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Stereoselective Synthesis of β-Naltrexol, β-Naloxol, β-Naloxamine, β-Naltrexamine and Related Compounds by the Application of the Mitsunobu Reaction

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Abstract: As a continuation of our work, aimed at adopting the Mitsunobu reaction in the morphine series, a few representatives of dihydroisocodeines and dihydroisomorphines and their 14β-hydroxy analogues were prepared. p-Nitrobenzoic acid was used as carboxylic acid and the prepared esters were cleaved to obtain the title compounds. Using phthalimide as acidic component several new 6β-phthalimidodihydromorphine and dihydrocodeine derivatives and their 14β-hydroxy analogues have been synthesized. Cleavage of the phthalimido derivatives with hydrazine hydrate afforded the corresponding 6β-amino derivatives.

In our recent papers we have described the successful application of the Mitsunobu reaction[1] in the morphine-alkaloid series. During these studies epimerization of the 6α hydroxyl group of related compounds carrying a $\Delta^{7,8}$ double bond[2,3], as well as conversion of the hydroxyl function into a primary amino moiety[4,5] have been investigated, and found that all of these reactions proceed with configurational inversion without allylic rearrangement. In addition, our results in case of derivatives substituted with bulky halogen atoms at position 14, have proved the literature findings that the Mitsunobu reaction with phthalimide is more sensitive to steric effects than those performed with carboxylic acids[6,7].

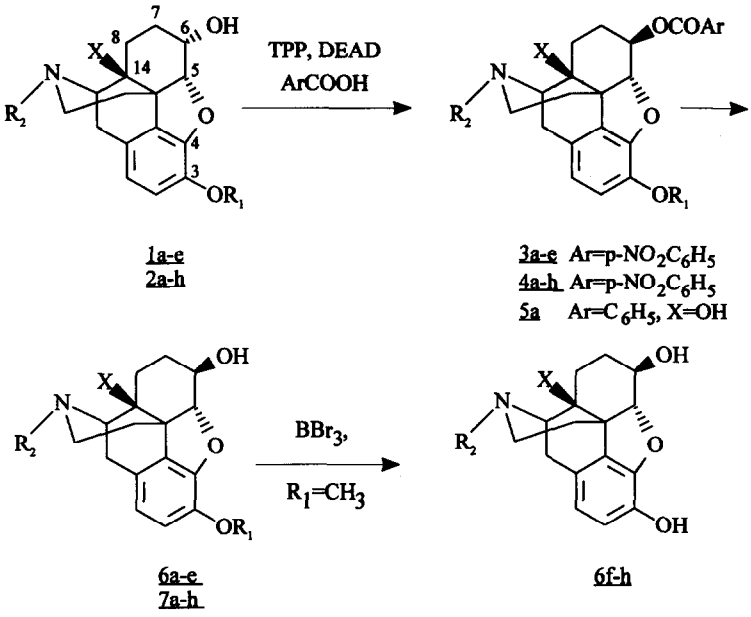
Preceding these studies most of the target compounds (C-6βOH) were unknown, and in many cases either the yield or the stereoselectivity of the transformations were unsatisfactory[8-16]. Except for the N-allyl analogues the isomorphine derivatives, saturated in ring C, could be prepared by means of catalytic hydrogenation of isomorphine and isocodeine derivatives with unsaturated ring C prepared in our laboratory earlier[2]. By elaborating an efficient procedure for the N-demethylation and N-alkylation[3,17] of dihydroisocodeine and dihydroisomorphine, as well as of their 14β-hydroxy analogues new completely

stereoselective* methods have been developed for the production of β-naltrexol (human metabolite of narcotic antagonist naltrexone) and β-naloxol. There is only one completely stereoselective synthesis known for the preparation of these compounds: the reduction of naloxone and naltrexone with formamidine sulfinic acid[11], but this method can not be applied in the case of other compounds[12,13,18].

Some of the target primary amines are known in the literature, and many of them have been prepared from the corresponding azide, obtained from sulphonate esters[19-21] and others were synthesized by Portoghese *et al.* by means of reductive amination of morphinan ketones[22-25]. The reported[24] synthesis of β-naloxamine is not completely stereoselective and only one procedure was reported for the completely stereoselective synthesis of β-naltrexamine[23], but its time consuming nature prompted us to examine a simple alternative approach.

The present paper deals with the synthesis of these and related compounds by means of treatment of the saturated ring C derivatives with p-nitrobenzoic acid and phthalimide respectively in the presence of triphenylphosphine and diethyl azodicarboxylate, and subsequent alkaline hydrolysis of the resulting esters to obtain the desired 6β epimers or cleavage of phthalimide derivatives with hydrazine hydrate to obtain the primary amine at 6β position. Investigation of such a reaction is theoretically also interesting, since the alcoholic hydroxyl is not of allylic character, and in case of the unsaturated and dihydro compounds the steric position of the hydroxyl function is pseudo-equatorial and axial, respectively.

