LONG-ACTING CONTRACEPTIVE AGENTS: NORETHISTERONE ESTERS OF MONOALKENYL AND MONOALKYNYL ACIDS

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ABSTRACT

The synthesis of nine new esters of norethisterone (17α-ethynyl-17β-hydroxyestr-4-en-3-one) is described, with the esterifying acids bearing an acetylenic or olefinic function in a chain of eight or nine carbon atoms, for evaluation as long-acting contraceptive agents.

INTRODUCTION

Although some injectable long-acting contraceptive steroids such as medroxyprogesterone acetate (17α-acetoxy-6α-methylpregn-4-ene-3,20-dione) and norethisterone enthanate have been evaluated and clinically used (1, 2), they suffer from a number of disadvantages. The Special Programme of Research, Development and Research Training in Human Reproduction of the World Health Organization established, in 1975, a task force to develop an international chemical synthesis programme directed to find new, long-acting contraceptive steroids (3). This was motivated by the continued demand for long lasting injectable contraceptive agents and in

the light of a reduction in research efforts in this field on the part of the pharmaceutical industry.

In this paper we describe the synthesis, physical properties and biological activities of some esters of norethisterone with unsaturated carboxylic acids. The biological activities of these compounds were examined in an estrus suppression assay in rats by Dr G. Bialy and co-workers and are reported in an accompanying paper in this Journal.

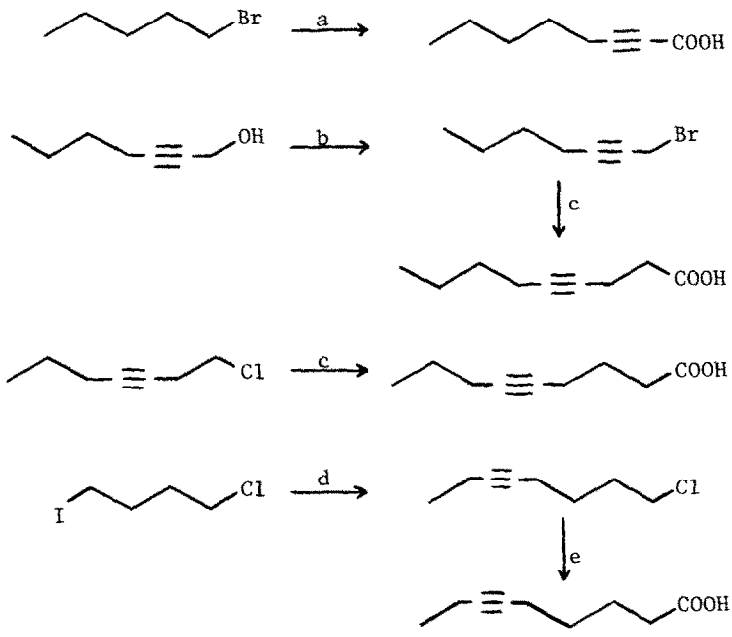
CHEMICAL SYNTHESIS

The synthesis of oct-2-ynoic acid and of nonynoic acids with the acetylenic function located at positions 4, 5, and 6, respectively, are shown in the Scheme. Oct-2-ynoic acid was obtained by alkylation of the dianion of propynoic acid with 1-bromopentane. Reaction of hept-2-ynol with phosphorous tribromide afforded the bromide, which by treatment with the sodium salt of diethyl malonate followed by saponification and decarboxylation gave non-4-ynoic acid. For the synthesis of non-5-ynoic acid a similar two-carbon homologation reaction was used, starting with 1-chlorohept-3-yne. Non-6-ynoic acid was prepared by alkylation with 1-iodo-4-chlorobutane of the anion of but-1-yne and subsequent one-carbon homologation with sodium cyanide.

Alkenoic acids of Z-stereochemistry were obtained from each of the three nonynoic acids by partial hydrogenation over $Pd/BaSO_4$. The E-non-5-enoic acid was obtained from the corresponding alkynoic acid by

reduction with sodium in liquid ammonia.

Esterifications of norethisterone with each of the nine unsaturated acids prepared were performed by reaction of the corresponding acid chlorides with the thallium alkoxide (4,5) for compounds I and VIII and with the lithium alkoxide (6) for the others. The structures and some physical data on the esters are collected in Table 1.

