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SYNTHESIS OF SOME PHENACYL NICOTINATES AS POTENTIAL ANTICHOLESTEROLEMIC AGENTS

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ABSTRACT

Three anticholesterolemic agents, 2,4- dimethoxy phenacyl nicotinium bromide, 2,5dimethosy-phenacyl-nicotinium bromide, and 2,3,6-tnbromo 35-dimethosyphenacyl-nicotinium bromide, were synthesized and their chemical structures were determined by spectroscopic method.

Introduction

This research work was carried out with the object to synthesize potential anticholesterolemic agents having phenacylamine type skeleton, as the hypercholesterolemic condition may lead to the clinical manifestations of atherosclerotic vascular diseases (Carlson, 1960, Fredrickson *et al.,* 1967, Keys, 1961 Lipid Research Clinics Program, 1984). For this purpose some derivatives of phenacyl nicotinate, having substitution at various positions of benzene ring were prepared and their anticholesterolemic activity was determined on rabbits.

Materials and Methods

General: Metler AE 100 (Switzerland) was used for weighing, Gerhart (W. Germany) water bath for heating and Electrothermal Gallenkamp apparatus (England) for determining melting point. Spectroscopic studies were carried out on Shimadzu SP UV-240 spectrophotometer with graphic printer PR-1 (Japan); IR on Jasco A-302 spectrophotometer (Japan); Mass on Finnigan MAT-312 Varian and PMR on Bruker AM-300 NMR spectrometer. Different chemicals of analytical grade were purchased from E. Merck (W. Germany) and Aldrich (England) for analysis and synthesis.

Synthesis

Compound 1: 2,4-dimethoxy-phenacyl nicotinium bromide:

Equimolar quantities of nicotinic acid (1.23 g) and 2,4-dimethoxy phenacyl bromide (2.58 g), were dissolved in 25 ml acetone in two separate flasks. The two solutions were then mixed together, refluxed for 30 minutes, the contents of flask were

filtered, washed and dried. Recrystallization of the crude product yielded dark brown crystals. The molecular weight of compound I is 381, molecular formula is CmH16O5 N Br, m.p. is 216°C, yield 67%. UV (EtOH) maximum absorption at 205, 218 and 280 ram. IR (KBr), 3400 (OH), 2900 (C-H), 1690 (C=0), 1625-1420 (C-N,C-C) cm^{1}. El-MS at m/z 381 (calc.), 301 (1%), 260, 259 (2%)b, 231 (1%), 213 (1%), 165 (100%), 150 (8%), 135 (70%), 123 (30%), 107 (28%), 92 (18%), 77 (66%). PMR is given in Table 1.

Table 1

PMR data of compound I, II, III and IV alongwith nicotinic acid 2,3-dimethoxy phenacyl bromide and 3,5-dimethoxy phenacyl bromide.

	1) Nicotinic acid	2) 2,4-dimethoxy phenacyl bromide	I	3) 3,5-dimethoxy phenacyl bromide	II	III	IV
H at C	ppm (J in Hz)	ppm (J in Hz)	ppm (J in Hz)	ppm (J in Hz)	ppm (J in Hz)	ppm (J in Hz)	ppm (J in Hz)
2	-	-	-	-	-	-	-
3		6.50,m	6.77,d (2.1)	7.30,m	7.35,m	-	-
4		-	-	6.95,m	7.35,m	-	-
5		6.50,m	6.77,dd (2.2,8.8)	6.95,m	7.35,m	-	-
6		7.90,d	7.85,d	-	-	-	--
8(CH_2)		4.60,s	3.88,s	4.60,s	2.5,*	3.85,s	2.5*
OCH_3		3.95,s	4.0,s	3.90,s	4.0,s	3.41,s	3.94,s
OCH_3		3.90,s	4.0,s	3.80,s	3.75,s	3.41,s	3.94,s
2	9.00,d (2.1)	-	9.55,s	-	9.48,s	-	9.0,d (2.1)
4	7.51,dd (4.9,8.0)	-	8.34,dd (6.1,8.0)	-	8.36,dd (6.1,8.1)	-	7.51,dd (1.8,2.1)
5	8.25,t (1.8,2.1)		9.0,d (8.1)	-	9.0,d (8.1)	-	8.25,tt (1.8,2.1)
6	8.75,dd (1.7,4.8)	-	9.22,d (6.0)	-	9.21d (6.1)	-	8.75,dd (1.6,4.8)

*Signals werenot clear due to overlapping. Spectra were recorded in DMSO-d_6 at 300 MHz. 1,2,3) Reportred value.

