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Synthesis of Some Substituted Indane-Amino Acid Derivatives

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Synthesis and antimicrobial evaluation of some new 3-keto-4,7-dimethylindane-1-carbonylamino acid methyl esters (III–VIII), 3-keto-4,5-benzoindane-1-carbonylamino acid methyl esters (IX–XII) and the corresponding hydrazides and some dipeptide methyl ester derivatives (XIII–XXXII) are described.

INTRODUCTION

Owing to the fact that amino acids play an important role in creating or improving the activities of many aromatic and heterocyclic derivatives[1–5], the synthesis of substituted indanes containing different amino acid residues incorporated in an amide linkage is reported in this paper. The present investigation is concerned with the synthesis of some 3-keto-4,7-dimethyl- or 3-keto-4,5-benzo-indane-1-carbonyl-amino acid methyl esters (III–XII) and their corresponding hydrazides (XIII–XXII) and some dipeptide derivatives (XXIII–XXXII) for their microbiological evaluation.

RESULTS AND DISCUSSION

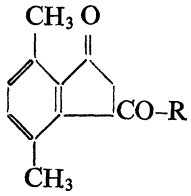
3-Keto-4,7-dimethyl- or 3-keto-4,5-benzo-indane-1-carbonylamino acid methyl esters (III–XII) were prepared by condensation of 3-keto-4,7-dimethylindane-1-carboxylic acid (I) or 3-keto-4,5-benzoindane-1-carboxylic acid (II) with amino acid methyl ester hydrochlorides in THF-Et_3N medium using the dicyclohexylcarbodiimide (DCC) procedure. The time required for completion of the reaction (3–4 hrs) was monitored by TLC. Most of the products (III–XII) were easily isolated, purified, recrystallized and obtained in 50–71% yield.

Treatment of the methyl esters (III–XII) with hydrazine hydrate in ethanol gave the corresponding 3-keto-4,7-dimethyl- or 3-keto-4,5-benzo-indane-1-carbonylamino acid hydrazides (XIII–XXII). All the products (XIII–XXII) were homogeneous on TLC, obtained in 73–83% yield and gave positive silver nitrate reactions.

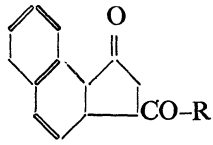
For the preparation of the dipeptide methyl esters (XXIII–XXXII), the hydrazides (XIII–XXII) were converted into the corresponding azides. The azides on coupling with amino acid methyl esters furnished the desired 3-keto-4,7-dimethyl- or 3-keto-4,5-benzoindane-1-carbonyldipeptide methyl esters (XXIII–XXXII). All the dipeptide derivatives (XXIII–XXXII) were highly purified through repeated recrystallizations and chromatographically homogeneous materials were obtained in 33–65%

yield. Complete acid hydrolysis of (XXX) (6N–HCl, 24 hrs at 100°C) followed by subsequent chromatography, afforded valine and tyrosine (positive ninhydrin spots).

The structures of the synthesized compounds (III–XXXII) were supported by their elemental analyses, IR, UV and ^{1}H–NMR spectral data, spot reactions and chromatographic studies (Table 1, compounds III–XXXII).



Compounds of type A



Compounds of type B

Biological Screening

The antimicrobial activities of the synthesized compounds (III–XXXII) were tested using the hole plate and filter paper disc method[6,7]. The effect was studied on different strains of various microorganisms, *Bacillus subtilis*, *Sarcina lutea*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Penicillium chrysogenum*. The results are given in Table 2.

EXPERIMENTAL

Thin layer chromatography (TLC, R_f values) was carried out on Silica Gel-G (BDH), using benzene-ethyl acetate-acetic acid (12 : 4 : 1) as solvent system and an iodine-potassium iodide (20%) solution or chlorosulphonic acid-acetic acid (1 : 3) as detection reagent. Benzidine, ninhydrin, silver nitrate and hydroxamate reactions were used for the detection of amino acid derivatives on Whatman No. 1 paper chromatograms (spot reactions). Optical rotations $[\alpha]_D^{20}$ were taken in a Zeiss polarimeter, 1 dm tube (c=5, in acetone). The IR spectra (KBr, ν_{max} in cm^{-1}) were recorded on a Unicam SP 1200 spectrophotometer. The UV spectra (ethanol, λ_{max} in nm, log ϵ), on a Unicam SP 8000 spectrophotometer and ^{1}H–NMR spectra in DMSO-d_6 were run on a Varian T-60 A instrument (chemical shift in (δ), ppm) using TMS as internal standard. Melting points are uncorrected.

