APPLICATION OF THE MITSUNOBU REACTION IN THE MORPHINE SERIES. PREPARATION OF 6β-AMINO-14β-HYDROXYMORPHINE AND 14-HYDROXYCODEINE DERIVATIVES

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Abstract --- By the application of the Mitsunobu reaction several 6β-phthalimido-14β-hydroxymorphine and 14β-hydroxycodeine derivatives have been synthesized. Cleavage of the phthalimido derivatives with hydrazine hydrate afforded 6β-amino-14β-hydroxymorphine and 14β-hydroxycodeine derivatives. Catalytic hydrogenation of the $\Delta^{7,8}$ double bond offered a stereoselective way for the synthesis of the corresponding 6β-amino-14β-hydroxydihydrocodeine and 14β-hydroxydihydromorphine derivatives.

In previous papers of this series we have recently described the successful application of the Mitsunobu reaction[1,2] in the field of morphine alkaloids.[3-6] Besides epimerization of the alcoholic hydroxyl group of *N*-demethyl-*N*-alkylcodeine and 3-*O*-acetyl-*N*-demethyl-*N*-alkylmorphine derivatives several 6β-phthalimido analogues have been prepared, and by splitting of the phthalimides compounds carrying a primary amino group have been synthesized. These latter amines could not be previously obtained by routine chemical transformation (sulphonate → azide displacement and subsequent reduction,[7] or reductive amination of morphinane ketones[8,9]).

Since during epimerization of the alcoholic hydroxyl group no difference between the behaviour of the 14β-H and 14β-OH derivatives was observed, the synthesis of the corresponding 14β-hydroxy derivatives carrying a primary amino function at 6β-position was decided. Of the unsaturated representatives of related morphine alkaloids the only known substance is 6-deoxy-6β-amino-14β-hydroxycodeine,[10] and among the saturated

ring-C compounds the corresponding dihydrocodeine[10] and 6β-amino-6-deoxy-14β-hydroxydihydromorphine and its *N*-allyl and *N*-cyclopropylmethyl analogues have been prepared by Portoghese and co-workers.[9]

Our previous experiences have revealed that no allyl-migration occurs in the Mitsunobu reaction. Therefore, it was supposed that the 6β-amino derivatives with a $\Delta^{7,8}$ double bond would be readily obtained with related derivatives, and thus;

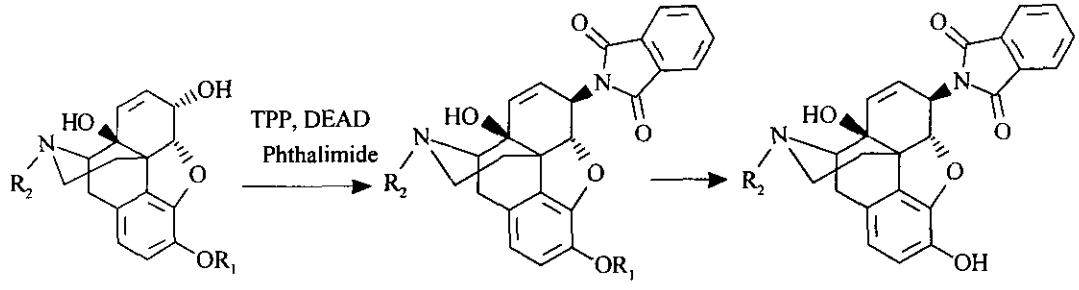
i.) informations for the structure-activity relationship of morphine alkaloids with respect to the different conformational properties of the unsaturated and saturated ring-C derivatives could be obtained,

ii.) by saturation of the unsaturated bond an independent, a stereoselective route for the preparation of the derivatives described earlier by Portoghese *et al.*[8,9] could be elaborated, and

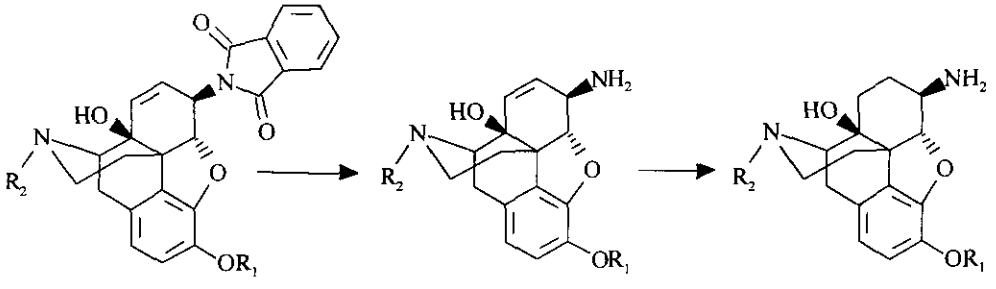
iii.) upon tritiation of the double bonds these latter substances could be obtained in labelled form.

