LONG-ACTING CONTRACEPTIVE AGENTS: CARBONATES AND CARBAMATES OF NORETHISTERONE

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ABSTRACT

The preparation of three carbonates and two carbamates of norethisterone (17α-ethynyl-17β-hydroxyestr-4-en-3-one) are described. Due to instability of the carbonates and the very low solubility of the carbamates these compounds could not be submitted to biological testing.

INTRODUCTION

The preparation of a number of carbonates and carbamates was undertaken within the World Health Organization programme for the synthesis and screening of new compounds for use as long-acting, injectable contraceptives. The carbonates proved to be too unstable to be submitted to biological testing, while the N,N-di-n-butyl carbamate of norethisterone was found to be too insoluble to be tested.

CHEMICAL SYNTHESIS

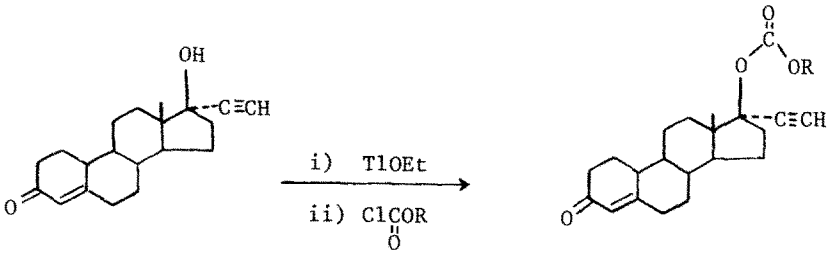
The alkyl chloroformates were prepared according to the method of Matzner et al. (1). They were then reacted in the usual way (2) with the prepared thallium salt of norethisterone in benzene to yield the carbonate derivative (Scheme 1).

Since N,N-diphenyl carbamoyl chloride (Eastman Chemical Co.) was

on hand, it was used as a model compound for the preparation of norethisterone carbamates. When reacted with the thallium salt of norethisterone the N,N-diphenyl carbamate was obtained without difficulty and in good yield.

The N,N-di-n-butyl carbamoyl chloride was prepared from the corresponding formamide (3) according to the method of Sindler (4). This compound proved to have low reactivity in the reaction with the thallium salt of norethisterone. Prolonged heating resulted in the formation of a mixture containing three products (V, VI and VII) in the proportions 2:2:1. The three products were very difficult to separate and were isolated by repeated dry-column chromatography (silica gel, hexane-benzene, 30-70) and identified by NMR, MS and IR (Scheme 2).

When the method of Takimoto and Inanaga (5) was tried, reacting norethisterone with N,N-di-n-butyl carbamoyl chloride in the presence of AgCN, after 48 hours a 15% yield of the norethisterone carbamate (V) was obtained. The N,N-butyl carbamate was finally synthesized by first forming the chlorocarbonate of norethisterone by reacting the thallium salt of norethisterone with an equimolar amount of phosgene. Once the chlorocarbonate of norethisterone was formed, the thallium salt of N,N-di-n-butylamine was added to the reaction mixture which was then worked up in the usual way. Using this method, the carbamate of norethisterone could be obtained without side products and in 75% yield.

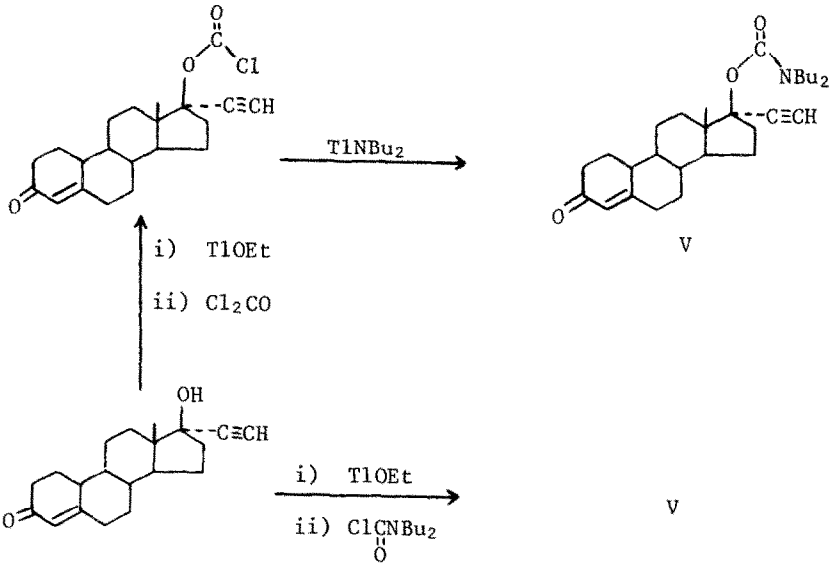


I R = $(CH_2)_6CH_3$

II R = $CH_2C(CH_3)_2(CH_2)_2CH_3$

III R = $CH_2C(CH_3)_2(CH_2)_3CH_3$

Scheme 1



Scheme 2

EXPERIMENTAL

n-Heptyl carbonate of norethisterone (I):

Norethisterone (900 mg, 3 mmole), TlOEt (900 mg, 3.6 mmole) and n-heptyl chloroformate (500 mg, 3 mmole) in dry benzene (150 ml) were reacted according to Herz et al (2). Oil, $[\alpha]_D$ -11° ($CHCl_3$).

IR: 1280, 1630, 1675, 1755, 3330, cm^{-1}
NMR: 0.90(s), 133(m), 2.5(s), 4.0(t), 5.6(s), δ ($CDCl_3$)
Yield: 60%
Anal: $C_{26}H_{40}O_3$ (MW 400.56) requires C: 77.96 H: 10.06
Found C: 78.04 H: 9.82

washed, evaporated and the residue purified by chromatography on silica gel. Oil, $[\alpha]_D$ +22° ($CHCl_3$)

IR: 1220, 1380, 1420, 1470, 1620, 1680, 1715, 2980, 3325 cm^{-1}
NMR: 0.9(s), 0.95(t), 2.58(s), 3.2(m), 5.75(s), δ
MS: 453, 438, 297, 281, 280, 265, 156
Yield: 75%
Anal: $C_{29}H_{43}O_3N$ (MW 453.67) requires C: 76.78 H: 9.55 N: 3.09
Found C: 76.82 H: 10.09 N: 3.02

Reaction of the thallium salt of norethisterone with di-n-butyl carbamoyl chloride:

The following products were isolated by chromatography:
Norethisterone N,N-di-n-butyl carbamate (V): identical to the product obtained above.
Estr-4-ene-3,17-dione (VI):identical to an authentic sample prepared according to the method of Vitali et al (6),

IR: 1630, 1675, 1740, cm^{-1}
NMR: 0.92(s), 5.78(s), δ
MS: 272(M^+)

17-Hydroxyestra-4,16-dien-3-one N,N-di-n-butyl carbamate (VII):

IR: 1715, 1750, 3040, cm^{-1}
NMR: 0.95(s), 1.0(t), 3.25(t), 5.45(d, br), 5.78(s), δ
MS: 427(M^+) (7), 384, 284, 241, 156, 128, 100, 43

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