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Studies on Trimethoxy Indan-1-yl-acetic Acids as Anti-hyperchlestrolemic Agents

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Trimethoxy indan derivatives having (R = alkyl group) at the α-carbon atom of acetic acid moiety were synthesized and screened for anti-hypercholesterolemic activity in male albino Charles Foster rats. It was observed that percentage yield as well as pharmacological activity of synthesized compounds decreased on increasing the α-alkyl group.

Key Words: Trimethoxy indan acetic acids, Clofibrate, Antihypercholesterolemic activity.

INTRODUCTION

Indan ring moiety having a peculiar combination of two nuclear protons was reported to possess significant pharmacological potentialites[1-3] and by suitable structural variation it was found to exhibit various pharmacological response[4,5]. Lahiri *et al.*[6] reported anti-hypercholesterolemic activity among a number of simple and methoxy substituted indan acids. Recently, we reported the smaller alkyl group ($-CH_3$, $-C_2H_5$) at α-carbon to the acetic acid moiety exhibited blood cholesterol lowering activity[7]. A logical extension of the above work was to explore anti-hypercholesterolemic activity among various synthetic compounds in order to ascertain whether trimethoxy substitution in the indan ring alone or subsequent α-alkyl substitution in the side chain leads to compound with better anti-hypercholesterolemic activity. The present works deal with the synthesis of the desired compound from their corresponding indan-1-acetic acids. These compounds were also subjected to anti-hypercholesterolemic screening test to normo and hyperlipidemic animal models.

EXPERIMENTAL

Indan acids were mostly prepared by cyclodehydration of the corresponding aryl-alkanoic diacids[8]. Melting points were determined by Adco capillary apparatus and were uncorrected. Identity and purity of the

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compound were ascertained by elemental micro analysis and spectral analysis. Spectral data of the compound gave characteristic bands of their respective functional groups[9-11]. Elemental microanalysis of all the compounds confirmed well with their proposed structures. Synthesis of the test compound was carried out by the following **Schemes I** and **II**.

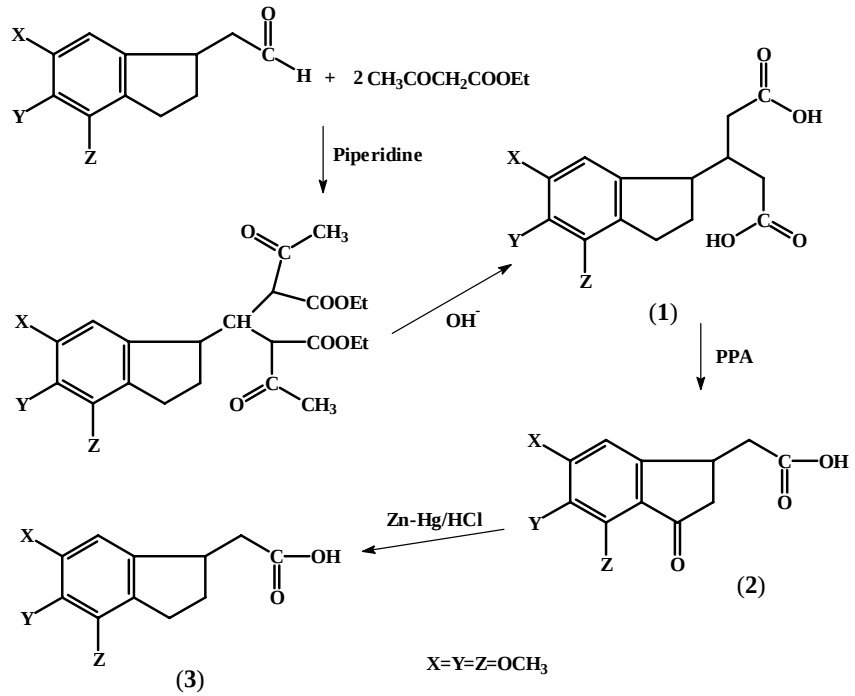
Synthesis

β-(3′,4′,5′-Trimethoxy phenyl)glutaric acid (1): Trimethoxy benzaldehyde (30 g, 0.16 mol) was condensed with ethyl acetoacetate (41 g, 0.32 mol) in presence of piperidine to give bis(acetoacetate) which was subsequently hydrolyzed by alcoholic potassium hydroxide under mild reflux. Alcohol was then removed by distillation and aqueous layer was acidified by cold hydrochloric acid to prove 3′,4′,5′-trimethoxy phenylglutaric acid. It was crystallized from water to give 32 g of the desired product which melted at 186-187ºC. Anal. Found (Calcd.) % for $C_{14}H_{18}O_7$: C 55.75 (56.38), H 5.95 (6.04), λ_{max} (CH_3OH) 260 nm.

