The Synthesis and Some Reactions of 1-Amino-4-methylestra-1,3,5(10)-trien-17-one

DUANE F. MORROW AND MARY E. BUTLER

Research Laboratories, Parke, Davis and Company, Ann Arbor, Michigan

Received February 4, 1964

The sodium salt of 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one was condensed with 4-chloro-2-phenylquinazoline to give 4-methyl-1-(2-phenyl-4-quinazolinyloxy)estra-1,3,5(10)-trien-17-one (IV). Thermal rearrangement of IV gave 4-methyl-1-[4-oxo-2-phenyl-3(4*H*)-quinazolinyl]estra-1,3,5(10)-trien-17-one (V), which was hydrolyzed to 1-amino-4-methylestra-1,3,5(10)-trien-17-one (VII). Replacement of the diazotized amino group afforded the 1-bromo (VIII) and 1-fluoro (IX) derivatives.

A series of substituted 1-chloro-4-methylestra-1,3,5-(10)-trienes (*e.g.*, I) was recently prepared in these laboratories by the reaction of androsta-1,4-dien-3-ones with oxalyl chloride.[1] The synthesis of 4-methylestra-1,3,5(10)-trienes with other substituents in the 1-position has now been investigated. The parent 1-unsubstituted[2-4] as well as the 1-methyl,[2] 1-hydroxy,[5,6] 1-acetoxy,[5] 1-methoxy,[5-7] and 1-(β-hydroxyethoxy)[7] substituted 4-methylestra-1,3,5(10)-trienes have already been reported in the literature.

We wish to describe the synthesis of 1-amino-4-methylestra-1,3,5(10)-trien-17-one (VII). The presence of the amino function makes possible the introduction of a variety of groups at position 1 by replacement reactions of the corresponding diazonium derivative. In this manner we have synthesized 1-bromo- and 1-fluoro-4-methylestra-1,3,5(10)-trien-17-one (VIII, IX). Hecker has previously prepared a series of 3-substituted estratrienes from 17β-acetoxy-3-aminoestra-1,3,5(10)-triene by replacement of the corresponding diazonium ion.[8]

The general procedure developed by Scherrer[9] for the conversion of phenols into anilines was adapted to the synthesis of the 1-amino steroid VII. Although Scherrer was able to condense salts of hindered phenols, such as 2,3,6-trimethylphenol with 4-chloro-2-phenylquinazoline (III)[10] in boiling diglyme, the sodium salt of 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one (II)[5,6] was recovered unchanged under these conditions. However, when these reactants were heated under nitrogen pressure at 200°, the condensation proceeded readily to give 4-methyl-1-(2-phenyl-4-quinazolinyloxy)estra-1,3,5(10)-trien-17-one (IV) in good yield. Thermal rearrangement[9] of this intermediate afforded 4-methyl-1-[4-oxo-2-phenyl-3(4*H*)-quinazolinyl]estra-1,3,5(10)-trien-17-one (V). This rearrangement gave an optimum yield in 5 hr. at 330°, and the course of the reaction was easily followed by spectroscopic techniques. As the reaction progressed, the strong infrared absorption peaks at 1622, 1492, 1385, 1224, and 1070 cm.$^{-1}$ of the quinazoline IV diminished in intensity as absorption peaks at 1689, 1604, and 1269 cm.$^{-1}$ due to the quinazolinone V appeared and increased in intensity. The ultraviolet absorption maximum at 257 mμ due to IV diminished in intensity as the rearrangement proceeded, and the spectrum of the final quinazolinone V exhibited a minimum at 260 and a maximum at 282 mμ.

The hydrolysis of the quinazolinone V was carried out essentially according to the method used by Scherrer[9] for the synthesis of simpler anilines. Treatment of crude V with ethanolic sodium hydroxide gave an intermediate assumed to be the substituted amidine VI. Further treatment of VI with dilute hydrochloric acid yielded 1-amino-4-methylestra-1,3,5(10)-trien-17-one (VII) and a large quantity of neutral material which appeared to be mostly quinazolinone V, resulting from recyclization of the amidine intermediate VI. Further hydrolyses of this material gave additional amounts of the desired product. The over-all yield of crude amino steroid VII from 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one (II) was 67%.

