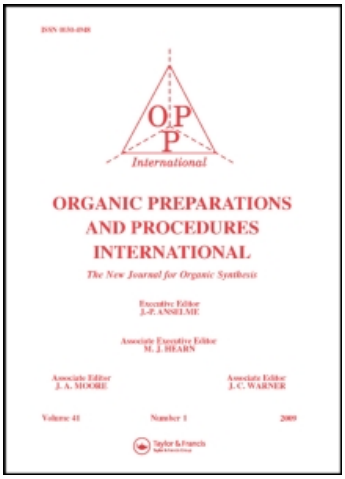


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# THE PREPARATION OF STEROIDAL AMIDES II. IMIDAZOLIDE METHOD AND EEDQ METHOD

J. E. Herz[a]; Rosa Elena Mantecón[a]
[a] Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, México, DF

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ORGANIC PREPARATIONS AND PROCEDURES INT. 4(3), 129-134 (1972)

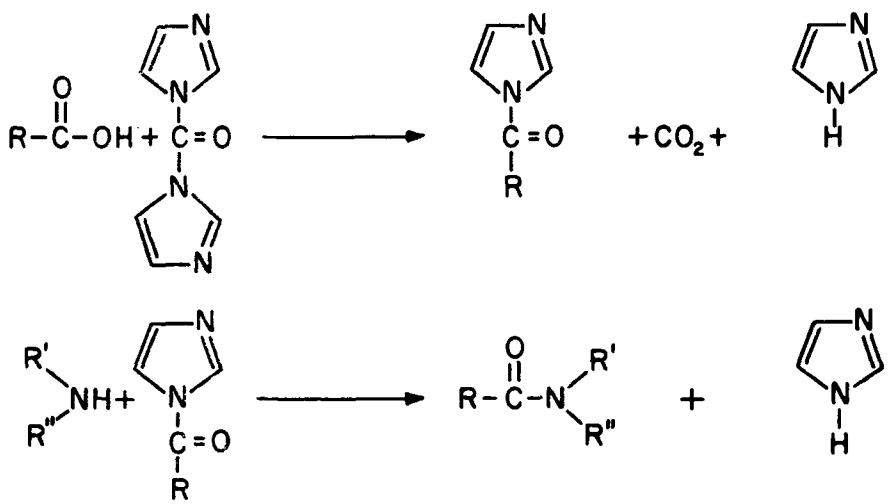
# The Preparation of Steroidal Amides II. Imidazolide Method and EEDQ Method

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.



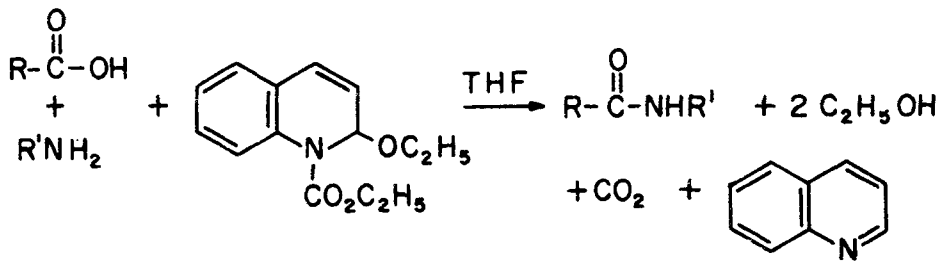
The formation of amides from acids and amines via the imidazolide of the acid is described by Staab et al[1], and proceeds according to the following scheme:



In our hands this method has been of limited use for the preparation of steroidal amides. In the particular case of lithocholic acid 3-formate[2] (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 -C-N- linkages in peptides[3]. 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 methods[4] for the preparation of amides of lithocholic acid 3-formate.

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

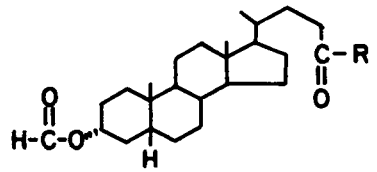
The infrared spectrum of this compound shows two peaks at 1755 $cm^{-1}$ and 1825 $cm^{-1}$ generally associated with carboxylic acid anhydrides.

## EXPERIMENTAL

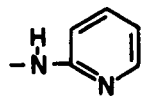
Imidazolide method:

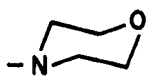
Lithocholic acid 3-formate (1g, 2.5 m moles) was dissolved in 15 ml dry tetrahydrofuran, previously distilled from $LiAlH_4$, and added to N, N'-carbonyl diimidazole (500 mg, 3 m moles) in a hypo-vial. When gas evolution ceased, 2.5 mmoles of the amine in 5 ml THF were added. The mixture was

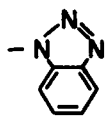
TABLE 1

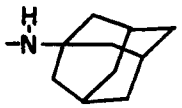


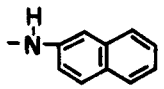
I R = -OH

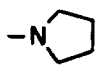
II R = 

III R = 

IV R = 

V R = 

VI R = 

VII R = 

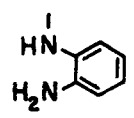
VIII R = 

TABLE 2

| Compound | mp. | $(\alpha)_D$ | Molecular Formula | Analyses | C | H | N | Solvent | Yield |
|---|---|---|---|---|---|---|---|---|---|
| II | 125-27° | +28.25° | $C_{30}H_{44}N_2O_3$ | Calc: | 74.96 | 9.23 | 5.83 | E | 53% |
| | | | | Found: | 74.78 | 9.41 | 5.72 | | |
| III | 205-06° | +48.50° | $C_{29}H_{47}NO_4$ | Calc: | 73.53 | 10.00 | 2.96 | M-E | 65% |
| | | | | Found: | 73.51 | 10.11 | 2.92 | | |
| IV | 144-45° | +40.1° | $C_{31}H_{43}N_3O_3$ | Calc: | 73.63 | 8.57 | 8.31 | E-M | 54% |
| | | | | Found: | 73.49 | 8.69 | 8.16 | | |
| V | 193-95° | + 8.1° | $C_{35}H_{55}NO_3 \cdot CH_3OH$ | Calc: | 75.88 | 10.44 | 2.46 | E-M-C | 78% |
| | | | | Found: | 75.95 | 10.49 | 2.53 | | |
| VI | 165-67° | +22.75° | $C_{35}H_{47}NO_3$ | Calc: | 79.35 | 8.94 | 2.64 | E | 81% |
| | | | | Found: | 79.33 | 9.20 | 2.89 | | |
| VII | 90-92° | +25.81° | $C_{29}H_{47}NO_3$ | Calc: | 76.10 | 10.35 | 3.06 | E | 61% |
| | | | | Found: | 76.00 | 10.54 | 3.37 | | |
| VIII | 213-14° | +14.0° | $C_{31}H_{46}N_2O_3$ | Calc: | 75.26 | 9.37 | 5.98 | M | 73% |
| | | | | Found: | 75.18 | 9.15 | 5.66 | | |

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

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° (CHF).

Analysis: $C_{50}H_{78}O_7$ 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

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

## REFERENCES

1) H.A. Staab, M. Lüking, 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.

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