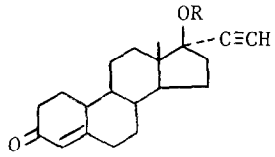


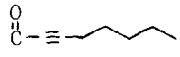
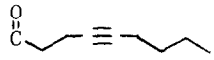
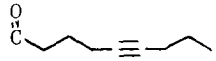
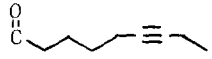
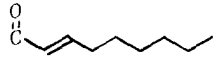
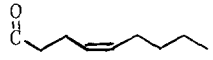
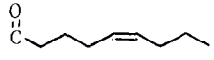
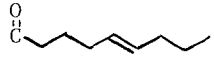
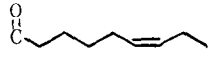
a) $HC{\equiv}C\text{-}COOH$, LDA; b) PBr_3; c) $NaCH(COOEt)_2$,KOH,HCl;

d) $CH_3CH_2C{\equiv}CH$, Li/NH_3; e) NaCN/NaI, KOH, HCl.

Scheme

Table 1. Properties of Norethisterone Esters



Ester	R	Prepared in	m.p.	$[\alpha]_D$
I		Mexico	oil	+37.7[b]
II		Spain	oil	0[a]
III		Spain	oil	-9[a]
IV		Spain	oil	-11[a]
V		Spain	oil	+12[a]
VI		Spain	oil	-9[a]
VII		Spain	oil	-8[a]
VIII		Mexico	oil	-10.5[b]
IX		Spain	oil	-10[a]

a) $CHCl_3$ b) MeOH

EXPERIMENTAL

Oct-2-ynoic acid:

Propynoic acid (6 g, 85 mmole) was added dropwise at room temperature to a solution of lithium diisopropylamide (17.2 g of diisopropylamine and 11.52 g of n-BuLi/hexane) in 100 ml of THF and 30 ml of HMPA. The mixture was stirred for 30 min. and then 1-bromopentane (12.9 g, 85 mmole) was added dropwise at room temperature. The reaction was maintained at reflux for 20 h. and, after addition of water (20 ml), was acidified with aq. HCl and extracted with ether. The organic layer was dried over anhydrous sodium sulphate and evaporated to dryness under vacuum, and the crude acid was purified by chromatography. IR(film): 3500-2500, 2230, 1710cm^{-1}; NMR($CDCl_3$): δ 11.3 (1H, br.s), 2.37 (2H, t), 0.93 (3H, t).

Non-4-ynoic acid:

Phosphorous tribromide (52 ml) was added to a mixture of hept-2-yn-1-ol (150 g), ether (200 ml) and pyridine (27 ml) at -15°C during 30 min. and then the mixture was refluxed for 3 h. The reaction mixture was then cooled in an ice bath, poured into water and extracted with ether, to give 1-bromohep-2-yne; NMR($CDCl_3$): δ 3.94 (2H, t), 2.25 (2H, m), 1.45 (4H, m), 0.91 (3H, t). A solution of 1-bromohept-2-yne and diethyl malonate was heated to 90° and then an ethanolic solution of EtONa (prepared from 637 ml of EtOH and 30 g of Na) was added dropwise to maintain a constant reflux (approx. 30 min.). The reaction was further refluxed for 4 h and then the EtOH was distilled off, KOH was added (277 g of KOH in 1 l. of water) and heating was continued for 5 h. The reaction was poured into ice water, washed with diethyl ether, acidified with dil. H_2SO_4 and extracted with ether/ethyl acetate (1:). The organic layer was dried over sodium sulphate and evaporated under vacuum to give 226 g of crude diacid that underwent decarboxylation by heating at 130° for 5 h. under argon. The acid was purified by vacuum distillation (105-110°, 0.05 mm Hg) giving 130 g of non-4-ynoic acid: m.p. 45-6°; IR(KBr): 3000, 1700 cm^{-1}; NMR($CDCl_3$): δ 2.50 (4H, m), 2.11 (2H, m), 1.40 (4H, m), 0.88 (3H, t). MS: m/e 154 (M^+); 112; 79.

Anal: $C_9H_{14}O_2$ requires C: 70.10 H: 9.15
Found C: 70.13 H: 9.21

Non-5-ynoic acid:

A mixture of 1-chlorooct-4-yne (102 g, 0.7 mole) in ethanol, sodium cyanide (103 g, 2.1 mole) and sodium iodide (105 g, 0.7 mole) was refluxed for 23 h. (the reaction was checked by GLC: Chromosorb W-100/110 UCW-98, 10%). The reaction mixture was filtered and KOH (2.1 mole) added to the solution and it was then refluxed for 12 h. The reaction was poured in to water, washed with ether, acidified with aq. HCl and extracted with ether. The acid was purified by vacuum distillation (115-117°, 0.7 mm Hg) giving 92 g of non-5-ynoic acid: IR(KBr): 3000, 1700 cm^{-1}; NMR($CDCl_3$): δ 10.5 (1H, br. s), 2.50 (2H, t), 2.20 (4H, m), 1.85 (2H, m), 1.40 (2H, m), 0.97 (3H, m); MS: m/e 154(M^+). 113.

