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Received November 29, 1979.
Accepted for publication February 28, 1980.
Supported by National Institutes of Health Grants AM16694 and AM21506 and grants-in-aid from Canada Packers Ltd., Eli Lilly Co., INTERx Corp., and The Upjohn Co.
The authors thank the Tokyo Tanabe Co., Tokyo, Japan, for a generous sample of ursodeoxycholic acid.
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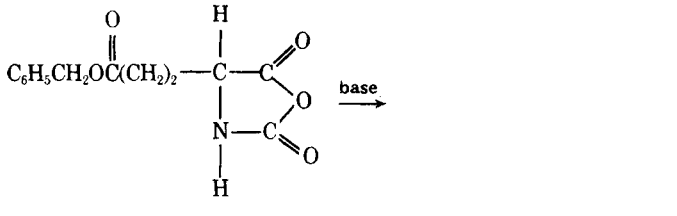
Coupling of Steroid Hormones to Biodegradable Poly(α-amino acids) I: Norethindrone Coupled to Poly-N^5-(3-hydroxypropyl)-L-glutamine

Keyphrases □ Norethindrone—coupling to poly(α-amino acids), controlled release from coupled compounds □ Contraceptives—norethindrone, coupling to poly(α-amino acids), controlled release from coupled compounds □ Polymers, biodegradable—poly(α-amino acids), coupling to norethindrone, controlled release of norethindrone from coupled compounds

To the Editor:

Sustained release of drugs from polymeric matrixes has received increased interest (1–5). Hormone release from such systems was investigated to obtain devices for long-term contraceptive purposes. A new approach in the release of hormones from polymeric systems is the use of covalently bound polymer–hormone compounds that are biodegradable and do not need removal after implantation. Although a few examples of steroids being bonded covalently to polymers have been reported (6–8), the coupling of steroids to biodegradable polymers was presented only recently (9). We wish to report a new derivatization of 17α-ethynyl-17β-hydroxy steroids, which are appropriate for attachment to biodegradable poly(α-amino acids).



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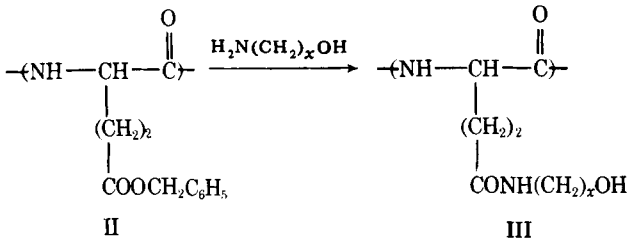


II III

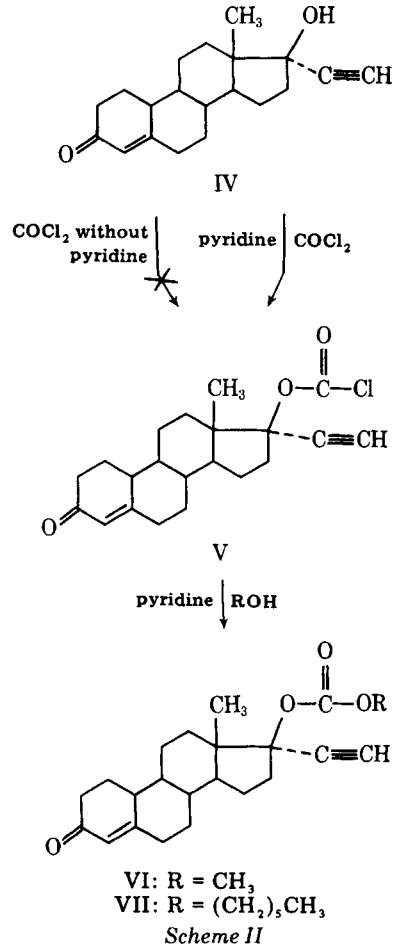
IIIa: $x = 3$

Scheme I

Poly(hydroxyalkyl)-L-glutamines (III) were studied by several investigators (10, 11). These polymers are prepared through the base-catalyzed polymerization of γ-benzyl-L-glutamate N-carboxyanhydride (I), giving the polymeric benzyl-L-glutamate (II), followed by displacement of the benzyl group with the desired hydroxyalkyl amines (12) (Scheme I). The polymers are water soluble but become water insoluble upon substitution with hydrophobic steroids.

