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THE DERIVATIVES OF 3-(1H-BENZIKMIDAZOLE-2) PROPANOIC ACID SYNTHESIS AND ANALGETIC AND ANTI INFLAMMATORY ACTIVITY

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ABSTRACT

Several derivatives of 3-(1H-benzimidazole-2) propanoic acid (Procodazol) were prepared using some aldehydes by the condensation reaction. The resulting products were lactam and acid derivatives. According to the spectral studies it was found that the hydrogen atoms of the 3-methylene group of 3-(1H-benzimidazole-2) propanoic acid take part in the reaction.

3-(2'-(Acetoxyphenyl) methylene)-2, 3-dihydro-lH-pyrrole (1, 2a) benzimidazole lone (3c) was found to possess some analgetic properties.

Introduction

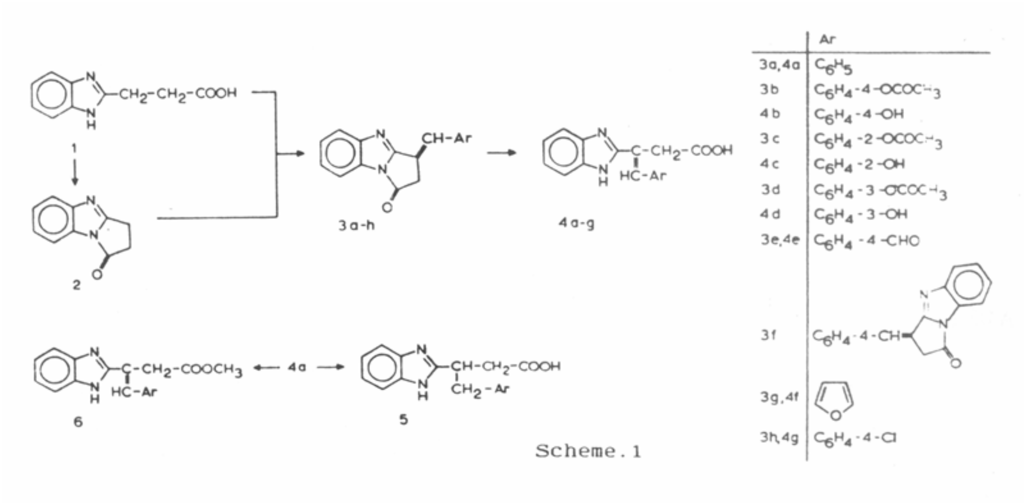
The hydrogen atoms of the methylene group located at second position of benzimidazole ring become acidic in properties because of the electron withdrawing effect of the benzimidazole system, therefore a number of derivatives, e.g. 2-methyl (Koshits-Porai, 1953), 2-ethyl (Sawlewicz and Kuzmierkiewicz, 1977) and 2-benzyl-benzimidazole (Sawlewicz and Kuzmierkiewicz, 1972) undergo condensation reaction with aromatic aldehydes.

The hydrogen atoms of the methylene groups of 3-(1H-benzimi-dazole-2) propanoic acid to show similar activity, as the hydrogen atoms are activated by carboxylic acid. This expectation was confirmed by condensation reaction of the immunosuppresive drug Procodazol with aromatic aldehydes.

Results and Discussion

The condensation reaction done by heating equimolar amounts of procodazol (1) and the aldehyde in acetic anhydride. When I was heated with acetic anhydrid, it undergoes transformation into the lactam (Stanek and Wollrab, 1960), the resulting products of the condensation are lactam derivatives (Scheme 1).

The same derivatives were also obtained by the reaction of lactam (2) with aldehydes. During the reaction with terephthaldehyde after 15 minutes heating a monosubstituted derivative (3c) precipitated. Further heating of this precipitate yielded the mixture composed of the compounds (3e) and (30, but pure compound (3f) was prepared by heat-



Scheme. 1

ing 1 mol of terephthaldehyde with 2 mol of I. For to get acids from lactams, the latter hydrolyzed with 10 % sodium hydroxide. After acidification with hydrochloric acid the respective acid derivative was precipitated (4a-g). Compound (4e) loses a water molecule when heated above melting and rearranges into the lactam derivatives (3e).