Scherrer[9] has shown that his procedure introduces the amino group on the same carbon atom to which the phenolic hydroxyl was originally attached, with no additional rearrangement of substituents. In accord with this, the infrared spectrum of VII exhibited a strong sharp absorption peak at 814 cm.$^{-1}$, characteristic of a 1,2,3,4-tetrasubstituted benzene.

The diazonium ion formed from 1-amino-4-methylestra-1,3,5(10)-trien-17-one (VII) was very unstable. Evolution of nitrogen with concurrent formation of an acid-insoluble precipitate, presumably the corresponding phenol II, was evident soon after the addition of sodium nitrite to a cooled solution of VII in acetic acid. Although only an 11% yield of 1-bromo-4-methylestra-1,3,5(10)-trien-17-one (VIII) could be obtained following diazotization at 0°,[8,11] lowering the temperature of the diazotization reaction to −15° slowed the decomposition of the diazonium ion sufficiently that a 27% yield of the bromo compound VIII was obtained. Further evidence for the unusual instability of the diazonium ion was found during its conversion to 1-fluoro-4-methylestra-1,3,5(10)-trien-17-one (IX). Whereas aromatic diazonium fluoborate salts normally are sufficiently stable to be isolated from the diazotization reaction and decompose to the aromatic fluorides generally at temperatures above 100°,[12] the diazotization of 1-amino-4-methylestra-1,3,5(10)-trien-

(1) G. W. Moersch, W. A. Neuklis, T. P. Culbertson, D. F. Morrow, and M. E. Butler, to be published.

(2) H. Dannenberg and H. G. Neumann, *Ann.*, **646**, 148 (1961).

(3) M. J. Gentles, J. B. Moss, H. L. Herzog, and E. B. Hershberg, *J. Am. Chem. Soc.*, **80**, 3702 (1958).

(4) E. Caspi, P. F. Grover, N. Grover, E. J. Lynde, and T. Nussbaumer, *J. Chem. Soc.*, 1710 (1962).

(5) A. S. Dreiding and A. Voltman, *J. Am. Chem. Soc.*, **76**, 537 (1954).

(6) A. L. Wilds and C. Djerassi, *ibid.*, **68**, 1712 (1946).

(7) J. Elks, J. F. Oughton, and L. Stephenson, *J. Chem. Soc.*, 4531 (1961).

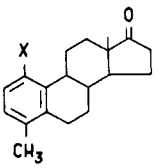
(8) E. Hecker, *Chem. Ber.*, **95**, 977 (1962).

(9) R. A. Scherrer, Abstracts of Papers, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963, p. 33Q.

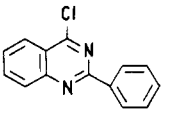
(10) M. M. Endicott, E. Wick, M. L. Mercury, and M. L. Sherrill, *J. Am. Chem. Soc.*, **68**, 1299 (1946).

(11) J. L. Hartwell, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 185.

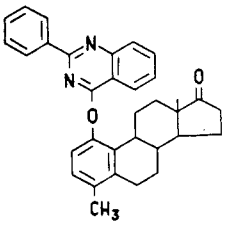
(12) A. Roe, *Org. Reactions*, **5**, 193 (1949).



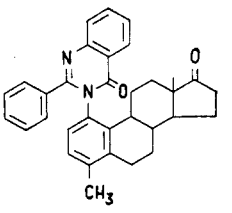
I X = Cl
II X = OH
VII X = NH_2
VIII X = Br
IX X = F



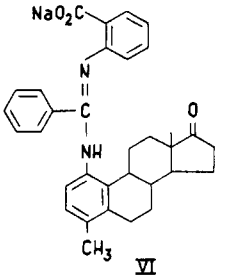
III



IV



V



VI

17-one (VII) in fluoroboric acid solution proceeded with spontaneous evolution of nitrogen at 0° to give IX directly in 29% yield. In both of these reactions, the primary by-product was 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one (II).

The biological activity of these compounds and their derivatives will be discussed in a later paper.

