Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of N-Demethyl-N-Substituted Dihydroisomorphine and Dihydroisocodeine Derivatives[+]

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Published online: 23 Sep 2006.

SYNTHETIC COMMUNICATIONS, 22(12), 1673-1682 (1992)

SYNTHESIS OF N-DEMETHYL-N-SUBSTITUTED DIHYDROISOMORPHINE AND DIHYDROISOCODEINE DERIVATIVES*

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Abstract: Several new N-demethyl-N-alkyl derivatives (1p, 1r, 1s, 1m, 1n and 1o) of dihydroisomorphine and dihydroisocodeine, and N-demethyl-N-cyclopropylmethylisocodeine (2g) have been prepared. The presented synthetic procedure allows a convenient access to a series of structurally related, stereochemically homogeneous substances for studies of the agonist/antagonist properties.

Our ongoing research program aimed at the synthesis of morphine-antagonist compounds and at the examination of the agonist/antagonist properties of these derivatives - permitting the recognition of fine details of the structure-activity relationship - requires the pharmacological examination of a great number of structually related derivatives belonging to certain groups of stereochemically homogeneous morphine alkaloids.

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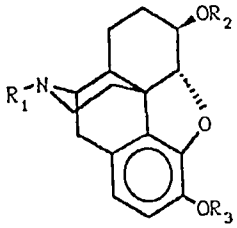
In a previous paper[1] we have described the preparation of isomorphine and isocodeine, as well as their N-demethyl-N-substituted analogues by means of the application of the Mitsunobu reaction.

Recently we have also reported[2] on the stereohomogeneous synthesis of the N-demethyl-N-substituted derivatives of 14-hydroxydihydromorphine.

The present paper deals, most particularly, with the N-demethylation and subsequent N-alkylation of dihydroisomorphine and dihydroisocodeine.



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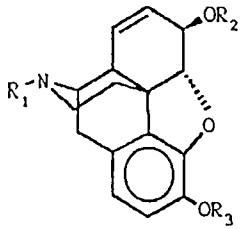

2

1a : R_1=CH_3, R_2=R_3=H

1b : R_1=CH_3, R_2=R_3=$COCH_3$

1c : R_1=CN, R_2=R_3=$COCH_3$

1d : R_1=CN, R_2=R_3=H

1e : R_1=R_2=R_3=H

1f : R_1=CO_2CH=CH_2, R_2=R_3=$COCH_3$

1g : R_1=H, R_2=R_3=$COCH_3$

1h : R_1=R_3=CH_3, R_2=H

1i : R_1=R_3=CH_3, R_2=$COCH_3$

2a : R_1=CH_3, R_2=R_3=H

2b : R_1=R_2=R_3=H

2c : R_1=CH_3, R_2=R_3=$COCH_3$

2d : R_1=CO_2-CH=CH_2, R_2=R_3=$COCH_3$

2e : R_1=H, R_2=R_3=$COCH_3$

2f : R_1=R_2=H, R_3=CH_3

2g : R_1=CH_2-c-C_3H_5, R_2=H, R_3=CH_3

2h : R_1=CH_2=CH-CH_2-, R_2=R_3=H

1j : R_1=CN, R_2=$COCH_3$, R_3=CH_3

1k : R_1=CN, R_2=H, R_3=CH_3

1l : R_1=R_2=H, R_3=CH_3

1m : R_1=n-C_3H_7, R_2=H, R_3=CH_3

1n : R_1=CH_2=CH-CH_2-, R_2=H, R_3=CH_3

1o : R_1=CH_2-c-C_3H_5 , R_2=H, R_3=CH_3

1q : R_1=n-C_3H_7, R_2=R_3=H

1r : R_1=CH_2=CH-CH_2-, R_2=R_3=H

1s : R_1=CH_2-c-C_3H_5 , R_2=R_3=H

The preparation of dihydroisomorphine (1a)[++] was carried out by the catalytic hydrogenation[3] of isomorphine (2a)[1].

The N-demethylation of 1a could be readily achieved by treatment of the corresponding 3,6-di-O-acetyl derivative (1b) either with BrCN or vinyl chloroformate[4]. In the former case the produced cyanamide ester 1c was hydrolyzed with acid into N-demetyl-dihydroisomorphine (1e) via 1d in two steps. Upon chloroformate-demetylation, the resulting urethane 1f was subjected to acid hydrolysis without isolation, and the formed mixture of 1g and 1e was transformed into homogeneous 1e by means of alkaline hydrolysis.

Vinyl chloroformate proved to be applicable for obtaining the hitherto also unknown N-demethyl-isomorphine (2b), as well, from 3,6-O-diacetylisomorphine (2c)[5] via 2d or 2e. N-Demethylation of isomorphine either with BrCN, or with diethyl azodicarboxylate - a reagent successfully employed[6] for N-demethylation of thebaine and neopin - remained unsuccessful.

