

This article was downloaded by:

On: 27 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



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 II. IMIDAZOLIDE METHOD AND EEDQ METHOD

J. E. Herz^a; Rosa Elena Mantecón^a

^a Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, México, DF

To cite this Article Herz, J. E. and Mantecón, Rosa Elena(1972) 'THE PREPARATION OF STEROIDAL AMIDES II. IMIDAZOLIDE METHOD AND EEDQ METHOD', *Organic Preparations and Procedures International*, 4: 3, 129 – 134

To link to this Article: DOI: 10.1080/00304947209355538

URL: <http://dx.doi.org/10.1080/00304947209355538>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

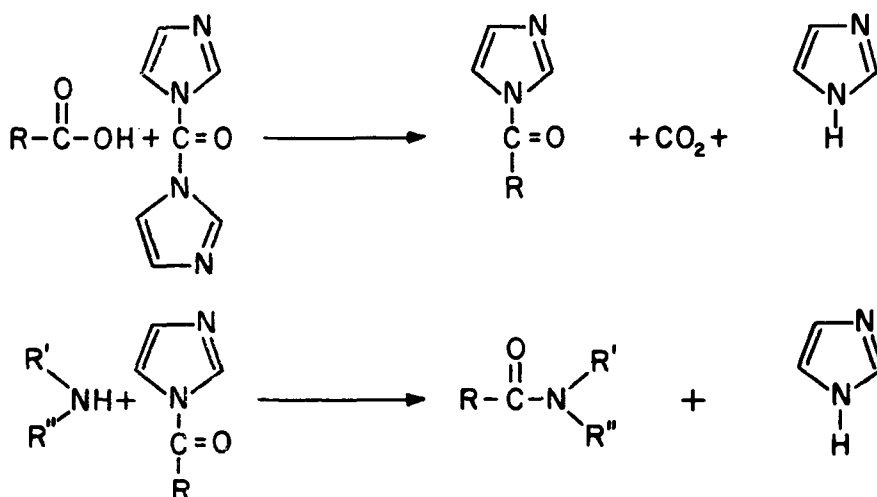
The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

The Preparation of Steroidal Amides II. Imidazolide Method
and EEDQ Method

J.E. Herz* and Rosa Elena Mantecón

Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado Postal 14-740, México 14, D.F.

The formation of amides from acids and amines via the imidazolide of the acid is described by Staab et al¹⁾, and proceeds according to the following scheme:

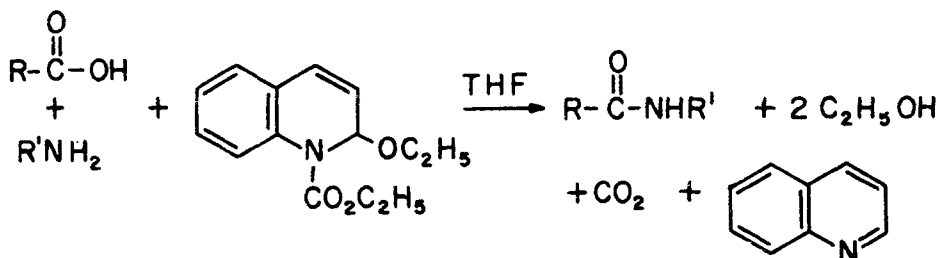


In our hands this method has been of limited use for the preparation of steroidal amides. In the particular case of lithocholic acid 3-formate²⁾ (I, Table 1) the imidazolide is unstable and cannot be isolated in pure form. Two amides

were prepared by this method from 2-aminopyridine (II) and from morpholine (III) (Table 1).

Belleau and Malek first proposed *N*-ethoxy carbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) as a condensing agent for the formation of $\text{-}\overset{\text{O}}{\parallel}{\text{C}}\text{-N-}$ linkages in peptides³⁾. The reagent

reacts according to the following scheme:



The five examples (IV-VIII) listed in (Tables 1 and 2) are cases where the EEDQ method was found to give the best results of the three methods⁴⁾ for the preparation of amides of lithocholic acid 3-formate.

Reaction of lithocholic acid 3-formate with 2-aminopyridine in the presence of EEDQ gave the anhydride of the acid.

The infrared spectrum of this compound shows two peaks at 1755 cm^{-1} and 1825 cm^{-1} generally associated with carboxylic acid anhydrides.

EXPERIMENTAL

Imidazolide method:

Lithocholic acid 3-formate (1g, 2.5 m moles) was dissolved in 15 ml dry tetrahydrofuran, previously distilled from LiAlH_4 , and added to *N*, *N'*-carbonyl diimidazole (500 mg, 3 m moles) in a hypo-vial. When gas evolution ceased, 2.5 mmoles of the amine in 5 ml THF were added. The mixture was

THE PREPARATION OF STEROIDAL AMIDES II.