For the preparation of the target phthalimido derivatives (2a-h) the *N*-demethyl-*N*-alkyl-14-hydroxycodeines (1a-d) and the corresponding morphine analogues[11] (1e-h) were applied. Temporary protection of the 14β-hydroxy group was negligible, but to avoid non-desired side reactions (formation of alkyl phenyl ethers[12]) the phenolic hydroxyl group of the morphine derivatives was protected by acetylation according to the Welsh procedure.[13] In the case of the *N*-demethyl-*N*-alkyl-14β-hydroxycodeine derivatives (1a-d) no difference in the course and yield of the reaction, as compared to those of the 14β-H analogues, was observed. It was found, however, that transformation of the 14β-hydroxymorphines (1e-h) is completed in about an hour under the usual conditions (as proved by tlc examinations), but the desired phthalimides either could not be isolated in pure form (i.e. the *N*-cyclopropylmethyl (CPM) derivative 2h) or the yields were unacceptably low, however we could not detect any by-product by monitoring the Mitsunobu reaction by tlc. In some cases the lower yields (30-40%) can be attributed to the decomposition of the phthalimides during the workup procedure. The yields are given (Table I.) for the recrystallized products and are not optimized. Cleavage of the 3-*O*-acetyl group of 2e-h was performed conveniently with the same procedure as for the 14β-H analogues (hydroxyl ammonium chloride in aqueous ethanol, 50 °C), but this method worked well only with the *N*-methyl and *N*-propyl derivatives (2e and 2f, respectively). The location and steric position of the phthalimido function in 2a-h were unambiguously proved by ^{1}H-nmr measurements; namely the $J_{5\beta,6\alpha}$ coupling constants indicated inversion of the configuration. Detailed ^{1}H-nmr analysis of these compounds has been published earlier.[14] Dephthaloylation of the phthalimides (2a-h) was accomplished by treatment with hydrazine in ethanol to give rise to the target primary amino derivatives (3a-h). Except for the *N*-allyl analogues (3c and 3g), subsequent saturation of the

$\Delta^{7,8}$ double bond then allowed the preparation of the corresponding dihydro compounds (4a-f). The 6β position of the phthalimide group has been verified not only by the ^{1}H-nmr spectra but also by the fact that the compounds prepared by dephthaloylation corresponded with the C-6β amines described earlier.[7]



1a-h 2a-h 2i-j



2a-h 3a-h 4a-f

Table I.