Table 1

Physical constants of compounds

Compound	m.p. (°C) (solvent)	Yield (%)	Compound	m.p. (°C) (solvent)	Yield (%)
1b	138-139 (EtOAc)	57	1n	121-123 (EtOH)	58
1c	202-204 (EtOH)	64	1o	136-138 (EtOH)	57
1d	287	88	1p	104-106 (EtOH)	53
1e	283	56	1r	180-182 (EtOAc)	63
1j	150-151 (EtOH)	78			
1k	234-236 (EtOH)	90	1s	286-290[x] (EtOH) (base, syrup)	51
1l	248-253 (EtOH)	45	2b	273-276 (base, amorphous powder)	83[xx]
1m	288-290[x] (EtOH) (base, syrup)	69			
			2g	146-148 (EtOAc)	81

[x] HCl salt

[xx] Calculated for 2c

Catalytic hydrogenation of isocodeine[1] readily furnished dihydroisocodeine (1h)[7], which was acetylated[7] to give 6-O-acetyl-dihydroisocodeine (1i). N-Demethylation of this latter compound could then be effected [11] with BrCN via 1j and 1k. An analogous N-demethylation could also be carried out by employing vinyl chloroformate without the isolation of the intermediates.

In a previous paper we have reported[8] on the N-demethylation of isocodeine, in connection with similar reaction of the additional codeine isomers.

N-Demethyl-dihydroisocodeine was transformed into the corresponding N-(n-propyl)-, N-allyl- and N-cyclopropylmethyl analogues (1m, 1n, and 1o, respectively). O-Dealkylation of these latter compounds with boron tribromide furnished the corresponding N-demethyl-N-substituted dihydroisomorphines 1p, 1r and 1s. 1r was also prepared by the direct allylation of 1e. N-Demethyl-isocodeine (2f) was converted into the N-cyclopropylmethyl analogue (2g). The N-allyl- and N-(n-propyl) derivatives (earlier synthesized[1] by the Mitsunobu reaction) were also prepared according to the same methodology. With the aid of this procedure N-demethyl-isomorphine (2b) was converted into the N-allyl compound 2h ("izonalorfin"[1]).

EXPERIMENTAL

Melting points were determined with an "Electrothermal" (8103) digital instrument in open capillary tubes, and the data are uncorrected. For thin layer chromatography precoated Kieselgel 60 F_{254} (MERCK 5554) layer and a 8:2 benzene-methanol mixture were

Table 2

Mass spectra and the caracteristic ^1H NMR data of compounds

Compound	Mass spectrum	PMR (ppm) $CDCl_3$; or[x] DMSO-d_6
1b	$C_{21}H_{25}NO_5$ (271.42)[xx] 371(M^+; 50%), 329(100%)	6.7 dd(H-1.2;2H), 4.55 m(H-5 and H-6;2H), 2.4 s(N-Me;3H), 2.3 s(OAc;3H), 2.1 s(OAc;3H)
1c	$C_{21}H_{22}N_2O_5$ (382.41) 382(M^+; 3%), 340(100%)	6.9-6.75 dd(H-1.2;2H), 5.5 m(H-5 and H-6;2H), 2.3 s and 2.1 s(acetyl-protons;6H)
1d[x]	$C_{17}H_{18}N_2O_3$ (298.33) 298(M^+; 25%)	6.6 dd(H-1.2;2H), 4.2 d(H-5; 1H)
1e[x]	$C_{16}H_{19}NO_3$ (273.3) 273(M^+; 12%)	6.6-6.4 dd(H-1.2;2H), 4.1 d(H-5;1H)
1j	$C_{20}H_{22}N_2O_4$ (354.40) 354(M^+; 100%), 341(69%)	6.7 dd(H-1.2;2H), 4.5 m(H-5; and H-6;2H), 3.9 s(OMe;3H)
1k	$C_{18}H_{20}N_2O_3$ (312.36) 312(M^+; 100%)	6.7 dd(H-1.2;2H), 4.4 d(H-5; 1H), 3.8 s(OMe;3H)
1l	$C_{17}H_{21}NO_3$ (287.34) 287(M^+; 100%), 244(54%)	6.7 dd(H-1.2;2H), 4.3 d(H-5; 1H), 3.8 s(OMe;3H)
1m	$C_{20}H_{27}NO_3$ (329.43) 329(M^+; 12%), 300(100%)	6.7-6.6 dd(H-1.2;2H), 4.35 d(H-5;1H), 3.85 s(OMe;3H), 0.9 t($CH_2CH_2CH_3$;3H)
1n	$C_{20}H_{25}NO_3$ (327.40) 327(M^+;100%)	6.7-6.6 dd(H-1.2;2H), 5.9 m(allylproton;1H), 5.3 m(allylprotons;2H), 4.4 d(H-5;1H), 3.85 s(OMe;3H)
1o	$C_{21}H_{27}NO_3$ (341.44) 341(M^+; 100%), 300(52%)	6.7-6.6 dd(H-1.2;2H), 4.35 d(H-5;1H), 3.85 s(OMe;3H) 1.1-0.1 m(cyclopropyl-protons;5H)
1p	$C_{19}H_{25}NO_3$ (315.4) 315(M^+; 12%), 286(95%)	6.7-6.5 dd(H-1.2;2H), 4.4 d(H-5;1H), 0.9 t($CH_2CH_2CH_3$; 3H)