Naik et al. (Naik et al. 1972) assumed that in the Vilsmcier reaction the hydrogen atoms of the methylene group of (1) take pan but there are no conclusive physicochemical data available at present allowing unequivocal interpretation of the reaction mechanism suggested.

The analysis of NMR spectra of 1 (Aubagnac et al. 1972) and compound 5, it was found that the signal caused by protons of 2-methylene group for both compounds appeared at the same value of chemical shift of 2.85 ppm (Table 1). The disappearence of the 3-methylene group protons signal suggest that in the reaction the hydrogen atoms of the 3-methylene group of (1) take part.

In the NMR spectrum of 4a,a shift of protons signal toward higher values of δ was observed. Probably this result from the effect of the phenyl group. It may suggest the possibility that the 4a-g derivatives exist as the trans isomers.

Table 1: The Chemical Shifts of the Protons at C-2, C-3 and Benzylidene-H.

Compound	C-2-H	C-3-H	Benzylidene-H
1	2.85 (m, 2H)	3.2 (m, 2H)	
4a	3.7 (s, 2H)		7.6 (S, 1H)
5	2.85 (d, J = 6Hz, 2H)	3.7 (m. 1H)	2.85 (d, J= 6 Hz, 2H)

Pharmacological Data:

3b, 3c and 3g of the lactam derivatives and 4c as acid derivative were chosen for pharmacological tests.

Analgetic activity was done by applying the hot plate method (Woolfe and McDonald, 1968) and according to the method described by Randall and Selitto (Randal and Selitto, 1957). Anti inflammatory effect was evaluated based on the measurements of the swelling induced by carragenin. Irritating properties of the compounds were deter-mined, using the stomach mucous membrane according to Corella (Corella and Jensen, 1979). The compounds were administered intravemricularly at 200 mg/kg dose. The pharmacological effects observed were compared with the reactions observed after ad-ministration of known drugs, e.g. Acetylsalicylic acid (2110 mg/kg) and Indomethacin (3 mg/kg).

Only compound 3c showed analygetic activity. Its activity was higher than that of the control drugs and was manifested especially between 2nd and 4th hrs after administration.

Compounds 3b, 3g and 4c reduced swelling induced with carragenin during the first 3 hrs of observation. The action of these compounds started earlier and lasted more briefly than either Acetylsalicyclic acid or Indomethaein. During the 2nd hr of the experiment, 3b, 3g and 4c reduced swelling by 12.3, 13.0 and 17.7%. The per cent of ulceration, calculated in comparison to the control test was 20.8, 39 and 15% with compounds 3b, 3c and 4c. The above reduction are less than those observed after administration of acetylsalicyclic acid (51%) and greater than those after Indomethacin (0%).

Experimental

Melting points were measured on Mettler FP-5, FP-51 and were uncorrected. The IR spectra were determined as KBr discs using Perkin-Elmer 567 grating IR spectrometer. The NMR spectra were recorded in TFA; on Varian T 60A, 60 MHz NMR spectrometer. The micro-analysis were done at Janssen Laboratories, Janssen Pharmaceutical, Beers, Belgium.

1. Lactam Derivatives of Procodazol (3a-h): General Method:

0.01 mol of 1 or its lactam and aromatric aldehyde were dissolved in 25 ml of acetic anhydride and refluxed 1-3 hrs. Precipitate occurred after cooling. The data of the compounds are given in Table II.

2. Hydrolysis of Lactam (4a-g); General Method:

Lactam derivatives were heated up to 95°C for 15 minutes with 10% of NaOH. The solution cooled, acidified with conc. HCl. The resulting precipitate filtered. The data of the compounds are given in Table III.

Table 2: Physicaland Spectroscopic Data of Lactam Derivatives *3a, e, f (DMF), others (ETOH).