When dihydrocodeine (1a) was allowed to react with benzoic acid in benzene no complete conversion was observed after several hours of reaction time and at elevated (reflux) temperature. Surprisingly in case of 14β-hydroxydihydrocodeine (2a) the reaction is complete within one hour and the desired benzoate ester (5a) could be prepared. We can not explain the difference between the reactivity of dihydrocodeine and 14β-hydroxydihydrocodeine. However, when p-nitrobenzoic acid was employed, the conversion completed in an hour at room temperature even in the case of dihydrocodeine. Similar results were published independently by Martin *et al.*[26] concerning the reactivity of benzoic acid and p-nitrobenzoic acid, using another substrates. Recently another paper has dealt with the effect of the acidic component on the Mitsunobu inversion[27]. The different reactivity of benzoic acid and p-nitrobenzoic acid can be interpreted in the knowledge of the reaction mechanism: the pK value of p-nitrobenzoic acid is lower, and the equilibrium between the alkoxyphosphorane and the alkoxyphosphonium salt is shifted towards the latter, as shown by the related mechanistic studies by Jenkins *et al.*[28,29]. In agreement with these results dihydrocodeine (1a) and N-demethyl-N-alkyldihydrocodeines (1b-d) could be readily converted with p-nitrobenzoic acid in benzene into the required p-nitrobenzoates 3a-d, whose alkaline hydrolysis gave rise to the dihydroisocodeines 5a-d. Boron tribromide mediated O-demethylation then afforded the corresponding dihydroisomorphine derivatives 6f-h. Dihydroisomorphine (6e) was prepared from dihydromorphine (1e R_1=H, R_2=CH_3) by using the known sequence (acetylation, epimerization, hydrolysis). The compounds obtained in this way were shown to be identical with those synthesized[17] by N-demethylation of dihydroisocodeine and subsequent N-alkylation.



1a-e
2a-h

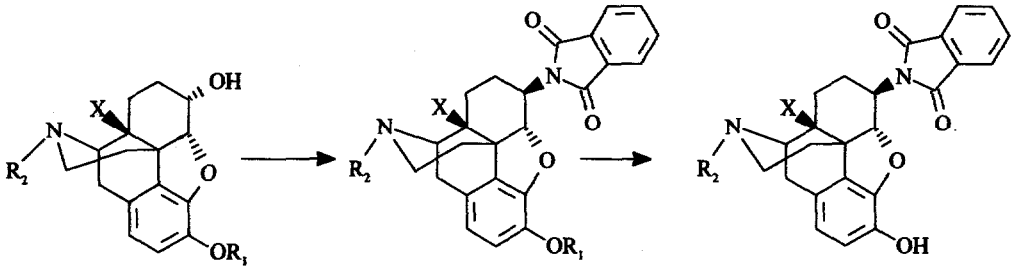
3a-e Ar=p-$NO_2C_6H_5$
4a-h Ar=p-$NO_2C_6H_5$
5a Ar=C_6H_5, X=OH

6a-e
7a-h

6f-h

The 14β-hydroxydihydroisocodeine derivatives 7a-d were also obtained as described for the corresponding dihydroisocodeines. Although O-demethylation with boron tribromide could also be employed for these compounds, the related 14-hydroxydihydromorphine derivatives 2e-h (R_1=H) were more easily accessible (through the corresponding ketones) than their 14-H analogues. Therefore the 3-O-acetyl derivatives (2e-h, R_1=Ac), prepared by the Welsh acetylation of the phenolic hydroxyl groups, were reacted with p-nitrobenzoic acid in the presence of triphenylphosphine and diethyl azodicarboxylate to obtain the p-nitrobenzoates (4e-h) of the 14-hydroxy-dihydroisomorphine derivatives. Due to their good water-solubility de-esterification of these latter compounds could be achieved with a catalytic amount of sodium methoxide in methanol, and the resulting alcohols 7e-h were isolated in form of their chlorohydrates. These compounds were also prepared[3] from the corresponding 14-hydroxy-dihydroisocodeines (via N-demethylation, N-alkylation and O-demethylation), and the physical data of these samples were found to be identical, in all respect with those synthesized by means of the Mitsonubu reaction.

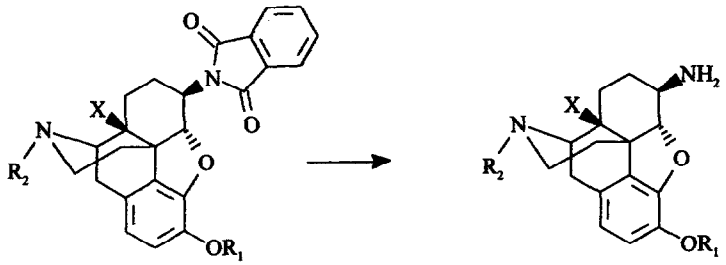
When the dihydrocodeine 1a-d, 2a-d and 3-O-acetyldihydromorphine derivatives 1e-h, and 2e-h were treated with phthalimide in benzene in the presence of triphenylphosphine and diethyl azodicarboxylate the target phthalimido compounds 8a-h and 9a-h could be readily obtained. Temporary protection of the 14β-hydroxy group was negligible, but to avoid undesired side-reaction (formation of alkyl phenyl ethers[30]) the phenolic hydroxyl group was temporarily protected by the usually employed Welsh acetylation procedure[31]. Removal of the acetyl group with hydroxylamine hydrochloride or sodium carbonate in aqueous ethanol gave rise to the derivatives 10a-d and 11a-d, bearing free phenolic hydroxyl functions. Cleavage of the phthalimido moiety with hydrazine hydrate then allowed the isolation of the primary amines 12a-h and 13a-h.



1a-h
2a-h

8a-h
9a-h

10a-d
11a-d



8a-h
9a-h

12a-h
13a-h

The stereochemistry of C-6 was proved not only by the chemical identity of the compounds synthesized in an independent way, but also by their ^{1}H-NMR spectra. The coupling constants of $C_{5\beta}$ and $C_{6\alpha}$-H ($J_{5\beta,6\alpha}$~6.5-8.5 Hz) verified the position of the substituent at C-6. The detailed analysis of the ^{1}H-NMR spectra of these compounds is published in the literature[10,32-34]

The in vitro studies and pharmacological properties of 6β-epimers prepared by us was reported in part[35]. The antagonist properties of β-naloxol and β-naltrexol are known in the literature[11,36].