Experimental[13]

4-Methyl-1-(2-phenyl-4-quinazolinyloxy)estra-1,3,5(10)-trien-17-one (IV).—A solution of 5.47 g. of 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one (II)[5] in 200 ml. of pure dry diglyme was stirred under nitrogen and treated with 0.94 g. of a 53% dispersion of sodium hydride in mineral oil. When the reaction ceased and no more hydrogen was evolved, 4.40 g. of 4-chloro-2-phenylquinazoline (III)[10] was added. The mixture was covered with a pressurized nitrogen atmosphere (50 p.s.i.) and heated at 200° for 10 hr. The mixture then was cooled to room temperature, poured into concentrated sodium chloride solution, and filtered. The precipitate was washed well with water and dried in air. The crude 4-methyl-1-(2-phenyl-4-quinazolinyloxy)-estra-1,3,5(10)-trien-17-one, 10.0 g., was sufficiently pure to be used directly for the next step.

An analytical sample recrystallized from ether had m.p. 213–214.5°; $[\alpha]^{24}D$ +243° (*c* 1.0, $CHCl_3$); λ_{max} 286 mμ (ε 16,900) and 257 mμ (ε 34,100); ν_{max} 1739, 1622, 1560, 1492, 1385, 1224, 1070, 782, and 711 cm.$^{-1}$.

Anal. Calcd. for $C_{33}H_{32}N_2O_2$: C, 81.12; H, 6.60; N, 5.73. Found: C, 80.98; H, 6.56; N, 5.80.

4-Methyl-1-[4-oxo-2-phenyl-3(4*H*)-quinazolinyl]estra-1,3,5(10)-trien-17-one (V).—A suspension of 10.3 g. of crude 4-methyl-1-(2-phenyl-4-quinazolinyloxy)estra-1,3,5(10)-trien-17-one (IV) in 100 ml. of heavy mineral oil was covered with an atmosphere of nitrogen and stirred and heated at 330° for 5 hr. The homogeneous mixture then was cooled to room temperature, diluted with 100 ml. of petroleum ether (b.p. 35–60°), cooled in ice, and filtered. The precipitate was washed with petroleum ether and dried in air, yielding 8.25 g. (80%) of crude 4-methyl-1-[4-oxo-2-phenyl-3(4*H*)-quinazolinyl]estra-1,3,5(10)-trien-17-one. The filtrate was concentrated on a steam bath, cooled, and extracted with methanol. The washings were concentrated to dryness on a steam bath, and the residue again was extracted with methanol. The extract was poured into water, and the precipitate was collected and dried in air, yielding an additional 1.28 g. (12%) of crude product. This material was sufficiently pure to be used directly for the next step.

An analytical sample recrystallized from ether had m.p. 231–232.5°; $[\alpha]^{24}D$ +147° (*c* 1.0); λ_{max} 282 mμ (ε 14,100), λ_{min} 260 mμ (ε 11,300); ν_{max} 1742, 1689, 1604, 1560, 1474, 1269, 773, and 701 cm.$^{-1}$.

Anal. Calcd. for $C_{33}H_{32}N_2O_2$: C, 81.12; H, 6.60; N, 5.73. Found: C, 81.03; H, 6.46; N, 5.80.

1-Amino-4-methylestra-1,3,5(10)-trien-17-one (VII).—A solution of 18.25 g. of crude 4-methyl-1-[4-oxo-2-phenyl-3(4*H*)-quinazolinyl]estra-1,3,5(10)-trien-17-one (V) in 1300 ml. of absolute ethanol was treated with 150 g. of sodium hydroxide in 300 ml. of water. The resulting solution was refluxed for 7 hr., cooled in ice, treated with 525 ml. of 12 *N* hydrochloric acid, and allowed to stand overnight at room temperature. The mixture then was stirred and refluxed for 1.5 hr., cooled, and filtered. The sodium chloride precipitate was washed well with ethanol and discarded. The filtrate and washings were concentrated under reduced pressure, poured into water, and filtered. The filtrate was made alkaline with concentrated sodium hydroxide solution, saturated with potassium carbonate, and filtered. The precipitate was washed well with water and dried under reduced pressure at 60°, affording 3.8 g. of 1-amino-4-methylestra-1,3,5(10)-trien-17-one.

The acid-insoluble precipitate appeared to consist mainly of quinazoline V, and rehydrolysis of this following the above procedure gave 1.11 g. of product. A third hydrolysis of the insoluble precipitate yielded an additional 0.61 g. of crude product. The total crude yield was 7.21 g., a 67% yield based on the starting 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one (II). This amino steroid was used directly for the next steps without further purification.