Compound II: 2,5-dimethoxy-phenacyl nicotinium bromide:

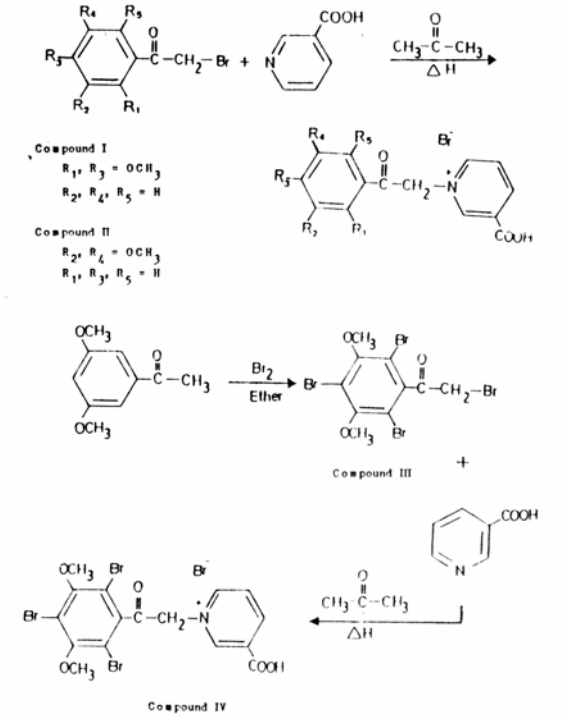
Nicotinic add (1.23 g) and 2,5-dimethoxy phenacyl bromide (2.58 g) were dissolved in 25 ml of acetone in two separate flasks. The two solutions were then mixed together and refluxed for 30 minutes. The crude product was then recrystallied from ethanol to furnish white crystals, yield is 67%, molecular weight is 381, molecular

formula $C_{16}H_{16}O_5N$ Br, m.p. 271.5^{0}C. UV spectrum (EtOH) showed maximum absorption at 209, 225, 272, and 310 ram. The IR (KBr) spectrum peaks were assigned to OH-group (3400 cm), C-H (2900 cm) C0 (1710 cm), C-N, C-C (1660-1410 cm^1), El-MS, ink 381 (talc.), 302 (6%), 135 (38%), 123 (2%), 195 (2%), 165 (100%), 150 (10%), 135 (38%), 123 (87%), 107 92 (16%) (60%), 80 (72%) and 77 (62%). The proton nmr data is given in Table 1.

Compound III: 2,4,6-Iribromo, 3,5-dimethoxy-phenacyl bromide:

2,4,6,-tribromo, 3,5-dimethoxy-phenacyl bromide was synthesized when 3,5-dimethoxy acetophenone (1.80g) was dissolved in 10 ml of ether and was cooled to O°C and the addition of bromine (0.53 ml)was carried out. Solution was allowed to stand overnight while keeping the temperature at 25°C. The solution was filtered and the solid was recrystallized from ethanol giving hexagonal light yellow crystals (yield 70%). The molecular formula is $_{C1011803}$ Brand molecular weight is 496. Melting point 165°C. Maximum UV- absorptionat 210, 325 nm. IR(K Br) spectrum showed peaks at 2900 (C-H), 1710 (C0) and 1600, 1470 (C= C). El-MS at m/z 496 (observed) (14%) 165 (24%), 165 (24%), 135, (34%), 77 (40%), 61 (36%). Proton nmr data is shown in table 1.

Compound IV: 2,4-6 tribromo 3,5-dimethoxy-phenacyl nicotinium bromide:



Compound IV was synthesized when equimolar quantities of nicotinic acid (123g) and 2,4,6-tribromo 3,5-dimethoxy phenacyl bromide (4.92g) were dissolved in acetone separately. The two solutions were mixed together and refluxed till a crude solid separated. The contents of the flask were filtered washed and recrystallized from ethanol (hot) into needle like crystals. The scheme of the reaction is given in Figure 1, and the percentage yield was 63. Compound IV has molecular formula as C16H13O5N Bra and molecular weight is 615. UV-spectrum (EtOH) of this compound showed maximum absorption at 215 and 262 nm. In IR (KBr) spectrum the functional group peaks were determined at 2900 (C-H), 2500 (OH) 1700 (C = 0), 1580-1420 (C-N,C-C) cm^{-1}. El-MS, at m/z 615 (calk.), 496 (4%) 416 (2%) 389 (1%), 323 (100%), 280 (20%), 227 (14%), 17. (6%), 135 (15%) 123 (33%), 105 (32%), 77 (34%) 61 (22%). The PMR chemical shifts are given in table 1.

Result and Discussion

The main objective of this research work was to prepare some new derivatives of nicotinic acid which could exhibit antciholesterolemic activity. The first objective of our research work was to test these derivatives on rabbits and observe the maximum activity. In this regard significant activity is shown by the compounds. The effect of some nicotinic acid derivatives on serum of rabbits were already published (Saify *et al,* 1985, 1987). Synthesis of novel derivatives of phenacyl bromide were carried out by reacting an equimolar amount of respective phenacyl bromide with nicotinic acid. The new compounds were formed by simple quarternization reaction, furnishing respective phenacyl nicotinium bromide. The salt thus obtained were recrystalized from absolute ethanol. Confirmation of their structures were carried out by spectroscopic analysis i.e., mass, nmr, r, uv. All compounds showed similarity in uv, it and mass spectra with slight difference which is due to the stereo chemical nature of the molecule. The confirmation of the structures of the synthesized compounds were done by proton nmr and mass spectra.

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