The opiate β-naltrexamine is employed as an intermediate in the synthesis of the affinity label β-funaltrexamine[37], which is employed as a tool in opioid research[38].

Table I.

Melting points and yields for the prepared compounds

Compound	R_1	R_2	X	Formula	M.w.	yield (%)	mp. (°C)
3a	CH_3	CH_3	H	$C_{25}H_{26}N_2O_6$	450.48	90	164-165
3b	CH_3	n-C_3H_7	H	$C_{27}H_{30}N_2O_6$	478.53	60	149-151
3c	CH_3	$CH_2CH{=}CH_2$	H	$C_{27}H_{28}N_2O_6$	476.51	60	158-160
3d	CH_3	CPM	H	$C_{28}H_{30}N_2O_6$	490.54	48	188-189
3e	$COCH_3$	CH_3	H	$C_{26}H_{26}N_2O_7$	478.49	40	250-253
4a	CH_3	CH_3	OH	$C_{25}H_{26}N_2O_7$	466.48	79	218-220
4b	CH_3	n-C_3H_7	OH	$C_{27}H_{30}N_2O_7$	494.53	57	189-191
4c	CH_3	$CH_2CH{=}CH_2$	OH	$C_{27}H_{28}N_2O_7$	492.51	61	170-172
4d	CH_3	CPM	OH	$C_{28}H_{30}N_2O_7$	506.54	71	223-225
4e	$COCH_3$	CH_3	OH	$C_{26}H_{26}N_2O_8$	494.49	39	215-217
4f	$COCH_3$	n-C_3H_7	OH	$C_{28}H_{30}N_2O_8$	522.54	59	166-168
4g	$COCH_3$	$CH_2CH{=}CH_2$	OH	$C_{28}H_{28}N_2O_8$	520.52	48	169-171
4h	$COCH_3$	CPM	OH	$C_{29}H_{30}N_2O_8$	524.55	33	154-156
5a	CH_3	CH_3	H	$C_{25}H_{27}NO_5$	421.48	43	180-182
6a	CH_3	CH_3	H	$C_{18}H_{23}NO_3$	301.38	57	204-205
6b	CH_3	n-C_3H_7	H	$C_{20}H_{27}NO_3$	329.43	61	146-147
6c	CH_3	$CH_2CH{=}CH_2$	H	$C_{20}H_{25}NO_3$	327.40	66	121-123
6d	CH_3	CPM	H	$C_{21}H_{27}NO_3$	341.44	36	136-138
6e	H	CH_3	H	$C_{17}H_{21}NO_3$	287.35	96	224-226
6f	H	n-C_3H_7	H	$C_{19}H_{25}NO_3$	315.40	53	104-106
6g	H	$CH_2CH{=}CH_2$	H	$C_{19}H_{23}NO_3$	313.37	63	180-182
6h	H	CPM	H	$C_{20}H_{25}NO_3$	327.40	51	286-290*
7a	CH_3	CH_3	OH	$C_{18}H_{23}NO_4$	317.38	78	171-173
7b	CH_3	n-C_3H_7	OH	$C_{20}H_{27}NO_4$	345.43	37	146-148
7c	CH_3	$CH_2CH{=}CH_2$	OH	$C_{20}H_{25}NO_4$	343.40	86	112-113
7d	CH_3	CPM	OH	$C_{21}H_{27}NO_4$	357.44	53	173-175
7e	H	CH_3	OH	$C_{17}H_{21}NO_4$	303.35	63	251-252
7f	H	n-C_3H_7	OH	$C_{19}H_{25}NO_4$	331.40	82	263-265*
7g	H	$CH_2CH{=}CH_2$	OH	$C_{19}H_{23}NO_4$	329.37	71	203*
7h	H	CPM	OH	$C_{20}H_{25}NO_4$	343.40	90	207*
8a	CH_3	CH_3	H	$C_{26}H_{26}N_2O_4$	430.49	49	190-193
8b	CH_3	n-C_3H_7	H	$C_{28}H_{30}N_2O_4$	458.54	74	212-214
8c	CH_3	$CH_2CH{=}CH_2$	H	$C_{28}H_{28}N_2O_4$	456.52	50	176-177
8d	CH_3	CPM	H	$C_{29}H_{30}N_2O_4$	470.53	68	219-221
8e	$COCH_3$	CH_3	H	$C_{27}H_{26}N_2O_5$	458.50	38	188-190
8f	$COCH_3$	n-C_3H_7	H	$C_{29}H_{30}N_2O_5$	486.55	26	144-146
8g	$COCH_3$	$CH_2CH{=}CH_2$	H	$C_{29}H_{28}N_2O_5$	484.53	53	167-169
8h	$COCH_3$	CPM	H	$C_{30}H_{30}N_2O_5$	498.56	53	147-149
9a	CH_3	CH_3	OH	$C_{26}H_{26}N_2O_5$	446.49	90	115-117
9b	CH_3	n-C_3H_7	OH	$C_{28}H_{30}N_2O_5$	474.54	73	234-236

