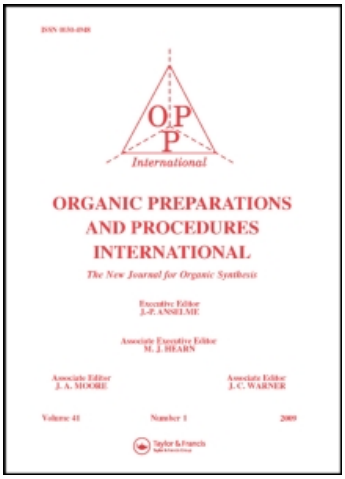

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

THE PREPARATION OF STEROIDAL AMIDES I. TRIPHENYLPHOSPHITE METHOD

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To cite this Article Herz, J. E. and Mantecón, Rosa Elena(1972) 'THE PREPARATION OF STEROIDAL AMIDES I. TRIPHENYLPHOSPHITE METHOD', Organic Preparations and Procedures International, 4: 3, 123 — 128
To link to this Article: DOI: 10.1080/00304947209355537
URL: http://dx.doi.org/10.1080/00304947209355537

ORGANIC PREPARATIONS AND PROCEDURES INT. 4(3), 123-128 (1972)

The Preparation of Steroidal Amides I. Triphenylphosphite Method

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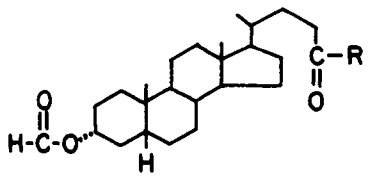
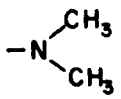
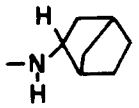
Steroidal amides have been prepared mainly by reaction of the steroidal acid chlorides with excess primary or secondary amines or with an equivalent amount of amine in the presence of a tertiary base such as triethylamine or pyridine[1]. We have found yields and purity of the products of these reactions to be in general unsatisfactory. In addition, this method involves two steps whereas our procedures avoid the preparation of the acid chloride. We therefore investigated the adaption of three methods used in peptide synthesis to the synthesis of steroidal amides: a) reaction of the steroid acid and an amine in presence of triphenyl phosphite and imidazole, b) reaction of the imidazolide of the steroidal acid with an amine c) preparation of the steroidal amide by reaction of an acid and an amine in presence of EEDQ (N-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline). For each amide we chose among the three methods of preparation the one that gave the least complex mixture of products, as shown by TLC,

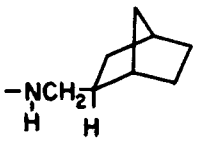
TABLE 1

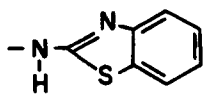


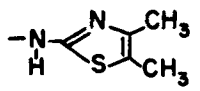
I R = -OH

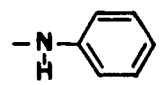
II R = 

III R = 

IV R = 

V R = 

VI R = 

VII R = 

and from which the desired amide could be obtained in at least 50% isolated yield, without having to make use of time consuming separation methods. Reaction a) is described in this paper, b) and c) in the following paper.

$$R\text{-}COOH + (C_6H_5O)_3P + R'NH_2 \xrightarrow[THF]{IMIDAZOLE} RCONHR' + (C_6H_5O)_2POH + C_6H_5OH$$

We have found the method of Mitin and Glinzkaya[2] for the preparation of peptides to be applicable to the preparation of a variety of amides of lithocholic acid 3-formate[3] (I, Table 1).

CARBOXYLIC ACID:

$$(C_6H_5O)_2P\text{-}O\text{-}C_6H_5 \quad + \quad R\text{-}\overset{\overset{O}{\|}}{C}\text{-}OH \xrightarrow{IMIDAZOLE} (C_6H_5O)_2P\text{-}O\text{-}\overset{\overset{O}{\|}}{C}\text{-}R \; (1) \; + \; HOC_6H_5 \; (2)$$

STRONGLY BASIC AMINE:

$$(1) \quad + \quad HN\begin{matrix}R'\\R''\end{matrix} \longrightarrow R\text{-}\overset{\overset{O}{\|}}{C}\text{-}N\begin{matrix}R'\\R''\end{matrix} \quad + \quad (C_6H_5O)_2P\text{-}OH \; (3)$$

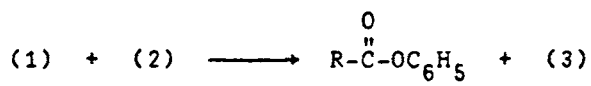
Very weakly basic amines, such as 2-aminopyrimidine, and lithocholic acid 3-formate do not yield the amide but a nitrogen free compound, identified as the phenyl ester of lithocholic acid 3-formate by combustion analysis, NMR and mass spectrometry.