3-Keto-4:7-Dimethylindane-1-Carboxylic Acid (I) and 3-Keto-4:5-Benzoindane-1-Carboxylic Acid (II)

The titled compounds were prepared according to the procedures described in literature[8,9].

TABI

PHYSICAL DATA OF VARIOUS 3-KETO-4: 7-DIMETHY
DERIVATIV

Comp. No.	R	Type	Yield %	m.pt. °C	R
III	L-Ala-OMe	A	71	235–237	0.9
IV	L-Val-OMe	A	63	178–180	0.8
V	L-Leu-OMe	A	50	182–184	0.7
VI	L-Phe-OMe	A	56	170–172	0.6
VII	L-Tyr-OMe	A	55	210–212	0.6
VIII	L-Ser-OMe	A	50	190–192	0.5
IX	L-Val-OMe	B	63	195–197	0.6
X	L-Leu-OMe	B	51	201–203	0.7
XI	L-Phe-OMe	B	56	208–210	0.9
XII	L-Tyr-OMe	B	61	210–212	0.8
XIII	L-Ala-N_2H_3	A	67	370–372	0.7
XIV	L-Val-N_2H_3	A	75	320–322	0.7
XV	L-Leu-N_2H_3	A	83	318–320	0.5
XVI	L-Phe-N_2H_3	A	80	360–362	0.4
XVII	L-Tyr-N_2H_3	A	73	310–312	0.6
XVIII	L-Ser-N_2H_3	A	70	220–222	0.9
XIX	L-Val-N_2H_3	B	73	314–316	0.9
XX	L-Leu-N_2H_3	B	77	265–267	0.8
XXI	L-Phe-N_2H_3	B	72	250–252	0.3
XXII	L-Tyr-N_2H_3	B	75	276–278	0.8
XXIII	L-Ala-L-Val-OMe	A	38	165–167	0.7
XXIV	L-Val-L-Tyr-OMe	A	35	295–297	[redacted]
XXV	L-Leu-L-Tyr-OMe	A	40	231–233	
XXVI	L-Phe-L-Leu-OMe	A	50	280–282	0.7
XXVII	L-Tyr-L-Ala-OMe	A	33	251–253	0.92
XXVIII	L-Ser-L-Tyr-OMe	A	65	308–310	0.72
XXIX	L-Val-L-Tyr-OMe	B	50	292–294	0.74
XXX	L-Leu-L-Tyr-OMe	B	40	245–247	0.85
XXXI	L-Phe-L-Tyr-OMe	B	43	248–250	0.86
XXXII	L-Tyr-L-Tyr-OMe	B	30	280–282	0.64

3- KETO- 4 : 5-BENZOINDANE-1-CARBONLAMINO ACID (XXXII)