Table I continued

Compound	R_1	R_2	X	Formula	M.w.	yield (%)	mp. (°C)
9c	CH_3	$CH_2CH=CH_2$	OH	$C_{28}H_{28}N_2O_5$	472.52	76	207-208
9d	CH_3	CPM	OH	$C_{29}H_{30}N_2O_5$	486.55	60	246-248
9e	$COCH_3$	CH_3	OH	$C_{27}H_{26}N_2O_6$	474.50	46	217-219
9f	$COCH_3$	n-C_3H_7	OH	$C_{29}H_{30}N_2O_6$	502.55	42	206-208
9g	$COCH_3$	$CH_2CH=CH_2$	OH	$C_{29}H_{28}N_2O_6$	500.53	30	186-188
9h	$COCH_3$	CPM	OH	$C_{30}H_{30}N_2O_6$	514.56	33	212-215
10a	H	CH_3	H	$C_{25}H_{24}N_2O_4$	416.46	58	261-263
10b	H	n-C_3H_7	H	$C_{27}H_{28}N_2O_4$	444.51	25	213-215
10c	H	$CH_2CH=CH_2$	H	$C_{27}H_{26}N_2O_4$	442.50	26	195-196
10d	H	CPM	H	$C_{28}H_{28}N_2O_4$	456.52	38	136-138
11a	H	CH_3	OH	$C_{25}H_{24}N_2O_5$	432.64	62	305-307
11b	H	n-C_3H_7	OH	$C_{27}H_{28}N_2O_5$	460.51	70	279-281
11c	H	$CH_2CH=CH_2$	OH	$C_{27}H_{26}N_2O_5$	458.50	61	250-252
11d	H	CPM	OH	$C_{28}H_{28}N_2O_5$	474.54	58	275-277
12a	CH_3	CH_3	H	$C_{18}H_{24}N_2O_2$	300.39	35	140-142
12b	CH_3	n-C_3H_7	H	$C_{20}H_{28}N_2O_2$	328.44	70	oil
12c	CH_3	$CH_2CH=CH_2$	H	$C_{20}H_{26}N_2O2$	326.43	98	oil
12d	CH_3	CPM	H	$C_{21}H_{28}N_2O_2$	340.46	98	109-110
12e	H	CH_3	H	$C_{17}H_{22}N_2O_2$	286.37	93	269-271
12f	H	n-C_3H_7	H	$C_{19}H_{26}N_2O_2$	314.42	88	106-108
12g	H	$CH_2CH=CH_2$	H	$C_{19}H_{24}N_2O_2$	312.40	66	102-103
12h	H	CPM	H	$C_{20}H_{26}N_2O_2$	326.43	78	216-218
13a	CH_3	CH_3	OH	$C_{18}H_{24}N_2O_3$	316.39	51	152-154
13b	CH_3	n-C_3H_7	OH	$C_{20}H_{28}N_2O_3$	344.44	70	127-129
13c	CH_3	$CH_2CH=CH_2$	OH	$C_{20}H_{26}N_2O_3$	342.43	90	145-147
13d	CH_3	CPM	OH	$C_{21}H_{28}N_2O_3$	356.46	90	125-126
13e	H	CH_3	OH	$C_{17}H_{22}N_2O_3$	302.37	90	260*
13f	H	n-C_3H_7	OH	$C_{19}H_{26}N_2O_3$	330.42	75	191-193
13g	H	$CH_2CH=CH_2$	OH	$C_{19}H_{24}N_2O_3$	328.40	44	295-302*
13h	H	CPM	OH	$C_{20}H_{26}N_2O_3$	342.43	61	277-279*

All compounds gave satisfactory elementary analytical data.

* as hydrochloride salt

Melting points of the known compounds:

6a: 201[14]; 6e:224-225[15]; 7a: 166-167[16]; 7d: 172-173[13];
7e: 248-250(HCl)[12]; 7g: 205-207(HCl)[11]; 7h: 205-208(HCl)[11]
12a: 139[19]; 12e: 265[20]; 12h: 216-217[22]; 13a: 147-148[21];
13e*: 260[23]; 13g*: >270[23]; 13h*: 270[23]

Table II

Representative ^{1}H-NMR and MS data for compounds (2-4)