TABLE 2

Compound	mp.	$(\alpha)_D$	Molecular Formula		Analyses C	H	N	Solvent	Yield
II	84-86°	+40.25°	$C_{27}H_{45}NO_3$	Calc	75.13	10.51	3.24	E-H	83%
				Found	75.19	10.46	3.09		
III	156-58°	+29.75°	$C_{32}H_{51}NO_3$	Calc	77.22	10.33	2.81	C-H	75%
				Found	77.07	10.14	2.74		
IV	179-81°	+18.0°	$C_{33}H_{53}NO_3$	Calc	77.45	10.44	2.74	C-M	76%
				Found	77.25	10.29	2.68		
V	190-91°	+20.1°	$C_{32}H_{44}N_2O_3S$	Calc	71.61	8.26	5.22	E	79%
				Found	71.46	8.01	5.37		
VI	188-90°	+17.22°	$C_{30}H_{46}N_2O_3S$	Calc	70.01	9.01	5.44	E-H	72%
				Found	70.28	9.02	5.48		
VII	205-06°	+20.0°	$C_{31}H_{45}NO_3$	Calc	77.62	9.46	2.92	M	65%
				Found	77.79	9.53	2.84		

E = Ether, H = Hexane, C = Methylene dichloride, M = Methanol

WEAKLY BASIC AMINE:



(1) + (2) ⟶ R-C(=O)-OC$_6$H$_5$ + (3)

EXPERIMENTAL

All melting points are uncorrected. Rotations are determined in chloroform solution with a Perkin-Elmer Model 141 Polarimeter.

Amides: Lithocholic acid 3-formate[3] (2.5 m moles, 1 g), the amine (2.5 m moles), imidazole (3.8 m moles, 260 mg) and triphenylphosphite (3.8 m moles, 1.18 g) were dissolved in about 15 ml anhydrous tetrahydrofuran (distilled over $LiAlH_4$) in a rubber stoppered hypo-vial, which was immersed in a constant temperature bath set at 40°C. After 12 hours, samples were withdrawn with a syringe and analyzed by TLC. When all the acid had reacted (18 to 24 hours) the mixture was poured into ice-water and extracted with ether. The ether was washed with 5% Na_2CO_3 solution, water, dried with anh. Na_2SO_4 and evaporated, and the resulting solid crystallized from a suitable solvent (See Table 2).

When the amine hydrochloride was used instead of the free amine an equivalent amount (2.5 m moles, 340 mg) of triethylamine was added to the reaction mixture after the addition of the triphenylphosphite.

Amines used were:

Compound (II) dimethylamine, (III) 2-norbornaneamine, (IV) endo 2-aminomethyl bicyclo [2·2·1]heptane hydrochloride, (V) 2-aminobenzothiazole, (VI) 2-amino-4,5-dimethylthiazole

hydrobromide, (VII) aniline hydrochloride.

Phenylester: When 2-aminopyrimidine was employed as the amine a compound mp. 102-3° (crystallized from methanol), $(\alpha)_D$ + 18° was obtained.

Analysis: Calc. for $C_{31}H_{44}O_4$ C: 77.46 H: 9.23
found C: 77.53 H: 9.32 N: 0.0

The NMR-spectrum showed multiple peaks between 7.0 and 7.7 ppm (δ) integrating for five aromatic protons. The mass spectrum showed M^+ = 480, 387 = $(M - C_6H_5O)^+$, 93 = $(C_6H_5O)^+$, 77.

REFERENCES

1) Example: N.A. Nelson, US Pat. 3,257,384, CA65, 12269 (1966).

2) Yu. V. Mitin, OV. Glinskaya, Tetrahedron Lett. 5267 (1969).

3) W.M. Hohen, R.B. Moffet, J. Am. Chem. Soc. 67, 740 (1945).

ACKNOWLEDGEMENT

We thank Dr. E.S. Waight, Imperial College, London for carrying out the MS-analysis, and Mr. Joseph F. Alicino, New Hope, Pa. for the C, H, N-analyses.

(Received April 21, 1972; in revised form June 15, 1972)