Melting points and elemental analytical data for the prepared compounds

Com-pound	R_1	R_2	yield (%)	Formula	mp. (°C)	Analytical data calculated		found	
						C %	N %	C %	N %
2a	CH_3	CH_3	65	$C_{26}H_{24}N_2O_5$	115-117	70.4	6.3	70.7	6.4
2b	CH_3	n-C_3H_7	40	$C_{28}H_{28}N_2O_5$	162-164	71.2	6.3	71.1	6.5
2c	CH_3	$CH_2CH{=}CH_2$	40	$C_{28}H_{26}N_2O_5$	186-188	71.5	6.0	71.1	6.1
2d	CH_3	CPM	45	$C_{29}H_{28}N_2O_5$	186-188	71.9	5.8	71.7	5.9
2e	$COCH_3$	CH_3	43	$C_{27}H_{24}N_2O_6$	218-219	68.6	5.9	68.8	5.7
2f	$COCH_3$	n-C_3H_7	40	$C_{29}H_{28}N_2O_6$	178-180	69.6	5.6	69.4	5.5
2g	$COCH_3$	$CH_2CH{=}CH_2$	30	$C_{29}H_{26}N_2O_6$	197-199	69.9	5.6	70.2	5.5
2i	H	CH_3	74	$C_{25}H_{22}N_2O_5$	238-240	69.8	6.5	69.9	6.6
2j	H	n-C_3H_7	20	$C_{27}H_{26}N_2O_5$	201-303	70.7	6.1	70.9	6.0
3a	CH_3	CH_3	70	$C_{18}H_{22}N_2O_3$	125-126#	68.8	8.9	68.5	8 8
3b	CH_3	n-C_3H_7	90	$C_{20}H_{26}N_2O_3$	oil	---	---	---	---
3c	CH_3	$CH_2CH{=}CH_2$	90	$C_{20}H_{24}N_2O_3$	oil	---	---	---	---
3d	CH_3	CPM	90	$C_{21}H_{26}N_2O_3$	oil	---	---	---	---
3e	H	CH_3	75	$C_{17}H_{20}N_2O_3$	207-209	68.0	9.3	67.8	9.2
3f	H	n-C_3H_7	44	$C_{19}H_{24}N_2O_3$	116-122	69.5	8.5	69.8	8.3
3g	H	$CH_2CH{=}CH_2$	61	$C_{19}H_{22}N_2O_3$	123-125	69.9	8.6	70.1	8.4
3h	H	CPM	10	$C_{20}H_{24}N_2O_3$	99-101	70.6	8.2	70.4	8.1
4a	CH_3	CH_3	64	$C_{18}H_{24}N_2O_3$	152-154#	68.3	8.9	68.0	9.1
4b	CH_3	n-C_3H_7	68	$C_{20}H_{28}N_2O_3$	127-129	69.7	8.1	70.1	7.9
4c	CH_3	CPM	59	$C_{21}H_{28}N_2O_3$	125-126	70.8	7.9	71.1	8.0
4d	H	CH_3	84	$C_{17}H_{22}N_2O_3$	260*#	67.5	9.3	67.3	9.1
4e	H	n-C_3H_7	80	$C_{19}H_{26}N_2O_3$	191-193	69.1	8.5	68.8	8.7
4f	H	CPM	85	$C_{20}H_{26}N_2O_3$	oil	---	---	---	---

3a:116-117[10]; 4a:147-148[10], 4d: > 260(2HCl)*[9]; 4f: >270(2HCl)[9]

* decomposition

Table 2

Representative ^{1}H-nmr and ms data for compounds (2-4)