Anal: $C_9H_{14}O_2$ requires C: 70.10 H: 9.15
Found C: 70.28 H: 9.14

Non-6-ynoic acid:

Preparation of 1-iodo-4-chlorobutane: A solution of sodium iodied (218 g) and 1,4-dichlorobutane (200 g) in dry acetone (1.1 l) was refluxed for 2.5 h. The reaction was followed by GLC (Chromosorb W-100/110, UCW-98, 10%) and stopped when 25% of 1,4-dichlorobutane, 25% of 1,4-diiodobutane and 50% of 1-iodo-4-chlorobutane were present. The mixture was separated by fractional distillation giving 1-iodo-4-chlorobutane (92 g), b.p. 64-7°, 5.5 mm Hg; MS: m/e 220 and 218 (M^+).

Preparation of 1-chlorooct-5-yne: Lithium (3.36 g) in small slices was added with vigorous stirring to liquid ammonia (1.5 l) previously dried over sodium and distilled. A stream of but-1-yne was then slowly bubbled through until the solution turned colourless (approx. 1 h.). After dropwise addition of 1-iodo-4-chlorobutane (90 g) the stirring was continued for 4 h. The ammonia was evaporated overnight with previous addition of ammonium chloride (3 g), and after extraction with ether the organic solvent was evaporated under vacuum to give 1-chlorooct-5-yne; NMR($CDCl_3$): δ 3.57 (2H, t), 2.20 (2H, t), 2.16 (2H, q), 1.9 (4H, m), 1.11 (3H, t).

Preparation of non-6-ynoic acid: A mixture of 1-chlorooct-5-yne (0.38 mole), ethanol (400 ml), sodium cyanide (1.14 mole) and sodium iodide (0.36 mole) was treated as indicated for the preparation of non-5-ynoic acid. The acid was purified by vacuum distillation (114-115°, 0.5 mm Hg) to give non-6-ynoic acid (50 g); IR(KBr): 3000, 1700 cm^{-1}; NMR($CDCl_3$): δ 2.38 (2H, t), 2.14 (4H, q), 1.65 (4H, m), 1.10 (3H, t); MS: m/e 154(M^+), 121, 112, 95.

Anal: $C_9H_{14}O_2$ requires C: 70.10 H: 9.15
Found C: 70.21 H: 9.00

Z-Non-4-enoic acid:

Non-4-ynoic acid (30 g) in dry pyridine (200 ml) was hydrogenated at room temperature over 10% $Pd/BaSO_4$ (0.42 g) until 1 equivalent of H_2 was consumed (the reaction was followed by GLC: Chromosorb W-100/110, UCW-98, 10%), and then filtered over celite, and ethyl acetate was added. The pyridine was removed by washing with aq. HCl and the acid was purified by vacuum distillation (102°, 0.3 mm Hg), yielding Z-non-4-enoic acid (25.5 g); NMR($CDCl_3$): δ 11.95 (1H, br.s), 5.44 (2H, m), 2.41 (4H, d), 2.07 (2H, m), 1.33 (4H, m), 0.90 (3H, t); MS: m/e 156(M^+), 149, 134, 119, 117.

Anal: $C_9H_{16}O_2$ requires C: 69.19 H: 10.32
Found C: 69.02 H: 10.12

Z-Non-5-enoic acid:

Non-5-ynoic acid (30 g) was hydrogenated as described above. Vacuum distillation of the crude material (104°, 0.4 mm Hg) gave Z-non-5-enoic acid (25 g); NMR($CDCl_3$): δ 11.19 (1H, br. s), 5.41 (2H, m), 2.38 (2H, t), 2.08 (4H, m), 1.74 (2H, m), 1.3 (2H, m), 0.90 (3H, t).

