.76 (1H, t, 1′-CH); 3.68 (3H, s, 6′-OCH_3); 3.74 (3H, s, 5′-OCH_3)· 6.68 (1H, s, 7′-ArH) and 7.18(1H, d, 4′-ArH).

2-*n*-Propyl-2-(5′,6′-dimethoxy indan-1-yl) acetic acid (11): (7.5 g, 0.03 mol) of corresponding ester was reacted with equimolar of diethyl carbonate and propyl iodide as an alkylating agent by following reaction procedure of compound 7. Yield 4.7 g (57%); m.p. = 183–184°C. (Found: C, 68.94; H, 7.86%; $C_{16}H_{22}O_4$ requires: C, 69.09, H, 7.91%); λ_{max} (H_2O) at 281 nm; ν_{max} (KBr) OH of COOH at 3443 cm^{-1}, —CH_2—CH_2— at 2953 cm^{-1}, C=O of COOH at 1714 cm^{-1} and OCH_3 at 1175 cm^{-1}.

2-*n*-Butyl-2-(5′,6′-dimethoxy indan-1-yl) acetic acid (12): The title compound **12** was obtained from the respective methyl ester (7.5 g, 0.03 mol) following the same reaction sequence as described earlier by using *n*-butyl iodide (5.5 g, 0.03 mol) as an alkylating agent. Yield 4.7 g (54%); m.p. = 185–186°C. (Found: C, 69.43; H, 8.12%; $C_{17}H_{24}O_4$ requires: C, 69.86; H, 8.21%); λ_{max} (H_2O) at 282 nm; ν_{max} (KBr) OH of COOH at 3440 cm^{-1}; —CH_2—CH_2— at 2953 cm^{-1}; C=O of COOH at 1714 cm^{-1} and OCH_3 at 1172 cm^{-1}.

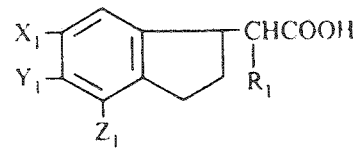
Pharmacology

The synthesized compounds were screened for antihypercholesterolemic activity in normogenic animal model. Male albino Charles Foster rats weighing 120 ± 10 g were used for pharmacological studies. After acclimatization for 7 d, the test compounds and the reference standard clofibrate were administered by oral route dissolved in aqueous alkali for 14 d. Blood samples were collected in non-heparinised microcapillary tube by tail vein bleeding. After clotting, centrifugation was performed at 1800 rpm for 10 min to separate the serum and total serum cholesterol level was measured by the method of Sperry[18]. At the end of experimental period, animals were sacrificed. Liver samples were taken out, washed with saline and dried by soaking with filter paper and total liver cholesterol was also assessed by the procedures of Folch[19].

RESULTS AND DISCUSSION

Conversion of the respective indane acetic acid esters to the corresponding α-substituted alkyl derivatives followed by hydrolysis of the final ester to the α-alkyl indane acetic acid could be done effectively by the present method. Yield obtained in each case was satisfactory.

TABLE-1
EFFECT OF INDAN DERIVATIVES ON SERUM CHOLESTEROL, LIVER WEIGHT AND LIVER CHOLESTEROL IN NORMOGENIC RATS



Compd. No.	Dose (mg/kg)	X_1	Y_1	Z_1	R_1	Serum cholesterol (mg %) (X ± SEM), $n = 6$			Liver weight (mg %) (X ± SEM), $n = 6$	Liver cholesterol (mg %) (X ± SEM), $n = 6$
						0 day	14th day	% decrease	14th day	14th day
1	50	H	H	H	CH_3	76.50 ± 0.43	67.16 ± 0.32	11[b]	5.30 ± 0.22	3.30 ± 0.21
2	50	H	H	H	C_2H_5	79.83 ± 0.48	72.50 ± 0.62	9[c]	5.89 ± 0.13	2.50 ± 0.22
3	50	H	H	H	C_3H_7	78.66 ± 0.70	72.66 ± 0.76	8[c]	5.80 ± 0.22	3.00 ± 0.36
4	50	H	H	H	C_4H_9	77.06 ± 0.42	72.00 ± 0.82	7	5.30 ± 0.10	2.33 ± 0.21
5	50	OCH_3	H	H	CH_3	79.00 ± 0.60	67.67 ± 0.99	14[a]	5.50 ± 0.08	2.60 ± 0.30
6	50	OCH_3	H	H	C_2H_5	81.00 ± 0.58	71.16 ± 0.70	12[b]	5.50 ± 0.05	3.00 ± 0.50
7	50	OCH_3	H	H	C_3H_7	82.00 ± 0.58	75.66 ± 0.84	8[c]	5.80 ± 0.18	2.50 ± 0.30
8	50	OCH_3	H	H	C_4H_9	78.50 ± 0.76	73.00 ± 0.77	7	5.75 ± 0.07	2.20 ± 0.10
9	50	OCH_3	OCH_3	H	CH_3	78.66 ± 0.67	62.18 ± 0.60	21[a]	5.30 ± 0.07	3.00 ± 0.50
10	50	OCH_3	OCH_3	H	C_2H_5	76.50 ± 0.43	63.50 ± 0.60	17[a]	5.60 ± 0.20	3.00 ± 0.50
11	50	OCH_3	OCH_3	H	C_3H_7	76.83 ± 0.48	70.83 ± 0.60	8[c]	5.50 ± 0.18	2.33 ± 0.21
12	50	OCH_3	OCH_3	H	C_4H_9	76.83 ± 0.95	69.00 ± 0.37	7	5.60 ± 0.21	2.50 ± 0.30
Clofibrate	50					77.00 ± 0.52	63.00 ± 0.52	18[a]	6.50 ± 0.21	2.80 ± 0.10
Control						76.50 ± 0.43	80.17 ± 0.48	+ 5	5.70 ± 0.90	2.90 ± 0.10

a-c Probability values (calculated as compared to zero day within group using student's t-test for pair set) a < 0.001, b < 0.01, c < 0.05.

Preliminary studies on the methoxy substituted α-alkyl indan-1-acetic acids (Table-1) exhibited varying degree of antihypercholesterolemic activity when compared with clofibrate. Two compounds **8** and **9** having methyl and ethyl group respectively at α-position of the acetic acid moiety had shown better cholesterol lowering activity. No change of liver weight and free cholesterol in liver were observed. Detailed pharmacological evaluation results will be communicated elsewhere.

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