Compd.	^{1}H-Nmr δ (ppm) $CDCl_3$ (* DMSO-d_6)	Ms (%)
2a	2.4(s, 3H, NMe); 3.9(s, 3H, OMe); 4.9(m, $J_{6\alpha,7}$=4.1 Hz, 1H, $C_{6\alpha}$H); 5.1(d, $J_{5\beta,6\alpha}$=3.1 Hz, 1H, $C_{5\beta}$H); 5.5(dd, $J_{6\alpha,8}$=3.0 Hz, $J_{7,8}$=10.0 Hz, 1H, C_8H); 5.9(m, 1H, C_7H); 6.7(ABq, $J_{1,2}$=8.1 Hz, 2H, C_1,C_2H); 7.8(m, 4H, Pht-H)	444[M^+](60) 426(15)
2b	0.9(t, J=7.0 Hz, 3H, propylMe); 3.8(s, 3H, OMe); 4.8(m, $J_{6\alpha,7}$=4.1 Hz, 1H, $C_{6\alpha}$H); 5.1(d, $J_{5\beta,6\alpha}$=3.1 Hz, 1H, $C_{5\beta}$H); 5.5(dd, $J_{6\alpha,8}$=3.0 Hz, $J_{7,8}$=10.0 Hz, 1H, C_8H); 5.8(m, 1H, C_7H); 6.7(ABq, $J_{1,2}$=8.2 Hz, 2H, C_1,C_2H); 7.8(m, 4H, Pht-H)	472[M^+](25) 443(100)
2c	3.9(s, 3H, OMe); 4.9(m, $J_{6\alpha,7}$=4.0 Hz, 1H, $C_{6\alpha}$H); 5.1(d, $J_{5\beta,6\alpha}$=3.2 Hz, 1H, $C_{5\beta}$H); 5.2-5.3(m, 2H, allylCH); 5.5(dd, $J_{6\alpha,8}$=3.1 Hz, $J_{7,8}$=10.0 Hz, 1H, C_8H); 5.9(m, 2H, C_7H and allylCH); 6.7(ABq, $J_{1,2}$=8.1 Hz, 2H, C_1,C_2H); 7.8(m, 4H, Pht-H)	470[M^+](15) 452(100)
2d	0.1-0.9(m, 5H, cyclopropylH); 3.9(s, 3H, OMe); 4.9(m, $J_{6\alpha,7}$=4.0 Hz, 1H, $C_{6\alpha}$H); 5.1(d, $J_{5\beta,6\alpha}$=3.1 Hz, 1H, $C_{5\beta}$H); 5.5(dd, $J_{6\alpha,8}$=3.0 Hz, $J_{7,8}$=10.0 Hz, 1H, C_8H); 5.9(m, 1H, C_7H); 6.7(ABq, $J_{1,2}$=8.1 Hz, 2H, C_1,C_2H); 7.8(m, 4H, Pht-H)	484[M^+](50) 369(10)
2e	2.3(s, 3H, $OCOCH_3$); 2.5(s, 3H, NMe); 4.9(m, $J_{6\alpha,7}$=4.0 Hz, 1H, $C_{6\alpha}$H); 5.1(d, $J_{5\beta,6\alpha}$=3.1 Hz, 1H, $C_{5\beta}$H); 5.5(dd, $J_{6\alpha,8}$=3.1 Hz, $J_{7,8}$=10.1 Hz, 1H, C_8H); 5.8(m, 1H, C_7H); 6.7(ABq, $J_{1,2}$=8.2 Hz, 2H, C_1,C_2H); 7.8(m, 4H, Pht-H)	472[M^+](20) 428(10)
2f	0.9(t, J=7.0 Hz, 3H, propylMe); 2.3(s, 3H, $OCOCH_3$); 4.8(m, $J_{6\alpha,7}$=4.0 Hz, 1H, $C_{6\alpha}$H); 5.2(d, $J_{5\beta,6\alpha}$=3.2 Hz, 1H, $C_{5\beta}$H); 5.6(dd, $J_{6\alpha,8}$=3.1 Hz, $J_{7,8}$=10.0 Hz, 1H, C_8H); 5.9(m, 1H, C_7H); 6.7(ABq, $J_{1,2}$=8.2 Hz, 2H, C_1,C_2H); 7.8(m, 4H, Pht-H)	500[M^+](10) 471(40)
2g	2.3(s, 3H, $OCOCH_3$); 4.9(m, $J_{6,7}$=4.0 Hz, 1H, $C_{6\alpha}$H); 5.1(d, $J_{5\beta,6\alpha}$=3.1 Hz, 1H, $C_{5\beta}$H); 5.2-5.3(m, 2H, allylCH_2); 5.5(dd, $J_{6\alpha,8}$=3.1 Hz, $J_{7,8}$=10.1 Hz, 1H, C_8H); 5.8-5.9(m, 2H, C_7H and allylCH); 6.7(ABq, $J_{1,2}$=8.2 Hz, 2H, C_1,C_2H); 7.8(m, 4H, Pht-H)	498[M^+](10)
2i*	2.3(s, 3H, NMe); 4.5(m, $J_{6\alpha,7}$=4.0 Hz, 1H, $C_{6\alpha}$H); 5.0(d, $J_{5\beta,6\alpha}$=3.1 Hz, 1H, $C_{5\beta}$H); 5.5(dd, $J_{6\alpha,8}$=3.1 Hz, $J_{7,8}$=10.0 Hz, 1H, C_8H); 5.8(m, 1H, C_7H); 6.7(ABq, $J_{1,2}$=8.2 Hz, 2H, C_1,C_2H); 7.8(m, 4H, Pht-H)	430[M^+](35)
2j	0.9(t, J=7.0 Hz, 3H, propylMe); 4.8(m, $J_{6\alpha,7}$=4.1 Hz, 1H, $C_{6\alpha}$H); 5.0(d, $J_{5\beta,6\alpha}$=3.2 Hz, 1H, $C_{5\beta}$H); 5.5(dd, $J_{6\alpha,8}$=3.0 Hz, $J_{7,8}$=10.1 Hz, 1H, C_8H); 5.9(m, 1H, C_7H); 6.7(ABq, $J_{1,2}$=8.1 Hz, 2H, C_1,C_2H); 7.8(m, 4H, Pht-H)	458[M^+](10) 429(10)
3a	2.4(s, 3H, NMe); 3.8(s, 3H, OMe); 4.7(dd, $J_{5\beta,6\alpha}$=1.0 Hz, $J_{5\beta,7}$=1.1 Hz, 1H, $C_{5\beta}$H); 5.6(d, $J_{7,8}$=9.7 Hz, 1H, C_8H); 6.2(dd, $J_{5\beta,7}$=1.1 Hz, $J_{6\alpha,7}$=6.0 Hz, 1H, C_7H); 6.7(ABq, $J_{1,2}$=8.1 Hz, 2H, C_1,C_2H);	314[M^+](100)
3b	0.9(t, J=7.0 Hz, 3H, propylH); 3.8(s, 3H, OMe); 4.7(dd, $J_{5\beta,6\alpha}$=1.0 Hz, $J_{5\beta,7}$=1.1 Hz, 1H, $C_{5\beta}$H); 5.6(d, $J_{7,8}$=9.7 Hz, 1H, C_8H); 6.2(dd, $J_{5\beta,7}$=1.1 Hz, $J_{6\alpha,7}$=5.9 Hz, 1H, C_7H); 6.7(ABq, $J_{1,2}$=8.2 Hz, 2H, C_1,C_2H);	342[M^+](60) 313(100)