An analytical sample recrystallized from hexane had m.p. 216–218°; $[\alpha]^{23}D$ +315° (*c* 0.6); λ_{max} 241 mμ (ε 7400) and 293 mμ (ε 2200); ν_{max} 3425, 3355, 1733, 1628, 1590, and 814 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{25}NO$: C, 80.51; H, 8.89; N, 4.94. Found: C, 80.33; H, 8.81; N, 4.95.

1-Bromo-4-methylestra-1,3,5(10)-trien-17-one (VIII).—A solution of 283 mg. of crude 1-amino-4-methylestra-1,3,5(10)-trien-17-one (VII) in 6 ml. of acetic acid, 2 ml. of propionic acid, 7 ml. of water, and 1 ml. of concentrated sulfuric acid was cooled to −15° in an ice–salt bath. A solution of 76 mg. of sodium nitrite in 2 ml. of water was added over a period of 10 min., keeping the temperature at −15 ± 1°. The reaction was stirred an additional 20 min. at −15°, during which time a slow evolution of gas commenced and a precipitate began to form. A cooled solution (−10°) of 500 mg. of cuprous bromide in 2 ml. of water and 3 ml. of 48% hydrobromic acid then was added, and the mixture was allowed to warm to 0° and was stirred for 1 hr. It then was warmed to room temperature over a 30-min. period and heated on a steam bath for 30 min. The solution was poured into very dilute hydrobromic acid (*ca.* 0.1%) and filtered. The precipitate was dried under reduced pressure at 60° to give 329 mg. of crude material, which was chromatographed on alumina (Woelm, neutral, activity grade I). Elution with 10% ether in benzene yielded 95 mg. (27%) of 1-bromo-4-methylestra-1,3,5(10)-trien-17-one, m.p. 172–174°. An analytical sample recrystallized from methanol had m.p. 175–176°; $[\alpha]^{23}D$ +292° (*c* 0.4); λ_{max} 271 mμ (ε 278); ν_{max} 1739 and 810 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{23}BrO$: C, 65.71; H, 6.68; Br, 23.01. Found: C, 65.97; H, 6.81; Br, 23.01.

This compound was identical with the 1-bromo-4-methylestra-1,3,5(10)-trien-17-one, m.p. 171–173°, prepared in low yield from androsta-1,4-diene-3,17-dione by treatment with oxalyl bromide and oxalic acid.[1]

Elution with pure ether afforded 91 mg. of crude phenolic material, shown to be mostly 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one by thin-layer chromatography and by comparison of infrared spectra.

(13) The melting points were determined on a Fisher-Johns block and are corrected. The infrared spectra were recorded on a Beckman IR-7 in KBr disks. The ultraviolet spectra and the optical rotations were run in methanol solution unless otherwise noted.

1-Fluoro-4-methylestra-1,3,5(10)-trien-17-one (IX).—A solution of 283 mg. of crude 1-amino-4-methylestra-1,3,5(10)-trien-17-one (VII) in 2.5 ml. of acetic acid, 3 ml. of water, and 7 ml. of 48% fluoroboric acid was cooled and treated with 0.7 g. of solid sodium hydroxide. The resulting solution was cooled to 2°, and a solution of 76 mg. of sodium nitrite in 2 ml. of water was added over a 5-min. period. Evolution of a gas was soon evident. The mixture was stirred at 0° for 30 min. and then warmed to room temperature over a 30-min. period. The mixture was poured into 400 ml. of water, and the precipitate was filtered and dried in air, yielding 274 mg. of crude material. This was chromatographed on alumina (Woelm, neutral, activity grade I). Elution with 10% ether in benzene afforded 83 mg. (29%) of 1-fluoro-4-methylestra-1,3,5-(10)-trien-17-one, m.p. 192–196°. An analytical sample recrystallized from methanol had m.p. 196–197°; $[\alpha]^{23}D$ +196° (*c* 0.6, $CHCl_3$); ν_{max} 1737, 1604, 1419, 1237, and 819 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{23}FO$: C, 79.69; H, 8.10; F, 6.63. Found: C, 79.42; H, 8.23; F, 6.74.

Acknowledgment.—The authors wish to thank Mr. C. E. Childs and his staff of our Microanalytical Laboratory, Dr. J. M. Vandenbelt and his staff of our Physical Chemical Laboratory, and Mr. W. M. Pearlman of our High Pressure Laboratory for their valuable technical assistance. The authors also wish to thank Dr. G. W. Moersch and Dr. R. A. Scherrer for helpful discussions.