The steroid selected for derivatization was norethindrone (IV), an active progestin (Scheme II). Reaction of IV in methylene chloride with a stoichiometric amount of pyridine and an excess of phosgene at room temperature resulted in a 77% yield of norethindrone-17β-chloroformate (V, mp 103–105° dec.). The reaction was monitored by TLC until IV had disappeared completely. The structure of V then was verified; IR (ν, KBr pellet): 1780 (chloroformate) cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$): 5.80 (s, 1H, 4[1]), 2.77 (s, 1H, 21), and 1.00 (s, 3H, 18).

Compound V is unstable and was derivatized to further confirm its structure and to investigate its potential for the coupling with polymer IIIa. Compound V was reacted with



IV V

VI: R = CH_3
VII: R = $(CH_2)_5CH_3$

Scheme II

[1] These numbers correspond to the standard nomenclature for carbon atoms of the steroid skeleton to which the protons are attached. The carbonate carbon is number 22, and the alkyl groups of the carbonate esters are numbered from 23 to 28, where 28 is the terminal carbon of the hexylcarbonate (VII).

0022-3549/80/0700-0871$01.00/0

a stoichiometric amount of pyridine and excess methanol or hexanol in dichloromethane to give norethindrone-17β-methylcarbonate (VI, 84% yield, mp 153–154°) or norethindrone-17β-hexylcarbonate (VII, 94% yield, oil).

The spectroscopic data for VI were: IR (ν, KBr pellet): 1750 (carbonate) cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$): 5.80 (s, 1H, 4), 3.77 (s, 3H, 23), 2.63 (s, 1H, 21), and 0.97 (s, 3H, 18); mass spectrum: *m/e* 356 (100%, M^+) and 342 (4.17, $M^+ - CH_3$); satisfactory combustion analysis was obtained. The spectroscopic data for VII were: IR (ν, oil film): 1750 (carbonate) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 5.80 (s, 1H, 4), 4.10 (t, 2H, 23), 2.63 (s, 1H, 21), 0.95 (s, 3H, 18), and 0.86 (t, 3H, 28); mass spectrum: *m/e* 426 (3.5%, M^+) and 342 [45, $M^+ - (CH_2)_5CH_3$].

It has been claimed that a base is not necessary for the conversion of primary alcohols into their chloroformates. When tertiary alcohols are converted to their chloroformates, a base is required (13). To check whether a selective reaction with a primary alcohol group in derivatized IV (*e.g.*, the 3-oxime derivative) would be possible, norethindrone (IV) was reacted with phosgene in the absence of pyridine. As anticipated, no chloroformate was formed.

Coupling reactions to poly-N^5-(3-hydroxypropyl)-L-glutamine were monitored using tritiated norethindrone[2]. Compound III*a*[3] was dried for 5 days under high vacuum at room temperature, dissolved in a mixture of anhydrous dimethylformamide and pyridine, and then reacted with the tritiated V, which was synthesized as described. The polymer was isolated from unreacted products by repeated precipitation in ethyl acetate.

The degree of substitution of norethindrone onto the available hydroxyl groups of III*a* was up to 60% as determined by liquid scintillation counting techniques. The following spectroscopic data were obtained: IR (ν, mineral oil): 1760 and 1265 (carbonate) cm^{-1}, 1660 and 1550 (amide) cm^{-1}, and 3300 (hydroxyl) cm^{-1}.

In vivo release studies using norethindrone coupled to poly-N^5-(3-hydroxypropyl)-L-glutamine microparticles, which were implanted subcutaneously in rats, showed a near zero-order release rate for >200 days (14).

[2] Nonspecific tritiated norethindrone, New England Nuclear, Boston, MA 02118.

[3] Obtained from poly(γ-benzyl-L-glutamate), which had a viscosity average molecular weight of 53,000.

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Received September 14, 1979.

Accepted for publication March 14, 1980.

Supported by National Institute of Child Health and Development Contract NO1-HD-7-2824.

The authors thank Dr. S. W. Kim, Dr. J. R. Cardinal, and Dr. S. M. Fang for stimulating discussions, Mr. H. Lam and Mr. F. Rejali for synthetic support, Mr. J. Silcox, University of Utah Regional Resource Center, for obtaining the NMR spectra, Dr. McCloskey for obtaining mass spectrometry data, and Ms. K. Eggen for typing the manuscript.