Table 2. continued

Compd.	^{1}H-Nmr δ (ppm) $CDCl_3$ (* DMSO-d_6)	Ms (%)
3c	3.8(s, 3H, OMe); 4.7(dd, $J_{5\beta,6\alpha}$=1.0 Hz, $J_{5\beta,7}$=1.1 Hz, 1H, $C_{5\beta}H$); 5.2(m, 2H, allylCH_2); 5.6(d, $J_{7,8}$=9.8 Hz, 1H, C_8H); 5.9(m, 1H, allylCH); 6.2(dd, $J_{5\beta,7}$=1.0 Hz, $J_{6\alpha,7}$=6.0 Hz, 1H, C_7H); 6.7(ABq, $J_{1,2}$=8.1 Hz, 2H, C_1,C_2H);	340[M^+](30) 277(20)
3d	0.1-0.9(m, 5H, cyclopropylH); 3.8(s, 3H, OMe); 4.7(dd, $J_{5\beta,6\alpha}$=1.0 Hz, $J_{5\beta,7}$=1.1 Hz, 1H, $C_{5\beta}H$); 5.6(d, $J_{7,8}$=9.7 Hz, 1H, C_8H); 6.2(dd, $J_{5\beta,7}$=1.1 Hz, $J_{6\alpha,7}$=6.0 Hz, 1H, C_7H); 6.7(ABq, $J_{1,2}$=8.2 Hz, 2H, C_1,C_2H);	354[M^+](25)
3e*	2.3(s, 3H, NMe); 4.5(dd, $J_{5\beta,6\alpha}$=1.0 Hz, $J_{5\beta,7}$=1.1 Hz, 1H, $C_{5\beta}H$); 5.6(d, $J_{7,8}$=9.8 Hz, 1H, C_8H); 6.0(dd, $J_{5\beta,7}$=1.1 Hz, $J_{6\alpha,7}$=6.1 Hz, 1H, C_7H); 6.7(ABq, $J_{1,2}$=8.2 Hz, 2H, C_1,C_2H);	300[M^+](100)
3f	0.9(t, J=7.0 Hz, 3H, propylH); 4.9(dd, $J_{5\beta,6\alpha}$=1.0 Hz, $J_{5\beta,7}$=1.0 Hz, 1H, $C_{5\beta}H$); 5.6(d, $J_{7,8}$=9.7 Hz, 1H, C_8H); 6.1(dd, $J_{5\beta,7}$=1.1 Hz, $J_{6\alpha,7}$=6.0 Hz, 1H, C_7H); 6.7(ABq, $J_{1,2}$=8.2 Hz, 2H, C_1,C_2H);	328[M^+](60) 299(100)
3g	4.9(dd, $J_{5\beta,6\alpha}$=1.0 Hz, $J_{5\beta,7}$=1.0 Hz, 1H, $C_{5\beta}H$); 5.2(m, 2H, allylCH_2); 5.6(d, $J_{7,8}$=9.7 Hz, 1H, C_8H); 5.9(m, 1H, allylCH); 6.1(dd, $J_{5\beta,7}$=1.1 Hz, $J_{6\alpha,7}$=6.0 Hz, 1H, C_7H); 6.7(ABq, $J_{1,2}$=8.2 Hz, 2H, C_1,C_2H);	326[M^+](50) 277(30)
3h	0.1-0.9(m, 5H, cyclopropylH); 4.9(dd, $J_{5\beta,6\alpha}$=1.0 Hz, $J_{5\beta,7}$=1.1 Hz, 1H, $C_{5\beta}H$); 5.7(d, $J_{7,8}$=9.8 Hz, 1H, C_8H); 6.1(dd, $J_{5\beta,7}$=1.0 Hz, $J_{6\alpha,7}$=6.1 Hz, 1H, C_7H); 6.7(ABq, $J_{1,2}$=8.1 Hz, 2H, C_1,C_2H);	340[M^+](20)
4a*	2.3(s, 3H, NMe); 3.8(s, 3H, OMe); 4.1(d, $J_{5\beta,6\alpha}$=7.3 Hz, 1H, $C_{5\beta}H$); 6.7(ABq, $J_{1,2}$=8.2 Hz, 2H, C_1,C_2H);	316[M^+](100)
4b*	0.9(t, J=7.0 Hz, 3H, propylH); 3.8(s, 3H, OMe); 4.3(d, $J_{5\beta,6\alpha}$=7.2 Hz, 1H, $C_{5\beta}H$); 6.7(ABq, $J_{1,2}$=8.2 Hz, 2H, C_1,C_2H);	344[M^+](25) 315(100)
4c	0.1-0.9(m, 5H, cyclopropylH); 3.8(s, 3H, OMe); 4.3(d, $J_{5\beta,6\alpha}$=7.2 Hz, 1H, $C_{5\beta}H$); 6.7(ABq, $J_{1,2}$=8.2 Hz, 2H, C_1,C_2H);	356[M^+](25)
4d	2.3(s, 3H, NMe); 4.1(d, $J_{5\beta,6\alpha}$=7.3 Hz, 1H, $C_{5\beta}H$); 6.7(ABq, $J_{1,2}$=8.2 Hz, 2H, C_1,C_2H);	302[M^+](100)
4e	0.9(t, J=7.0 Hz, 3H, propylH); 4.3(d, $J_{5\beta,6\alpha}$=7.1 Hz, 1H, $C_{5\beta}H$); 6.7(ABq, $J_{1,2}$=8.1 Hz, 2H, C_1,C_2H);	330[M^+](20) 301(70)
4f	0.1-0.9(m, 5H, cyclopropylH); 4.3(d, $J_{5\beta,6\alpha}$=7.2 Hz, 1H, $C_{5\beta}H$); 6.7(ABq, $J_{1,2}$=8.2 Hz, 2H, C_1,C_2H);	342[M^+](30)