$[\alpha]_D^{20}$	Molecular formula	Elemental analysis %					
		Calculated			Found		
		C	H	N	C	H	N
59.1	$C_{16}H_{19}NO_4$	66.44	6.57	4.84	66.53	6.62	4.91
63.5	$C_{18}H_{23}NO_4$	68.14	7.26	4.42	68.10	7.30	4.45
69.1	$C_{19}H_{25}NO_4$	68.88	7.55	4.23	68.93	7.60	4.30
67.1	$C_{22}H_{23}NO_4$	72.33	6.30	3.84	72.41	6.35	3.90
73.5	$C_{22}H_{23}NO_5$	69.29	6.04	3.67	69.33	6.09	3.72
63.2	$C_{18}H_{17}NO_5$	66.05	5.20	4.28	66.12	5.31	4.40
70.4	$C_{20}H_{21}NO_4$	70.80	6.19	4.13	70.84	6.20	4.15
75.5	$C_{21}H_{23}NO_4$	71.39	6.52	3.97	71.52	6.66	4.01
79.1	$C_{24}H_{21}NO_4$	74.42	5.43	3.62	74.51	5.54	3.67
63.5	$C_{24}H_{21}NO_5$	71.46	5.21	3.47	71.53	5.26	3.48
65.3	$C_{15}H_{19}N_3O_3$	62.28	6.57	14.53	62.33	6.61	14.62
69.5	$C_{17}H_{23}N_3O_3$	64.35	7.26	13.25	64.41	7.30	13.31
74	$C_{18}H_{25}N_3O_3$	65.26	7.55	12.69	65.33	7.59	12.73
72	$C_{21}H_{23}N_3O_3$	69.04	6.30	11.51	69.07	6.37	11.57
81.4	$C_{21}H_{23}N_3O_4$	66.14	6.04	11.02	66.22	6.09	11.06
-69.1	$C_{17}H_{17}N_3O_4$	62.39	5.20	12.84	62.45	5.34	12.97
-73.1	$C_{19}H_{21}N_3O_3$	67.25	6.19	12.39	67.35	6.25	12.45
-81.4	$C_{20}H_{23}N_3O_3$	67.99	6.52	11.90	68.03	6.62	11.92
-84.7	$C_{23}H_{21}N_3O_3$	71.32	5.43	10.85	71.41	5.52	10.91
-85	$C_{23}H_{21}N_3O_4$	68.49	5.21	10.42	68.71	5.41	10.39
-73.4	$C_{21}H_{28}N_2O_5$	64.95	7.22	7.22	65.03	7.30	7.25
-77	$C_{27}H_{32}N_2O_6$	67.50	6.67	5.83	67.59	6.73	5.90
-83.8	$C_{28}H_{34}N_2O_6$	68.02	6.88	5.67	68.07	6.93	5.72
-74.5	$C_{28}H_{34}N_2O_5$	70.29	7.11	5.86	70.31	7.15	5.91
+80.4	$C_{25}H_{28}N_2O_6$	66.37	6.19	6.19	66.41	6.22	6.25
+69.2	$C_{27}H_{26}N_2O_7$	66.12	5.31	5.71	66.16	5.45	5.83
+77	$C_{29}H_{30}N_2O_6$	69.32	5.98	5.58	69.41	5.03	5.70
+83	$C_{30}H_{32}N_2O_6$	69.77	6.20	5.43	69.85	6.41	5.49
+89.5	$C_{33}H_{30}N_2O_6$	72.00	5.45	5.09	72.31	5.61	5.11
+74.5	$C_{33}H_{30}N_2O_7$	69.96	5.30	4.95	70.02	5.41	5.03

TABLE 2

ANTIMICROBIAL ACTIVITY (A)* AND MINIMUM INHIBITORY CONCENTRATION (MIC) CALCULATED AS μg/mL OF 3-KETO-4 : 7-DIMETHYL- OR 3-KETO-4 : 5-BENZOINDANE-1-CARBONYLAMINO ACID DERIVATIVES

Comp. No.	*Bacillus subtilis*		*Staphylococcus aureus*		*Sarcina lutea*		*Escherichia coli*		*Pseudomonas aeruginosa*		*Penicillium chrysogenum*	
	A	M.I.C.	A	M.I.C.	A	M.I.C.	A	M.I.C.	A	M.I.C.	A	M.I.C.
V	+	250	—	—	+	250	+	250	+	250	—	—
VII	++	125	—	—	++	125	+	250	+	250	—	—
VIII	+	250	—	—	++	125	++	125	—	—	—	—
X	+	250	—	—	++	125	++	125	—	—	—	—
XVIII	+++	60	++	125	++	125	—	—	—	—	—	—
XIX	++	125	+++	60	+++	60	—	—	—	—	—	—
XX	+	250	—	—	—	—	—	—	—	—	—	—
XXI	—	—	—	—	—	—	—	—	+	250	—	—
XXVIII	+	250	+	250	+	250	—	—	—	—	+	250
XXIX	—	—	—	—	—	—	—	—	—	—	+	250
XXXII	—	—	—	—	++	125	—	—	—	—	++	125

(A)*: +++ = high active; ++ = moderately active; + = slightly active; — = inactive.