Cmpd.	^{1}H-NMR δ (ppm) $CDCl_3$ (* DMSO-d_6)	MS (%)
3a	2.4(s, 3H, NMe); 3.8(s, 3H, OMe); 4.7(d, 1H, $C_{5\beta}H$); 4.9(m, 1H, $C_{6\alpha}H$); 6.7(ABq, 2H, C_1,C_2H); 8.3(m, 4H, $OCOC_6H_4NO_2$)	450[M^+](10)
3b	0.9(t, 3H, propylMe); 3.8(s, 3H, OMe); 4.7(d, 1H, $C_{5\beta}H$); 4.9(m, 1H, $C_{6\alpha}H$); 6.7(ABq, 2H, C_1,C_2H); 8.3(m, 4H, $OCOC_6H_4NO_2$)	478[M^+](10) 449(90)
3c	3.8(s, 3H, OMe); 4.7(d, 1H, $C_{5\beta}H$); 4.9(m, 1H, $C_{6\alpha}H$); 5.2-5.3(m, 2H, allylCH_2); 5.9(m, 1H, allylCH); 6.7(ABq, 2H, C_1,C_2H); 8.3(m, 4H, $OCOC_6H_4NO_2$)	476[M^+](30) 446(20)
3d	0.1-0.9(m, 5H, cyclopropylH); 3.8(s, 3H, OMe); 4.7(d, 1H, $C_{5\beta}H$); 4.9(m, 1H, $C_{6\alpha}H$); 6.7(ABq, 2H, C_1,C_2H); 8.3(m, 4H, $OCOC_6H_4NO_2$)	490[M^+](20) 449(15)
3e	2.2(s, 3H, $OCOCH_3$); 2.4(s, 3H, NMe); 4.7(d, 1H, $C_{5\beta}H$); 4.8(m, 1H, $C_{6\alpha}H$); 6.7(ABq, 2H, C_1,C_2H); 8.3(m, 4H, $OCOC_6H_4NO_2$)	478[M^+](10) 436(15)
4a	2.4(s, 3H, NMe); 3.8(s, 3H, OMe); 4.8(d, 1H, $C_{5\beta}H$); 5.0(m, 1H, $C_{6\alpha}H$); 6.7(ABq, 2H, C_1,C_2H); 8.3(m, 4H, $OCOC_6H_4NO_2$)	466[M^+](30)
4b	0.9(t, 3H, propylMe); 3.8(s, 3H, OMe); 4.8(d, 1H, $C_{5\beta}H$); 5.0(m, 1H, $C_{6\alpha}H$); 6.7(ABq, 2H, C_1,C_2H); 8.3(m, 4H, $OCOC_6H_4NO_2$)	494[M^+](10) 465(20)
4c	3.8(s, 3H, OMe); 4.8(d, 1H, $C_{5\beta}H$); 5.0(m, 1H, $C_{6\alpha}H$); 5.2(m, 2H, allylCH_2); 5.8(m, 1H, allylCH); 6.7(ABq, 2H, C_1,C_2H); 8.3(m, 4H, $OCOC_6H_4NO_2$)	492[M^+](10)
4d	0.1-0.9(m, 5H, cyclopropylH); 3.8(s, 3H, OMe); 4.8(d, 1H, $C_{5\beta}H$); 5.0(m, 1H, $C_{6\alpha}H$); 6.7(ABq, 2H, C_1,C_2H); 8.3(m, 4H, $OCOC_6H_4NO_2$)	506[M^+](35) 465(15)
4e	2.2(s, 3H, $OCOCH_3$); 2.4(s, 3H, NMe); 4.8-5.0(m, 2H, $C_{5\beta}H$ and $C_{6\alpha}H$); 6.7(ABq, 2H, C_1,C_2H); 8.3(m, 4H, $OCOC_6H_4NO_2$)	494[M^+](35) 452(40)
4f	0.9(t, 3H, propylMe); 2.2(s, 3H, $OCOCH_3$); 4.8-5.0(m, 2H, $C_{5\beta}H$ and $C_{6\alpha}H$); 6.7(ABq, 2H, C_1,C_2H); 8.3(m, 4H, $OCOC_6H_4NO_2$)	522[M^+](10) 493(30)
4g	2.2(s, 3H, $OCOCH_3$); 4.8-5.0(m, 2H, $C_{5\beta}H$ and $C_{6\alpha}H$); 5.2(m, 2H, allylCH_2); 5.8(m, 1H, allylCH); 6.7(ABq, 2H, C_1,C_2H); 8.3(m, 4H, $OCOC_6H_4NO_2$)	520[M^+](10)
4h	0.1-0.9(m, 5H, cyclopropylH); 2.2(s, 3H, $OCOCH_3$); 4.8-5.0(m, 2H, $C_{5\beta}H$ and $C_{6\alpha}H$); 6.7(ABq, 2H, C_1,C_2H); 8.3(m, 4H, $OCOC_6H_4NO_2$)	534[M^+](10) 492(10)
5a	2.4(s, 3H, NMe); 3.8(s, 3H, OMe); 4.8(d, 1H, $C_{5\beta}H$); 4.9(m, 1H, $C_{6\alpha}H$); 6.7(ABq, 2H, C_1,C_2H); 7.5(m, 3H) and 8.0(m, 2H, $OCOC_6H_5$)	421[M^+](40)
6a	2.4(s, 3H, NMe); 3.9(s, 3H, OMe); 4.4(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, C_1,C_2H)	301[M^+](100) 286(20)
6b	0.9(t, 3H, propylMe); 3.9(s, 3H, OMe); 4.4(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, C_1,C_2H)	329[M^+](10) 300(100)
6c	3.9(s, 3H, OMe); 4.4(d, 1H, $C_{5\beta}H$); 5.3(m, 2H, allylCH_2); 5.9(m, 1H, allylCH); 6.7(ABq, 2H, C_1,C_2H);	327[M^+](100)
6d	0.1-1.1(m, 5H, cyclopropylH); 3.9(s, 3H, OMe); 4.4(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, C_1,C_2H)	341[M^+](100) 300(52)
6e	2.4(s, 3H, NMe); 4.4(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, C_1,C_2H)	287[M^+](70)
6f	0.9(t, 3H, propylMe); 4.4(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, C_1,C_2H)	315[M^+](12) 286(95)
6g	4.4(d, 1H, $C_{5\beta}H$); 5.3(m, 2H, allylCH_2); 5.8(m, 1H, allylCH); 6.7(ABq, 2H, C_1,C_2H);	313[M^+](100) 286(10)
6h	0.2-0.9(m, 5H, cyclopropylH); 4.4(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, C_1,C_2H)	327[M^+])60) 286(30)