Anal: $C_9H_{16}O_2$ requires C: 69.19 H: 10.32
Found C: 69.01 H: 10.55

E-Non-5-enoic acid:

Non-5-ynoic acid (17 g) in THF (50 ml) was added dropwise to a solution of sodium (20.4 g) in dry liquid ammonia (1.3 l). The reaction was stirred for 20 h. and after the ammonia was evaporated the acid was extracted with ether and purified by vacuum distillation (95-103°, 0.3 - 0.4 mm Hg) to yield E-non-5-enoic acid (15.4 g); IR(film): 3400 - 3000, 1710 cm^{-1}; NMR($CDCl_3$): δ 12.25 (1H, br. s), 5.49 (2H, m), 2.37, 0.92 (3H, t).

Z-Non-6-enoic acid:

Non-6-ynoic acid (30 g) was hydrogenated as indicated above in the preparation of Z-non-4-ynoic acid. Vacuum distillation of the crude material (102°, 0.3 mm Hg) yielded Z-non-6-enoic acid (22.5 g); NMR ($CDCl_3$): δ 5.35 (2H, m), 2.36 (2H, t), 2.04 (4H, m), 1.52 (4H, m), 0.94 (3H, t).

Anal: $C_9H_{16}O_2$ requires C: 69.19 H: 10.32
Found C: 69.28 H: 10.30

General procedure for preparation of acid chlorides:

Thionyl chloride (8 equivalents) was added dropwise to a solution of the acid in dry benzene (4 ml/g) cooled to 0° and the reaction was allowed to warm to room temperature and was then refluxed for 6 h. In order to eliminate the excess of thionyl chloride, benzene was distilled off and after the addition of fresh benzene the operation was repeated twice. The acid chloride was purified by vacuum distillation. In an alternative procedure oxalyl chloride was used (1.1 equivalents, 3 h., room temp.) instead of thionyl chloride.

General procedure for esterification of norethisterone:

Ethylene glycol (120 ml) and Dowex-50X acidic cation exchange resin (6 g) were added to a solution of norethisterone (36 g) in benzene (1.2 l). The mixture was refluxed for 5-10 h using a Dean-Stark charged with silica gel to eliminate water. After filtration, the benzene solution was washed with water and concentrated under vacuum. The residue was crystallized from methanol to give norethisterone ethylene ketal, m.p. 164-6°.

Formation of norethisterone esters, method A:

n-Butyl lithium in hexane (32 mmole) was slowly added, at 0° under argon, to a solution of norethisterone ethylene ketal (20.5 mmole) in dry THF (170 ml) and the reaction kept at room temperature for 30 min. After addition of the acid chloride (35 mmole) dissolved in THF (100 ml) the reaction was refluxed for 6 h. and then poured into water and extracted with ether. The organic solvent was concentrated and the crude product was dissolved in dry acetone (175 ml) containing p-toluenesulphonic acid (175 mg) and refluxed for 7 h. The reaction mixture was poured into water and then extracted with ether. The organic layer was washed with water, dried over anhydrous sodium sulphate, filtered and evaporated to dryness under vacuum. The crude ester was purified by column chromatography on silica gel (0.2 - 0.05 mm) using benzene/ethyl acetate (95:5) as eluent.

Formation of norethisterone esters, method B:

Thallous oxide (43 mmole) was added at room temperature under nitrogen to a solution of norethisterone (29 mmole) in dry benzene (800 ml). Benzene (500 ml) was distilled off while being replaced with the same volume of fresh benzene (approx. 2.5 h.). The reaction mixture was cooled to room temperature and after addition, with stirring, of the acid chloride (43 mmole) in dry benzene (100 ml), was refluxed for 2 h. The precipitated thallium chloride was filtered off and the benzene solution was thoroughly washed with water. After evaporation of the solvent under reduced pressure the crude mixture was purified by preparative thin layer chromatography.

Norethisterone oct-2-ynoate (I). Method B (7):
UV(MeOH): λ_{max} 239 nm (ε 15697); IR(film): 3280, 2960, 2230, 1715, 1670 cm^{-1}; NMR($CDCl_3$): δ 5.8 (1H, s), 2.63 (1H, s), 0.96 (3H, s).

Norethisterone non-4-ynoate (II). Method A:
UV(EtOH): λ_{max} 239.5 nm (ε 15300); IR(film): 3270, 1740, 1670, 1620 cm^{-1}; NRM($CDCl_3$): δ 5.85 (1H, s), 2.60 (1H, s), 0.95 (3H, t), 0.95 (3H, s); MS: m/e 434(M^+), 282.