General Procedure for the Synthesis of 3-Keto-4:7-Dimethyl or 3-Keto-4:5-Benzoindane-1-Carbonylamino Acid Methyl Esters (III–XII)

To a solution of amino acid methyl ester hydrochloride (0.01 mole) in THF (50 ml) was added Et_3N (1 ml). The solution was stirred for 25 min at 5°C and the precipitated triethylamine hydrochloride was filtered off. To the filtrate at −5°C were added 3-keto-4:7-dimethyl- or 3-keto-4:5-benzoindane-1-carboxylic acid (I and II, 0.01 mole) and dicyclohexyl-carbodiimide (2.06 g, 0.01 mole). The reaction mixture was stirred for 3 hrs at 0°C and left for 24 hrs at room temperature. The precipitated dicyclohexylurea was filtered off and the solvent evaporated in vacuo. The residue was recrystallized from ethanol/water or ethanol/ether (1 : 1) mixture. The products (III–XII) were soluble in alcohols, DMF, DMSO, dioxane and insoluble in water and ether. Compounds (III–XII) were homogeneous on TLC when developed with benzidine or iodine solution and all gave negative test with ninhydrin.

The IR spectra of compounds (III–XII) showed characteristic bands at 3370 (CONH); 1750, 1720 (C=O); 1750; 1340, 1260 ($COOCH_3$) and other bands characteristic of indane and amino acid residues. The UV spectrum of compounds (VIII) showed λ_{max} (log ϵ) at 246 (3.72) and 284 (3.86). The ^{1}H–NMR spectra of compounds (III–XII) has characteristic chemical shifts at δ : 6.65 (s, 1H, NH); 3.68 (s, 3H, $COOCH_3$), 3.20 (s, 1H, >CH), 7.20 (s, 2H, aromatic protons, for compounds III–VIII) and six aromatic protons in the range 7.40–7.75 for compounds (IX–XII).

General Procedure for the Synthesis of 3-Keto-4:7-Dimethyl- or 3-Keto-4:5-Benzoindane-1-Carbonylamino Acid Hydrazides (XIII–XXII)

A solution of the methyl ester (III–XII, 0.01 mole) in ethanol (50 ml) and 1M alcoholic hydrazine hydrate (10 ml) was stirred for 1 hr at room temperature and the reaction mixture set aside in a refrigerator for 24 hrs. The crystalline hydrazide was filtered and recrystallized from ethanol. The hydrazides (XIII–XXII) were TLC homogeneous when developed with iodine solution, benzidine and silver nitrate reactions.

The IR spectra of compounds (XIII–XXII) showed characteristic bands at 3430, 3380, 3080 (NH_2, NH, CONH) 1750, 1720 (C=O); 1650, 1550, 1360 (amide I, II and III) and 2920, 2860, 1510, 1260, 1070, 960, 870 characteristic of indane and amino acid moieties.

General Procedure for the Synthesis of 3-Keto-4:7-Dimethyl or 3-Keto-4:5-Benzoindane-1-Carbonyldipeptide Methyl Esters (XXIII–XXXII)

The amino acid hydrazide (XIII–XXII, 0.001 mole) was dissolved in a mixture of acetic acid (3 ml), 5N-HCl (2 ml) and water (25 ml) and cooled to −5°C. Sodium nitrite (0 32 g) in water (3 ml) was added and

the mixture stirred for 10 min at −5°C. The azide was extracted with ethyl acetate (30 ml) and the extract washed successively with water, sodium bicarbonate (3%), and water and dried (Na_2SO_4). The dipeptides (XXIII–XXXII) were prepared by the addition of ethyl acetate solution of the corresponding azide to a cooled (−5°C) solution of the free amino acid methyl ester (prepared from 0.001 mole of the amino acid methyl ester hydrochloride and 0.5 ml triethylamine) and stirring of the reaction mixture for 6 hrs at 0°C and keeping it for 24 hrs at 0°C and for another 25 hrs at room temperature. It was washed successively with HCl (0.5 N), water, sodium bicarbonate (3%) and water and dried (Na_2SO_4). The solvent was removed and the residual material was recrystallized from ethanol/water (1 : 1) mixture. The products (XXIII–XXXII) were TLC homogeneous when developed with chlorosulphonic-acetic acid mixture (1 : 3) and gave ninhydrin negative reaction.

The ^{1}H-NMR of compounds (XXIII–XXXII) showed signals at δ : 6.64 (s, 1H, NH); 3.71 (s, 3H, $COOCH_3$); 3.21 (s, 1H, $\rangle CH$), 2.32 (s, 3H, Ar–CH_3 for compounds XXIV–XXVIII); 7.17 (s, aromatic protons for compounds XXIV–XXVIII) and aromatic protons in the range 7.38–7.72 for compounds (XXIX–XXII).

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