Table II continued

Cmpd.	^{1}H-NMR δ (ppm) $CDCl_3$ (* DMSO-d_6)	MS (%)
7a	2.4(s, 3H, NMe); 3.6(m, 1H, $C_{6\alpha}H$); 3.9(s, 3H, OMe); 4.5(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, C_1,C_2H)	317[M^+]
7b	0.9(t, 3H, propylMe); 3.6(m, 1H, $C_{6\alpha}H$); 3.9(s, 3H, OMe); 4.5(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, C_1,C_2H)	345[M^+](0) 361(100)
7c	3.6(m, 1H, $C_{6\alpha}H$); 3.9(s, 3H, OMe); 4.5(d, 1H, $C_{5\beta}H$); 5.3(m, 2H, allylCH_2); 5.8(m, 1H, allylCH); 6.7(ABq, 2H, C_1,C_2H);	343[M^+](10)
7d	0.1-0.9(m, 5H, cyclopropylH); 3.6(m, 1H, $C_{6\alpha}H$); 3.9(s, 3H, OMe); 4.5(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, C_1,C_2H)	357[M^+]
7e*	2.4(s, 3H, NMe); 4.2(m, 1H, $C_{6\alpha}H$); 5.0(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, C_1,C_2H)	303[M^+](65)
7f	0.9(t, 3H, propylMe); 3.6(m, 1H, $C_{6\alpha}H$); 4.5(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, C_1,C_2H)	331[M^+](10) 302(100)
7g	3.6(m, 1H, $C_{6\alpha}H$); 4.6(d, 1H, $C_{5\beta}H$); 5.1-5.3(m, 2H, allylCH_2); 5.7-5.9(m, 1H, allylCH); 6.7(ABq, 2H, C_1,C_2H);	329[M^+](10)
7h	0.1-0.9(m, 5H, cyclopropylH); 3.6(m, 1H, $C_{6\alpha}H$); 4.6(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, C_1,C_2H)	343[M^+](25) 302(10)
8a	2.4(s, 3H, NMe); 3.8(s, 3H, OMe); 4.0(m, 1H, $C_{6\alpha}H$); 5.2(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, $C_{1,2}$H); 7.8(m, 4H, Pht)	430[M^+](45) 373(15)
8b	0.9(t, 3H, propylMe); 3.8(s, 3H, OMe); 4.0(m, 1H, $C_{6\alpha}H$); 5.2(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, $C_{1,2}$H); 7.8(m, 4H, Pht)	458[M^+](15) 429(100)
8c	3.8(s, 3H, OMe); 4.0(m, 1H, $C_{6\alpha}H$); 5.2(m, 3H, $C_{5\beta}H$ and allylCH_2); 5.9(m, 1H, allylCH)6.7(ABq, 2H, $C_{1,2}$H); 7.8(m, 4H, Pht)	456[M^+](80)
8d	0.1-0.9(m, 5H, cyclopropylH); 3.8(s, 3H, OMe); 4.0(m, 1H, $C_{6\alpha}H$); 5.2(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, $C_{1,2}$H); 7.8(m, 4H, Pht)	470[M^+](60)
8e	2.2(s, 3H, $OCOCH_3$); 2.4(s, 3H, NMe); 4.0(m, 1H, $C_{6\alpha}H$); 5.2(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, $C_{1,2}$H); 7.8(m, 4H, Pht)	458[M^+](15) 416(20)
8f	0.9(t, 3H, propylMe); 2.2(s, 3H, $OCOCH_3$); 4.0(m, 1H, $C_{6\alpha}H$); 5.2(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, $C_{1,2}$H); 7.8(m, 4H, Pht)	457[M^+](10)
8g	2.2(s, 3H, $OCOCH_3$); 4.0(m, 1H, $C_{6\alpha}H$); 5.2(m, 3H, $C_{5\beta}H$ and allylCH_2); 5.9(m, 1H, allylCH)6.7(ABq, 2H, $C_{1,2}$H); 7.8(m, 4H, Pht)	484[M^+](40) 442(40)
8h	0.1-0.9(m, 5H, cyclopropylH); 2.2(s, 3H, $OCOCH_3$); 4.0(m, 1H, $C_{6\alpha}H$); 5.2(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, $C_{1,2}$H); 7.8(m, 4H, Pht)	498[M^+](100) 456(50)
9a	2.4(s, 3H, NMe); 3.8(s, 3H, OMe); 4.1(m, 1H, $C_{6\alpha}H$); 5.3(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, $C_{1,2}$H); 7.8(m, 4H, Pht)	446[M^+](70)
9b	0.9(t, 3H, propylMe); 3.8(s, 3H, OMe); 4.1(m, 1H, $C_{6\alpha}H$); 5.3(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, $C_{1,2}$H); 7.8(m, 4H, Pht)	474[M^+](15) 445(100)
9c	3.8(s, 3H, OMe); 4.1(m, 1H, $C_{6\alpha}H$); 5.3(m, 3H, $C_{5\beta}H$ and allylCH_2); 5.8(m, 1H, allylCH); 6.7(ABq, 2H, $C_{1,2}$H); 7.8(m, 4H, Pht)	472[M^+](15)
9d	0.1-0.9(m, 5H, cyclopropylH); 3.8(s, 3H, OMe); 4.1(m, 1H, $C_{6\alpha}H$); 5.3(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, $C_{1,2}$H); 7.8(m, 4H, Pht)	486[M^+](25)
9e	2.2(s, 3H, $OCOCH_3$); 2.4(s, 3H, NMe); 4.0(m, 1H, $C_{6\alpha}H$); 5.3(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, $C_{1,2}$H); 7.8(m, 4H, Pht)	474[M^+](30) 432(35)
9f	0.9(t, 3H, propylMe); 2.2(s, 3H, $OCOCH_3$); 4.0(m, 1H, $C_{6\alpha}H$); 5.3(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, $C_{1,2}$H); 7.8(m, 4H, Pht)	502[M^+](20) 472(50)
9g	2.2(s, 3H, $OCOCH_3$); 4.0(m, 1H, $C_{6\alpha}H$); 5.3(m, 3H, $C_{5\beta}H$ and allylCH_2); 5.8(m, 1H, allylCH); 6.7(ABq, 2H, $C_{1,2}$H); 7.8(m, 4H, Pht)	500[M^+](10) 458(10)