* DMSO-d_6 as solvent

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 adsorbent and 9:1 benzene-methanol eluent were applied. ^{1}H-Nmr spectra were recorded with a Varian-Gemini 200 instrument and mass spectra were obtained with a VG-TRIO-2 spectrometer.

General procedure for the preparation of the 6β-phthalimido (2a-h) derivatives

Compound (1) (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 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 (2i-j)

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, 2.2 mmol) 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 10% aqueous solution of ammonium hydroxide or sodium carbonate and extracted with chloroform. The organic layer was washed with brine and water, dried over sodium sulphate and evaporated. The residual product was crystallized from ethanol.

General procedure for the preparation of 6β-amino derivatives

A solution of the 6β-phthalimido derivative (1.0 g) in ethanol (15ml) was treated with 98% hydrazin 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.

General procedure for the hydrogenation of the 6β-amino derivatives with unsaturated C-ring

A solution of the starting compound (0.5 g) in ethanol (30 ml) was hydrogenated in the presence of 10% palladium-on-charcoal. The catalyst was filtered off, the filtrate was concentrated under diminished pressure and the residue was crystallized from ethanol or ether.

ACKNOWLEDGEMENTS

This work was financially supported in part, by a grant (OTKA I/3 1722) obtained from the National Science Foundation (Hungary).

The authors thank Mrs. Zoltán Kovács and Mrs. Sándor Kolozsi for their conscientious technical assistance.

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Received, 14th January, 1994