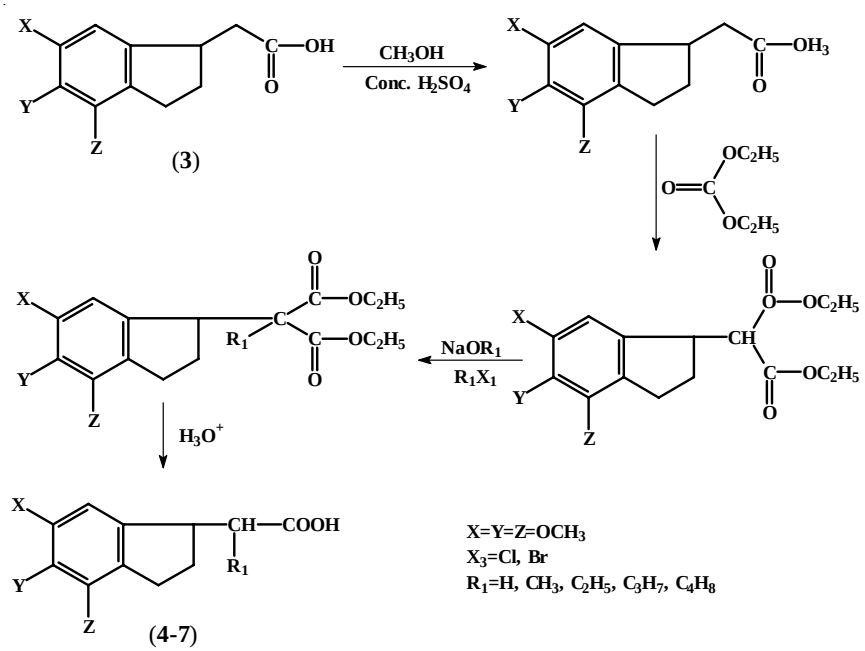
4′,5′,6′-Trimethoxy-3-oxo-indan-1-acetic acid (2): Finally powdered β-(3′,4′,5′-trimethoxy phenyl)-glutaric acid (30 g, 0.1 mol) was mixed thoroughly with polyphosphoric acid (PPA) 300 g and heated in water bath for 4 h with occasional shaking. The dark red mass was poured in crushed ice and extracted with chloroform. The solvent was removed by distillation and the solid residue was purified by crystallization from hot water, yield = 21 g (70 %) m.p. 179-180ºC. Anal. Found (Calcd.) % for $C_{14}H_{16}O_6$: C 59.50 (60.00) H 5.61 (5.71), λ_{max} (CH_3OH) at 272 nm, ν_{max} (KBr, cm^{-1}) OH of COOH at 3390, OCH_3 at 1193, C = O of COOH at 1720.

4′,5′,6′-Trimethoxy-indan-1-acetic acid (3): Trimethoxy keto acid (10 g, 0.04 mol) was reduced by classical method using zinc amalgam and conc. hydrochloric acid to 4′,5′,6′-trimethoxy-indan-1-acetic acid and crystallized from hot water with decolouring charcoal to give the pure product, yield = 8 g (80 %) m.p. 105-106ºC, Anal. Found (Calcd.) % for $C_{14}H_{18}O_5$: C 62.90 (63.65), H 6.70 (6.87), λ_{max} (CH_3OH) at 284 nm, ν_{max} (KBr, cm^{-1}) OH of COOH at 3391, OCH_3 at 1208, C = O of COOH at 1725, ^{1}H NMR ($CDCl_3$, δ) 2.50 (2H, m, 2-CH_2), 2.88 (2H, quin, 3′-CH_2), 3.65 (3H, s, 6′-OCH_3), 3.75 (3H, s, 5′-OCH_3), 3.50 (3H, s, 4′-OCH_3), 6.74 (1H, s, 7′-ArH).