Compound 3	M.P. (*C) (Crystallization solvent*)	Reaction time (h)	Yield (%)	Molecular For.	Analysis Calc./Found	IR (KBr)		
						υ C = O	υ N = C	υ C = C
a	188-190	3	39	$C_{17}H_{12}N_2O$	C 78.07/78.19 H 4.98/ 4.76 N 10.72/10.75	1750	1650	1605
b	197-199	3	36	$C_{19}H_{14}N_2O_3$	C 71.69/71.80 H 4.43/ 4.47 N 8.80/ 8.61	1750	1650	1610
c	161-163	3	33	$C_{19}H_{14}N_2O_3$	C 71.69/71.53 H 4.43/ 4.61 N 8.80/ 8.63	1750	1655	1610
d	144-146	3	20	$C_{19}H_{14}N_2O_3$	C 71.69/71.81 H 4.43/ 4.55 N 8.80/ 8.69	1760	1650	1610
e	241-243	0.30	17	$C_{18}H_{12}N_2O_2$	C 71.04/71.22 H 3.98/ 3.69 N 9.21/ 9.39	1755	1640	1620
f	365-367	1	45	$C_{28}H_{18}N_4O_2$	C 76.00/76.15 H 4.10/ 4.02 N 12.66/12.45	1755	1655	1620
g	203-205	1	51	$C_{15}H_{10}N_2O_2$	C 71.99/71.83 H 4.03/ 4.17 N 11.20/11.42	1760	1650	1620
h	207-210	3	28	$C_{17}H_{11}ClN_2$	C 68.98/68.75 H 4.06/ 3.88 N 9.47/ 9.29	1760	1650	1610

Table 3: Physical and Spectroscopic Data of Acid Derivatives *4a ($MeOH/H_2O$), 4b, c, d, g (ETOH), 4e (DMF/H_2O), 4f (H_2O).

Compound 4	M.P. (*C) (Crystallization solvent*)	Yield (%)	Molecular For.	Analysis Calc./Found	IR (KBr)	
					υ C = N	υ OH
a	232–234	81	$C_{17}H_{14}N_2O_2$	C 73.36/73.23 H 5.07/ 5.13 N 10.07/10.14	1630	2350–3400
b	261–263	76	$C_{17}H_{14}N_2O_3$	C 69.37/69.42 H 4.08/ 4.18 N 9.52/ 9.71	1620	2400–3450
c	276–278	85	$C_{17}H_{14}N_2O_3$	C 69.37/69.43 H 4.80/ 4.73 N 9.52/ 9.60	1620	2350–3500
d	195–196	79	$C_{17}H_{14}N_2O_3$	C 69.37/69.44 H 4.80/ 4.75 N 9.52/ 9.46	1610	2300–3400
e	189–191	67	$C_{18}H_{14}N_2O_3$	C 70.58/70.46 H 4.61/ 4.53 N 9.15/ 9.02	1630	2450–3350
f	235–237	86	$C_{15}H_{12}N_2O_3$	C 67.15/67.23 H 4.51/ 4.55 N 10.44/10.33	1640	2400–3400
g	204–206	89	$C_{17}H_{13}ClN_2O_2$	C 65.23/65.36 H 4.16/ 4.27 N 8.95/ 8.77	1620	2350–3450

3.3-(1H-benzimidazole-2) 3-benzylpropanoic Acid (5):

1g of 4a (3.6 mol) was dissolved in 50 ml of abs. ethanol on-to this solution 50 mg of Raney's Ni was added. The reduction was carried out with hydrogen at normal pressure at 50°C. After 1.5 h it was filtered and ethanol *evaporated,* crystallized from MeOH. Yield 0.92 g (92%).

M.P.: 253-255°C

IR (cm^{-1}): 3000-2400 (NH_2OH), 1640 (C = 0)

UV (nm): λ_{max} 284 (lg ε = 279)

NMR (δ, ppm) 2.85 (d, J = 6 Hz,4H, C-2H and benzyl-H), 3.6-3.8 (m, 1H, C-3-H), 6.78 (m, 5H,C_6H_5), 7.25 (m, 4H, benzimidazole).

$C_{17}H_{16}N_2O_2$

Calcd : C 72.84, H 5.75

Found: C 72.73, H 5.79

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