TABLE 1

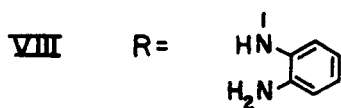
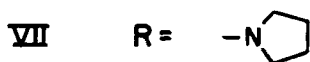
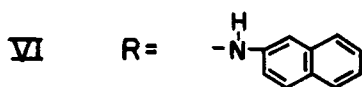
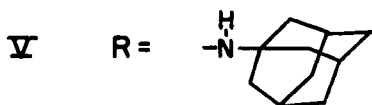
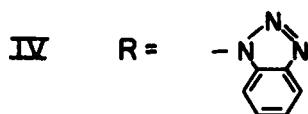
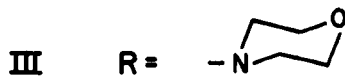
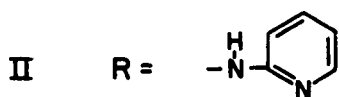
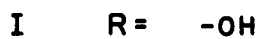
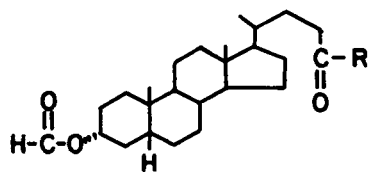


TABLE 2

Compound	mp.	$(\alpha)_D$	Molecular Formula	Analyses			Solvent	Yield
				C	H	N		
II	125-27°	+28.25°	$C_{30}H_{44}N_2O_3$	Calc: 74.96 Found: 74.78	9.23 9.41	5.83 5.72	E	53%
III	205-06°	+48.50°	$C_{29}H_{47}NO_4$	Calc: 73.53 Found: 73.51	10.00 10.11	2.96 2.92	M-E	65%
IV	144-45°	+40.1°	$C_{31}H_{43}N_2O_3$	Calc: 73.63 Found: 73.49	8.57 8.69	8.31 8.16	E-M	54%
V	193-95°	+ 8.1°	$C_{35}H_{55}NO_3 \cdot CH_3OH$	Calc: 75.88 Found: 75.95	10.44 10.49	2.46 2.53	E-M-C	78%
VI	165-67°	+22.75°	$C_{35}H_{47}NO_3$	Calc: 79.35 Found: 79.33	8.94 9.20	2.64 2.89	E	81%
VII	90-92°	+25.81°	$C_{29}H_{47}NO_3$	Calc: 76.10 Found: 76.00	10.35 10.54	3.06 3.37	E	61%
VIII	213-14°	+14.0°	$C_{31}H_{46}N_2O_3$	Calc: 75.26 Found: 75.18	9.37 9.15	5.98 5.66	M	73%

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

THE PREPARATION OF STEROIDAL AMIDES II.

allowed to react at 40°C. When TLC-analysis indicated the absence of starting material (about 18 hours), the solvent was removed under vacuum, the residue dissolved in ether or methylene chloride and washed with water, dried with anh. Na_2SO_4 and evaporated.

Amines used were: Compound (II) 2-aminopyridine, (III) morpholine.

EEDQ Method:

To 2.5 m moles (1 g) of lithocholic acid 3-formate, 2.5 m moles of the amine, and 3 m moles of EEDQ (650 mg) in a hypo-vial was added 20 ml dry THF. After 18 hours at 40°C, a TLC was run, and when the starting material had disappeared (18 to 24 hours), the mixture was evaporated to dryness, the residue dissolved in ether, washed with water, dried with anh. Na_2SO_4 and evaporated.

Amines used were: Compound (IV) benzotriazol, (V) 1-adamantane amine, (VI) 2-naphtylamine, (VII) tetrahydropyrrol, (VIII) o-phenylenediamine.

Anhydride of lithocholic acid 3-formate:

Lithocholic acid 3-formate (1g, 2.5 m moles), 2-aminopyrimidine (240 mg, 2.5 m moles) and EEDQ (650 mg, 3 m moles) were dissolved in 10 ml dry THF and reacted as above. The product was crystallized from methanol-ether; mp. 121-3°, $(\alpha)_D -2^\circ$ (CHF).

Analysis: $\text{C}_{50}\text{H}_{78}\text{O}_7$ Calc: C: 75.91; H: 9.94
Found: C: 75.79; H: 9.91

The same product could be obtained by reacting 1 equivalent of acid with 0.5 equivalent of EEDQ in the absence of

J. E. HERZ AND R. E. MANTECON

amine, in the same way as described in the previous experiment.

REFERENCES

- 1) H.A. Staab, M. Lükking, F.H. Dürr, Chem. Ber., 95, 1275 (1962).
- 2) W.M. Hohen, R.B. Moffet, J. Am. Chem. Soc., 67, 740 (1945).
- 3) B. Belleau, G. Malek, J. Am. Chem. Soc., 90, 1651 (1968).
- 4) See preceeding paper.

ACKNOWLEDGEMENT

We thank Mr. Joseph F. Alicino, New Hope, Pa. for carrying out the C, H, N-analyses.

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