2-Methyl-2-(4′,5′,6′-trimethoxy-indan-1-yl)-acetic acid (4): 5.4 g (0.03 mol) of 4′,5′,6′-trimethoxy-indan-1-yl-methyl acetate (m.p. 90ºC) was refluxed with 0.8 g of metallic sodium in absolute alcohol under mild reflux and 3.5 g (0.03 mol) of diethyl carbonate was then added and refluxing was continued for 6 h. To the resulting malonate ester, 4.3 g (0.03 mol) of methyl iodide in absolute methanol was slowly added in anhydrous medium and refluxing was continued for 24 h. The solvent was distilled



Scheme-I



Scheme-II

off and the residual ester was extracted in benzene and benzene was distilled out. The crude ester so obtained was refluxing with 6 N HCl (50 mL) for 12 h. The percipitate was filtered and recrystallized from alcohol-water, yield 3.5 g (63 %), m.p. 109-109.5ºC, Anal. Found (Calcd.) % for $C_{15}H_{20}O_5$: C 64.42 (64.44), H 7.00 (7.14), λ_{max} (H_2O) at 281 nm, ν_{max} (KBr, cm^{-1}) OH of COOH at 3340, $–CH_2– CH_2$ at 2956, C = O of COOH at 1718 and OCH_3 at 1188, ^1H NMR ($CDCl_3$, δ), 2.51 (2H, m, 2´-CH_2), 2.90 (2H, quin, 3´-CH_2), 3.66 (3H, s, 6´-OCH_3), 3.78 (3H, s, 5´-OCH_3), 3.81 (3H, s, 4´-OCH_3), 3.74 (1H, s, 7´-ArH).

2-Ethyl-2-(4´,5´,6´-trimethoxy-indan-1-yl)acetic acid (5): The compound was obtained from the corresponding ester following the same procedures as described for earlier compound by using ethyl bromide (3.3 g, 0.03 mol) as an alkylating agent, yield 4.5 g (60 %), m.p. 110-110.5ºC, Anal. Found (Calcd.) % for $C_{16}H_{22}O_5$: C 65.21 (65.30), H 7.40 (7.48), λ_{max} (H_2O) at 282 nm, ν_{max} (KBr, cm^{-1}) OH of COOH at 3348, $–CH_2– CH_2$ at 2957, C = O of COOH at 1720 and OCH_3 at 1189, ^1H NMR ($CDCl_3$, δ), 2.52 (2H, m, 2´-CH_2), 2.92 (2H, quin, 3´-CH_2), 3.65 (3H, s, 6´-OCH_3), 3.79 (3H, s, 5´-OCH_3), 3.82 (3H, s, 4´-OCH_3), 6.75 (1H, s, 7´-ArH).

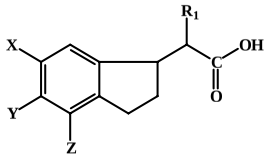
2-*n*-Propyl-2-(4´,5´,6´-trimethoxy-indan-1-yl)-acetic acid (6): The compound was prepared from the corresponding ester using *n*-propyl iodide as an alkylating agent in a similar way as mentioned earlier, yield 4.7 g (57 %), m.p. 111.5-112.5ºC, Anal. Found (Calcd.) % for $C_{17}H_{24}O_5$: C 60.00 (66.23), H 7.69 (7.79), λ_{max} (H_2O) at 283 nm, ν_{max} (KBr, cm^{-1}) OH of COOH at 3350, $–CH_2–CH_2–$ at 2955, C = O of COOH at 1722 and OCH_3 at 1189.

2-*n*-Butyl-2-(4´,5´,6´-trimethoxy-indan-1-yl)-acetic acid (7): The compound was obtained from the respective ester following the same reaction procedures as described above using *n*-butyl bromide as an alkylating agent, yield 4.3 g (50 %), m.p. 112-112.5ºC, Anal. Found (Calcd.) % for $C_{18}H_{26}O_5$: C 67.00 (67.08), H 8.00 (8.07), λ_{max} (H_2O) at 285 nm, ν_{max} (KBr, cm^{-1}) OH of COOH at 3352, $–CH_2–CH_2–$ at 2960, C = O of COOH at 1722 and OCH_3 at 1192.

Pharmacology

Groups of six normal, healthy male albino Charles Foster rats 110 ± 30 g and 130 ± 40 g body weight were used for screening of normolipidemic and hyperlipidemic activity, respectively. The test compound and standard drug clofibrate (IP) both in aqueous solution were administered orally at a dose level of 50 mg/kg for 14 d. The high cholesterol diet was prepared from normal rat food by adding 1 % cholesterol and 0.5 % sodium cholate[12]. Experimental animals were distributed at random and total serum cholesterol concentration was measured by the method of Sperry *et al.*[13].