Table II continued

Cmpd.	^{1}H-NMR δ (ppm) $CDCl_3$ (* DMSO-d_6)	MS (%)
9h	0.1-0.9(m, 5H, cyclopropylH); 2.2(s, 3H, $OCOCH_3$); 4.0(m, 1H, $C_{6\alpha}H$);	514[M^+](10)
	5.3(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, $C_{1,2}H$); 7.8(m, 4H, Pht)	472(10)
10a	2.4(s, 3H, NMe); 4.0(m, 1H, $C_{6\alpha}H$); 5.1(d, 1H, $C_{5\beta}H$); 6.7(ABq, 2H, $C_{1,2}H$);	416[M^+](100)
	7.8(m, 4H, Pht)	359(20)
10b	0.9(t, 3H, propylMe); 4.0(m, 1H, $C_{6\alpha}H$);5.1(d, 1H, $C_{5\beta}H$);	444[M^+](10)
	6.7(ABq, 2H, $C_{1,2}H$); 7.8(m, 4H, Pht)	415(100)
10c	4.0(m, 1H, $C_{6\alpha}H$); 5.2(m, 3H, $C_{5\beta}H$ and allylCH_2);	442[M^+](100)
	5.9(m, 1H, allylCH)6.7(ABq, 2H, $C_{1,2}H$); 7.8(m, 4H, Pht)	415(15)
10d	0.1-0.9(m, 5H, cyclopropylH); 4.0(m, 1H, $C_{6\alpha}H$); 5.1(d, 1H, $C_{5\beta}H$);	456[M^+](90)
	6.7(ABq, 2H, $C_{1,2}H$); 7.8(m, 4H, Pht)	
11a	2.3(s, 3H, NMe); 3.9(m, 1H, $C_{6\alpha}H$); 5.1(d, 1H, $C_{5\beta}H$);	432[M^+](65)
	6.7(ABq, 2H, $C_{1,2}H$); 7.8(m, 4H, Pht)	357(25)
11b	0.9(t, 3H, propylMe); 4.0(m, 1H, $C_{6\alpha}H$)5.2(d, 1H, $C_{5\beta}H$);	460[M^+](15)
	6.7(ABq, 2H, $C_{1,2}H$); 7.8(m, 4H, Pht)	431(100)
11c	4.0(m, 1H, $C_{6\alpha}H$); 5.2(m, 3H, $C_{5\beta}H$ and allylCH_2);	458[M^+](10)
	5.8(m, 1H, allylCH)6.7(ABq, 2H, $C_{1,2}H$); 7.8(m, 4H, Pht)	
11d	0.1-0.9(m, 5H, cyclopropylH); 4.0(m, 1H, $C_{6\alpha}H$); 5.2(d, 1H, $C_{5\beta}H$);	472[M^+](20)
	6.7(ABq, 2H, $C_{1,2}H$); 7.8(m, 4H, Pht)	
12a	2,4(s, 3H, NMe); 3,9(s, 3H, OMe); 4.2(d, 1H, $C_{6\alpha}H$); 6.7(ABq, 2H, $C_{1,2}H$);	300[M^+](100)
12b	0.9(t, 3H, propylMe); 3.9(s, 3H, OMe); 4.2(d, 1H, $C_{6\alpha}H$);	328[M^+](15)
	6,7(ABq, 2H, $C_{1,2}H$);	
12c	3.9(s, 3H, OMe); 4.2(d, 1H, $C_{6\alpha}H$); 5.2(m, 2H, allyl CH_2); 5.9(m, 1H, allylCH); 6.7(ABq, $2HC_{1,2}H$)	326[M^+](10)
12d	0.1-0.9(m, 5H, cyclopropylH); 3.9(s, 3H, OMe); 4.2(d, 1H, $C_{6\alpha}H$);	340[M^+](85)
	6.7(ABq, 2H, $C_{1,2}H$);	322(20)
12e	2.3(s, 3H, NMe); 4.4(d, 1H, $C_{6\alpha}H$); 6.7(ABq, 2H, $C_{1,2}H$);	286[M^+](100)
12f	0.9(t, 3H, propylMe); 4.1(d, 1H, $C_{6\alpha}H$); 6.7(ABq, 2H, $C_{1,2}H$);	312[M^+](25)
12g	4.1(d, 1H, $C_{6\alpha}H$); 5.2(m, 2H, allyl CH_2); 5.9(m, 1H, allylCH);	314[M^+](10)
	6.7(ABq, $2HC_{1,2}H$)	285(20)
12h	0.1-0.9(m, 5H, cyclopropylH); 4.1(d, 1H, $C_{6\alpha}H$); 6.7(ABq, 2H, $C_{1,2}H$);	326[M^+](100)
13a	2.3(s, 3H, NMe); 3.8(s, 3H, OMe); 4.1(d, 1H, $C_{6\alpha}H$); 6.7(ABq, 2H, C_1,C_2H);	316[M^+](100)
13b	0.9(t, 3H, propylH); 3.8(s, 3H, OMe); 4.3(d, 1H, $C_{6\alpha}H$);	344[M^+](25)
	6.7(ABq, 2H, C_1,C_2H);	315(100)
13c	3.9(s, 3H, OMe); 4.4(d, 1H, $C_{6\alpha}H$); 5.2(m, 2H, allyl CH_2); 5.9(m, 1H, allylCH);	342[M^+](25)
	6.7(ABq, $2HC_{1,2}H$)	
13d	0.1-0.9(m, 5H, cyclopropylH); 3.8(s, 3H, OMe); 4.3(d, 1H, $C_{6\alpha}H$);	356[M^+](25)
	6.7(ABq, 2H, C_1,C_2H);	
13e	2.3(s, 3H, NMe); 4.1(d, 1H, $C_{6\alpha}H$); 6.7(ABq, 2H, C_1,C_2H);	302[M^+](100)
13f	0.9(t, 3H, propylH); 4.3(d, 1H, $C_{6\alpha}H$); 6.7(ABq, 2H, C_1,C_2H);	330[M^+](20)
		301(70)
13g	4.3(d, 1H, $C_{6\alpha}H$); 5.2(m, 2H, allyl CH_2); 5.9(m, 1H, allylCH);	328[M^+](40)
	6.7(ABq, $2HC_{1,2}H$)	
13h	0.1-0.9(m, 5H, cyclopropylH); 4.3(d, 1H, $C_{6\alpha}H$); 6.7(ABq, 2H, C_1,C_2H);	342[M^+](30)