1r	$C_{19}H_{23}NO_3$ (313.37) 313(M^+; 100%), 286(12%)	6.7-6.6 dd(H-1.2;2H), 5.8 m(allylproton;1H), 5.3 m(allylprotons;2H), 4.4 d (H-5;1H)
1s	$C_{20}H_{25}NO_3$ (327.40) 327(M^+; 62%), 286(28%)	6.7-6.5 dd(H-1.2;2H), 4.4 d (H-5;1H), 1.0-0.1 m(cyclo-propylprotons;5H)
2b	$C_{16}H_{17}NO_3$ (271.31) 271(M^+; 100%), 252(10%)	6.5-6.3 dd(H-1.2;2H), 5.75 m(H-7;1H), 5.5 d(H-8;1H), 4.5 s(H-5;1H)
2g	$C_{21}H_{25}NO_3$ (339.41) 339(M^+; 78%)	6.65-6.55 dd(H-1.2;2H), 6.0 m(H-7;1H), 5.65 m(H-8;1H), 4.8 s(H-5;1H), 4.25 d(H-6; 1H), 3.85 s(OMe;3H), 0.9-0.2 m(cyclopropylprotons;5H)

++All compounds gave acceptable elemental analysis

applied. Visualization of the chromatograms was carried out with the Dragendorff-reagent. For column chromatography Kieselgel 60 M adsorbent and 9:1 benzene-methanol and 9:1 chloroform-methanol eluents were applied. The ^{1}H-NMR- and mass spectra were obtained with Varian-Gemini 200 and VG-TRIO-2 spectrometers, respectively.

The von Braun reaction

To a solution of 10 mmol of the dihydroisomorphine or dihydroisocodeine ester (1b or 1i) in dry chloroform (30 ml) a solution of BrCN (1.6 g, 15 mmol) in chloroform (20 ml) was added. T.L.C. examination showed that the reaction was complete after

reflux for 4 hours. Following evaporation of the solvent the residue was crystallized from ethanol.

Hydrolysis of 1c, 1j

The cyanamide-ester (2.0 g) was hydrolized with conc. hydrochloric acid (20 ml) at 100°C for 5 minutes. The mixture was quickly cooled, diluted with water (80 ml) and the precipitated crystalline N-cyano derivative was washed with water.

Hydrolysis of the N-cyano compounds

2.0 g of the N-cyano derivative (1d, 1k) was mixed with hot 6% aq. hydrochloric acid, and after complete dissolution the mixture was refluxed for additional 10 hours. After cooling, the hydrochloride salt of the N-demethyl derivative precipitated, from which the liberated free base was obtained by means of extraction with chloroform.

N-Demethylation with vinyl chloroformate

To a solution of the acetyl derivative (10 mmol) in dry 1,2-dichloro-ethane (50 ml) 2.5 g of powdered sodium hydrogen carbonate was added, and under stirring and ice-cooling a solution of vinyl chloroformate (3.6 ml, 40 mmol) in 1,2-dichloroethane (20 ml) was dropwise added. After stirring for half an hour at room temperature, and then under reflux for 6 hours T.L.C. examination showed that the starting material had disappeared. The inorganic salt was filtered off and the filtrate was washed with water, dried and evaporated. The residue was dissolved in dry dichloromethane

(100 ml) and then dry hydrochloric acid gas was passed through the solution with stirring and cooling for one hour. The mixture was evaporated to dryness, and the residue was mixed with methanol (80 ml) and boiled for 2 hours. The solvent was removed by evaporation and the hydrochloride salt of the N-demethyl derivative was suspended with ethanol (100 ml), mixed with 10% aq. NaOH (10 ml) and kept under gentle reflux for 5 minutes.

N-Demethyl-dihydroisocodeine was obtained in form of the crystalline free base by the removal of ethanol, followed by dilution with water.

In the case of N-demethyl-isomorphine and N-demethyl--dihydroisomorphine the free bases were isolated by adjusting the pH of the solution to 8.5-9.

N-Alkylation of the N-demethyl derivatives

To a mixture of the N-demethyl compound (10 mmol), abs. N,N-dimethylformamide (50 ml) and powered sodium hydrogen carbonate (1.0 g) 12 mmol of the alkyl bromide was added. After stirring at 70°C for 20 hours the reaction mixture was cooled and the inorganic salt was removed by filtration. The filtrate was concentrated under diminished pressure, the residue was suspended in water and then extracted with chloroform. The organic layer was dried, evaporated and the residual crude product was purified either by crystallization or by column chromatography.

This work was supported, in part, by a grant (OTKA I/3 reg. No.: 1722) obtained from the Hungarian Academy of Sciences.

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(Received in UK 3 February, 1992)