Anal: $C_{29}H_{38}O_3$ requires C: 80.14 H: 8.81
Found C: 80.09 H: 9.01

Norethisterone non-5-ynoate (III). Method A:
UV(EtOH): λ_{max} 240 nm (ε 16500); IR(film): 3270, 1755, 1665, 1620 cm^{-1} NMR($CDCl_3$): δ 5.84 (1H, s), 2.60 (1H, s), 0.96 (3H, t), 0.94 (3H, s); MS: m/e 434(M^+), 282.

Anal: $C_{29}H_{38}O_3$ requires C: 80.14 H: 8.81
Found C: 80.23 H: 8.78

Norethisterone non-6-ynoate (IV). Method A:
UV(EtOH): λ_{max} 239.5 nm (ε 17600); IR(film): 3270, 1735, 1665, 1620 cm^{-1} NMR($CDCl_3$): δ 5.85 (1H, s), 2.60 (1H, s), 0.95 (3H, s), 1.12 (3H, t); MS: m/e 434 (M^+), 281.

Anal: $C_{29}H_{38}O_3$ requires C: 80.14 H: 8.81
Found C: 79.95 H: 8.93

Norethisterone E-non-2-enoate (V). Method A:
UV(EtOH): λ_{max} 215 nm (ε 19600), 239 nm (ε 18100); IR(film): 3260 1725, 1670, 1625 cm^{-1}; NMR($CDCl_3$): δ 7.07, 6.89 (1H, t,t), 5.87, 5.71, (1H, t,t), 5.85 (1H, s), 2.60 (1H, s), 0.95 (3H, s), 0.87 (3H, t); MS: m/e 436(M^+), 298.

Anal: $C_{29}H_{40}O_3$ requires C: 79.77 H: 9.23
Found C: 79.65 H: 9.33

Norethisterone Z-non-4-enoate (VI). Method A:
UV(EtOH): λ_{max} 240 nm (ε 17700); IR(film): 3270, 1740, 1670, 1620 cm^{-1}; NMR($CDCl_3$): δ 5.85 (1H, s), 5.40 (2H, m), 2.58 (1H, s), 0.92 (3H, s), 0.91 (3H, t); MS: m/e 436(M^+), 282.

Anal: $C_{29}H_{40}O_3$ requires C: 79.77 H: 9.23
Found C: 79.59 H: 9.12

Norethisterone Z-non-5-enoate (VII). Method A:
UV(EtOH): λ_{max} 239.5 nm (ε 16500); IR(film): 3260, 1735, 1670, 1620 cm^{-1}; NMR($CDCl_3$): δ 5.85 (1H, s), 5.40 (2H, m), 2.58 (1H, s), 0.94 (3H, s), 0.92 (3H, t); MS: m/e 436(M^+), 282.

Anal: $C_{29}H_{40}O_3$ requires C: 79.77 H: 9.23
Found C: 79.89 H: 9.15

Norethisterone E-non-5-enoate (VIII). Method B (7):
UV(MeOH): λ_{max} 239 nm (ε 16851); IR(film): 3270, 2960, 1750, 1680 cm^{-1}; NMR($CDCl_3$): δ 5.65 (1H, s), 2.5 (1H, s), 0.9 (3H, s).

Norethisterone Z-non-6-enoate (IX). Method A:
UV(EtOH): λ_{max} 239.5 nm (ε 17400); IR(film): 3260, 1740, 1670, 1620 cm^{-1}; NMR($CDCl_3$): δ 5.85 (1H, s), 5.37 (2H, m), 2.58 (1H, s), 0.95 (3H, t), 0.93 (3H, s); MS: m/e 436(M^+), 282.

Anal: $C_{29}H_{40}O_3$ requires C: 79.77 H: 9.23
Found C: 79.59 H: 9.29

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REFERENCES

1. Fraser I.S. and Weisberg E.A., MED. J. AUST. 1 (Special Suppl. 1), 1 (1981).
2. World Health Organization, 9TH ANNUAL REPORT p. 62 (1980).
3. Crabbé P., Diczfalusy E., and Djerassi C., SCIENCE 209, 992 (1980).
4. Herz J.E., Cruz S., Torres J.V., and Murillo A., SYNTHETIC COMMUN. 7, 383 (1977).
5. Muller J. and Herz J.E., STEROIDS 34, 793 (1980).
6. Kaiser E.M. and Woodruff R.A., J. ORG. CHEM. 35, 1198 (1970).
7. Elemental analysis data for this compound was slightly outside normal limits. The compound was subsequently purified by the Quality Control Laboratory.