Experimental

Melting points were determined with an "Electrotermal" digital instrument (Type 8103) in open capillary tubes and the data are uncorrected. Thin layer chromatography was performed on precoated Merck 5554 Kieselgel 60 F254 foils using 8:2 benzene:methanol, 9:1 chloroform:methanol, 5:4:1 chloroform:acetone:diethylamine and 8:2:1 ethyl acetate:methanol:25% ammonia solution developing systems. The spots were visualised by Dragendorff-reagent. For column chromatography Kieselgel 60 H absorbent and 9:1 benzene-methanol eluent were applied. 1H-NMR spectra were recorded with a Varian-Gemini 200 instrument and mass spectra were obtained with a VG-TRIO-2 spectrometer.

Preparation of Compounds 3a-e, 4a-h, 5a (Mitsunobu-esterification procedure)

Compound (1a-e or 2a-h) (10 mmol), triphenylphosphine (5.24 g, 20mmol) and p-nitrobenzoic acid (3.34 g, 20 mmol) or benzoic acid (2,24 g, 20 mmol) were dissolved in anhydrous benzene (100 ml) and diethyl azodicarboxylate (3.4 ml, 20 mmol) dissolved in anhydrous benzene(10 ml) was dropwise added over a period of 5-10 min. The reaction mixture was stirred for another 1 h and the precipitate was filtered off. The solvent was evaporated, the syrupy residue treated with D-tartaric acid (2.0-2.5 g) dissolved in 100 ml of water and extracted with ether. The aqueous phase was alkalized with 10% ammonium hydroxide and extracted with chloroform. The chloroform solution was washed with brine, then with water, dried over sodium sulfate, the solvent was evaporated, and the residue was crystallized from ethanol.

General Procedure for the Hydrolysis of p-nitrobenzoic acid esters

A mixture of compound (3a-e or 4a-h) (1.0 g), 10% aqueous KOH solution (10ml), and ethanol (10ml) was refluxed for 10 min, then the pH of the mixture was adjusted to 8-9 with 10% ammonium hydroxide and extracted with chloroform. The organic phase was washed with brine, then with water, dried over sodium sulfate, the solvent was evaporated and the residue was crystallized to afford compounds (6a-e, 7a-h).

O-Demethylation with Boron Tribromide

To a cold (0 °C) solution of boron tribromide (1.2 ml, 12mmol) in dry chloroform (50 ml) a solution of the codeine derivative (5.8 mmol) in chloroform (30 ml) was dropwise added over a period of 20 min with stirring and under nitrogen atmosphere. Stirring was continued for 60 min at 0-5 °C and then the mixture was poured onto ice (100 g) and the pH of the aqueous layer was adjusted to 8.5-9.0 by the addition of ammonium hydroxide. The chloroform layer was separated and the aqueous phase was extracted with chloroform (3x20 ml). The combined organic extract was washed with aq. sodium chloride, dried and concentrated.

Cleavage of esters of 14-hydroxyisomorphine derivatives

A solution of the ester (4e-h) in methanol (15 ml) was treated with a 0.1% solution of sodium methoxide in methanol under reflux temperature for 30 min. The solvent was removed under diminished pressure and the product was prepared as the chlorohydrate.

General procedure for the preparation of the 6β-phthalimido (8a-h and 9a-h) derivatives

Compound (1a-h or 2a-h) (10 mmol), triphenylphosphine (5.24 g, 20 mmol) and phthalimide (2.94 g, 20 mmol) were dissolved in anhydrous benzene (100 ml) and diethyl azodicarboxylate (3.4 ml, 20 mmol) dissolved in anhydrous benzene(10 ml) was dropwise added over a period of 5-10 min. The reaction mixture was stirred for another 1 h and the precipitate was filtered off. The solvent was evaporated, the syrupy residue treated with D-tartaric acid (2.0-2.5 g) dissolved in 100 ml of water and extracted with ether. The aqueous

phase was alkalized with 10% ammonium hydroxide and extracted with chloroform. The chloroform solution was washed with brine, then with water, dried over sodium sulphate, the solvent was evaporated, and the residue was crystallized from ethanol.

General procedure for splitting of the phenol esters (preparation of (10a-d and 11a-d)

To a solution of the 3-*O*-acetyl derivative (1.0 g) in ethanol (45 ml) an aqueous solution (5 ml) of hydroxylamine hydrochloride (0.15 g) was added and the mixture was stirred at 50 °C for 10 min. After completion of the reaction, ethanol was distilled off in vacuo, the residue was taken up with water, made alkaline with a dilute aqueous solution of ammonium hydroxide or sodium carbonate and extracted with chloroform. The organic layer was washed with aqueous sodium chloride and water, dried over sodium sulphate and evaporated. The residual product was crystallized from ethanol.

General procedure for the preparation of 6β-amino derivatives (12a-h and 13a-h)

A solution of the 6β-phthalimido derivative (1.0 g) in ethanol (15ml) was treated with 98% hydrazine hydrate (0.4ml, 8 mmol). After completion of the reaction the hot mixture was poured into 30 ml of 1.5 N acetic acid and the precipitated ftalazin-1,4-dione was filtered off. The filtrate was neutralized with 10% aqueous solution of ammonium hydroxide and extracted with chloroform or (in the case of morphine derivatives) with a 2:1 chloroform:isopropanol mixture. The organic layer was washed with brine and water, dried over sodium sulfate and concentrated under reduced pressure. The residue was crystallized or purified by column chromatography.

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