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Application of the Mitsunobu Reaction for the Preparation of Isomorphine and Isocodeine Derivatives

Csaba Simon [a], Sándor Hosztafi [a] & Sándor Makleit [b]
[a] Alkaloida Chemical Factory, H 4440, Tiszavasvári, Hungary
[b] Department of Organic Chemistry, L. Kossuth University, H 4010, Debrecen, Hungary

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MORPHINE ALKALOIDS, 111[1]

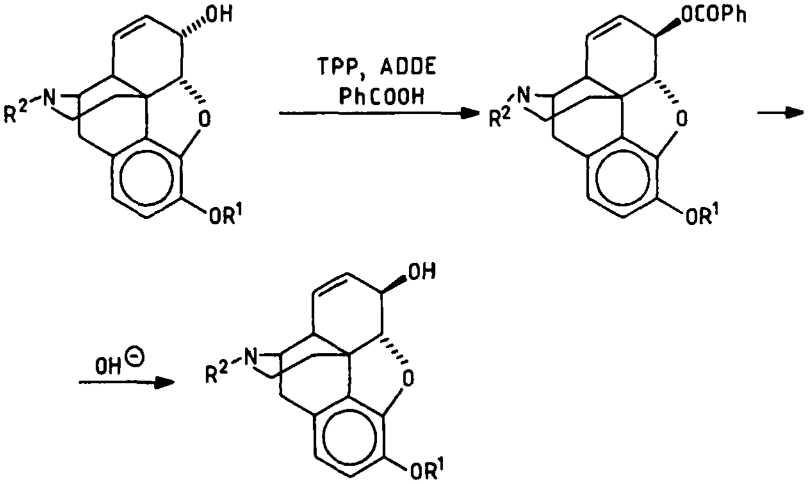
APPLICATION OF THE MITSUNOBU REACTION FOR THE PREPARATION OF ISOMORPHINE AND ISOCODEINE DERIVATIVES

Csaba Simon[a], Sándor Hosztafi[a], and Sándor Makleit[b]

[a]Alkaloida Chemical Factory, H 4440 Tiszavasvári, Hungary and [b]Department of Organic Chemistry, L. Kossuth University, H 4010 Debrecen, Hungary

Abstract: New isomorphine and isocodeine derivatives have been prepared by the application of the Mitsunobu reaction. Compounds prepared will be utilized for various pharmacological investigations to obtain new data concerning the structure-activity relationships.

Relatively few isomorphine and isocodeine derivatives have hitherto been described in the literature. Various procedures have been developed and applied for their preparation.[2-8] The reason for such studies can be a comprehensive pharmacological trial, e.g. effectiveness, toxicity,[9] change of the agonist-antagonist ratio, etc. The Mitsunobu reaction[10] has been used for the preparation of such substances. Up to now this reaction was utilized by Japanese authors[11] who used thioacetic acid to synthesize 6β-thiols from morphine alkaloids. Data of compounds prepared are summarized in Tables 1 and 2.



Scheme

Structure of compounds prepared has been elucidated by ^{1}H-NMR (Bruker WP 200 SY spectrometer) spectra and by MS(VG 7035 GC-MS-DS) spectra[14]. No allylic rearrangement[15] has been observed. Pharmacological studies of substances synthesized will be published elsewhere.

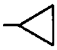
Experimental

General Procedure for the Preparation of Compounds 2

Compound 1 (10 mmol), triphenylphosphine (20 mmol), and benzoic acid (20 mmol) were dissolved in anhydrous benzene (100 ml) and diethyl azodicarboxylate (20 mmol) dissolved in anhydrous benzene (10 ml) was added in drops for 5 - 10 min. The reaction mixture was stirred for another 1 h and the precipitate filtered off. The solvent was evaporated, the oily residue treated with D-tartaric acid (1.5 g) dissolved in water (100 ml)

Table 1

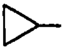
Physical constants of compounds 2

Compound	R^1	R^2	Yield %	M.p. °C	$[\alpha]_D$
2a	CH_3	CH_3	66.3	148-150	-259.6
2b	CH_3	$n-C_3H_7$	63.9	oil	-
2c	CH_3	$CH_2-CH=CH_2$	62.8	oil	-
2d	C_2H_5	CH_3	71.2	140-142	-222.8
2e	$C_6H_5CH_2$	CH_3	74.6	151-153	-216.2
2f	$(CH_2)_2NC_4H_8O$	CH_3	75.3	171-172	-212.3
2g	$COCH_3$	CH_3	54.2[a]	224-227	-254.7
2h	$COCH_3$	$n-C_3H_7$	29.8[a]	138-140	-229.4
2i	$COCH_3$	$CH_2-CH=CH_2$	45.2[a]	112-113	-236.4
2j	$COCH_3$	H_2C 	63.5[a]	138-139	-240.6

[a] Calculated for R^1 = H. Acetylation has been performed according to L.H. Welsh[12] to avoid the formation of the alkyl phenyl ethers.[13]

Table 2

Physical constants of compounds 3

Compound	R^1	R^2	Yield %	M.p.[a] °C	$[\alpha]_D$[b]
3a	CH_3	CH_3	100	173-174	-153.6
3b	CH_3	$n\text{-}C_3H_7$	29.5	62-64	-143.1
3c	CH_3	$CH_2\text{-}CH{=}CH_2$	32.2	112-113	-174.9
3d	C_2H_5	CH_3	100	132-134	-135.7
3e	$C_6H_5CH_2$	CH_3	85.6	172-173	-115.1
3f	$(CH_2)_2NC_4H_8O$	CH_3	100	74-77	-100.2
3g	H	CH_3	61.5	249-250	-143.1
3h	H	$n\text{-}C_3H_7$	51.3	205-206	-173.6
3i	H	$CH_2\text{-}CH{=}CH_2$	43.0	197-198	-174.8
3j	H	 $-CH_2$	36.2	oil	-

[a] Lit. m.p. 3a 173-174 °C,[6] 3d 128-130 °C,[8] 3g 251-252 °C[4]. [b] Lit. $[\alpha]_D$ 3a -149[6], 3d -143.7[8], 3g -162.9[4].

and extracted with diethyl ether. The aqueous phase was alkalized with ammonium hydroxide and extracted with chloroform. The chloroform solution was washed with brine, then with water, dried, the solvent evaporated, and the residue crystallized from ethanol.

General Procedure for the Preparation of Compounds 3

A mixture of compound 2 (1.0 g), 10% KOH aqueous solution (10 ml), and ethanol (10 ml) was refluxed for 10 min, then the ethanol evaporated, and the precipitate filtered off. In case no precipitate was obtained, the pH of the aqueous solution was adjusted to 8-9 and extracted with chloroform. The organic phase was washed with brine, then with water, dried, the solvent evaporated and the residue crystallized to afford compounds 3.

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