TABLE-1
EFFECT OF SIMPLE AND α-ALKYL SUBSTITUTED TRIMETHOXY INDAN ACETIC ACIDS IN NORMO AND HYPERLIPIDEMIC RATS



Compound No.	X	Y	Z	R_1	Serum cholesterol (mg %) (X ± SEM) n = 6				Decrease (%)
					0 d	3 d	7 d	14 d	
Normolipidemic rats									
1	OCH_3	OCH_3	OCH_3	H	76.17 ± 1.31	75.33 ± 1.34	74.16 ± 1.28	72.00 ± 1.19	5.23 ± 4.03
4	OCH_3	OCH_3	OCH_3	CH_3	80.67 ± 1.20	79.16 ± 0.98	77.50 ± 1.03	74.14 ± 0.46	6.97 ± 0.47
5	OCH_3	OCH_3	OCH_3	C_2H_5	76.34 ± 1.34	76.00 ± 1.32	73.00 ± 1.32	69.50 ± 1.48	8.97 ± 0.72[a]
6	OCH_3	OCH_3	OCH_3	*n*-C_3H_7	75.67 ± 1.73	74.84 ± 1.91	74.84 ± 1.54	71.83 ± 1.95	5.10 ± 0.52
7	OCH_3	OCH_3	OCH_3	*n*-C_4H_9	79.83 ± 1.17	75.50 ± 1.09	79.50 ± 2.09	76.16 ± 1.08	4.58 ± 0.29
Clofibrate					77.00 ± 0.52	74.04 ± 0.73	70.17 ± 0.40	63.00 ± 0.58	18.17 ± 0.60[b]
Control					75.5 ± 0.43	76.83 ± 0.40	78.17 ± 0.48	80.17 ± 0.48	-4.80 ± 0.45
Hyperlipidemic rats									
1	OCH_3	OCH_3	OCH_3	H	97.34 ± 1.46	96.33 ± 1.69	95.00 ± 1.52	93.00 ± 1.68	4.12 ± 0.30
4	OCH_3	OCH_3	OCH_3	CH_3	95.16 ± 0.95	94.50 ± 0.72	92.50 ± 0.85	90.00 ± 1.16	4.87 ± 0.46
5	OCH_3	OCH_3	OCH_3	C_2H_5	95.67 ± 0.89	94.34 ± 1.23	93.17 ± 0.84	90.34 ± 0.33	5.87 ± 0.93
6	OCH_3	OCH_3	OCH_3	*n*-C_3H_7	96.16 ± 0.66	97.00 ± 0.73	95.17 ± 0.88	94.50 ± 0.72	3.74 ± 0.34
7	OCH_3	OCH_3	OCH_3	*n*-C_4H_9	97.00 ± 0.93	95.50 ± 0.80	94.50 ± 0.99	93.84 ± 1.28	3.28 ± 0.63
Clofibrate					99.33 ± 1.43	99.33 ± 1.34	98.00 ± 1.24	98.33 ± 1.44	1.34 ± 0.20
Control					98.60 ± 1.05	99.00 ± 0.98	99.33 ± 1.02	100.00 ± 0.82	-1.71 ± 1.65
Normal					79.83 ± 0.31	80.50 ± 0.56	83.33 ± 0.21	85.66 ± 0.21	-6.60 ± 0.41

[a,b] Probability values (calculated as compared to 0 day within group using student's-test for pair set) a < 0.001; b < 0.01.

RESULTS AND DISCUSSION

Synthesis of the 4´,5´,6´-trimethoxy indan-1-acetic acid and its α-alklyl substituted indan acids from their corresponding ester following hydrolysis could be done effectively by this present procedure percentage of yield in each case was satisfactory.

The pharmacological data presented in Table-1 indicated that all the test compounds showed varying degrees of activity at a dose level of 50 mg/kg. 2-Ethyl-2-(4´,5´,6´-trimethoxy-indan-1-yl)acetic acid (**5**) exhibited little better effect among their homologues but lower than that of standard compound clofibrate. No activity was shown by the test compounds as well as standard in hyperlipidemic test model. It was clear from the above result that indiscriminate chain lengthening of α-alkyl derivative would not be beneficial for pharmacology activity. Earlier work had also established that the pharmacology activity reside in a small structural frame work[4]. From these observations it seemed likely that further modification of chemical structure of the indan-1-yl-acetic acids parent compounds may improved the cholesterol lowering activity. Work in this direction is in progress and will be reported in near future.

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