Base-Catalyzed Aromatization of *p*-Quinone Disulfonimide–Cyclopentadiene Adducts

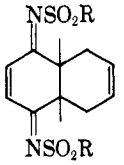
JOSEPH E. DUNBAR

Bioproducts Department, The Dow Chemical Company, Midland, Michigan

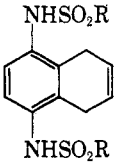
Received December 26, 1963

Simple monoadducts (IV) of *p*-quinone disulfonimides and cyclopentadiene were isomerized to their aromatic forms (V) by base catalysis. Structures of several quinone imide–cyclopentadiene adducts were thus confirmed. The alleged 4a-chloro-1,4,4a,8a-tetrahydro-1,4-methanonaphthalene-5,8-bis(dimethylaminosulfonimide) (VI) of Adams and Shafer was shown to be the isomeric 6-chloro compound (IVg). Treatment of ring-unsubstituted *p*-quinone disulfonimides with equimolar amounts of cyclopentadiene has previously been shown to result only in the formation of the diadducts (III). When *p*-quinonedimethanesulfonimide was treated with an excess of cyclopentadiene in the presence of triethylamine catalyst, the aromatized monoadduct (VII) was obtained exclusively.

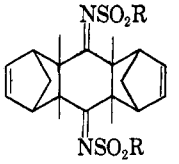
Quinone disulfonimides have been shown to undergo the Diels–Alder reaction with dienes to give either the simple adducts (I) or the aromatized adducts (II).[1–6]



I



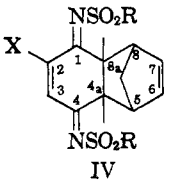
II



III

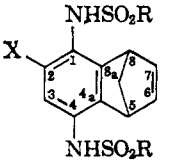
Simple adducts of dienes, other than cyclopentadiene, were caused to isomerize to the corresponding aromatized forms by treatment with catalytic amounts of hydrobromic acid.[1–3,5] Cyclopentadiene was shown to react with ring-unsubstituted *p*-quinone disulfonimides to give diadducts (III) exclusively[1] and with ring-substituted imides to give simple monoadducts (IV) which resisted isomerization to the aromatic forms upon treatment with acid catalyst.[2,5] Our initial interest in adducts of type IV was related to certain fungicidal activities of this series.

We have found that cyclopentadiene adducts of type IV can be isomerized to the aromatic forms (V) by treatment with a catalytic amount of amine base in an inert solvent. Thus, 2-chloro-4a,5,8,8a-tetrahydro-5,8-methano-1,4-naphthoquinonedimethanesulfonimide (IVa) was converted instantaneously to the corresponding 2-chloro-5,8-dihydro-5,8-methano-1,4-naphthalenedimethanesulfonamide (Va) by a catalytic amount of triethylamine in benzene solution. Similar aromatized adducts prepared in this way are 2-chloro-5,8-dihydro-5,8-methano-1,4-naphthalenebis(*p*-chlorobenzenesulfonamide) (Vb), 2-chloro-5,8-dihydro-5,8-methano-1,4-



IV

Compound	R	X	Yield, %
IVa	CH_3	Cl	84
b	*p*-ClC_6H_4	Cl	88
c	C_6H_5	Cl	96[5]
d	*n*-C_4H_9	Cl	86
e	CH_3	SCH_3	80
f	CH_3	SC_6H_{11}	...
g	$N(CH_3)_2$	Cl	34[4]



V

Compound	R	X	Yield, %
Va	CH_3	Cl	74
b	*p*-ClC_6H_4	Cl	89
c	C_6H_5	Cl	94
d	*n*-C_4H_9	Cl	46
e	CH_3	SCH_3	87
f	CH_3	SC_6H_{11}	58
g	$N(CH_3)_2$	Cl	55

(1) R. Adams and C. R. Walter, Jr., *J. Am. Chem. Soc.*, **73**, 1152 (1951).
(2) R. Adams and W. Moje, *ibid.*, **74**, 2593 (1952).
(3) R. Adams and J. D. Edwards, Jr., *ibid.*, **74**, 2603 (1952).
(4) R. Adams and P. R. Shafer, *ibid.*, **75**, 667 (1953).
(5) R. Adams and R. W. P. Short, *ibid.*, **76**, 2408 (1954).
(6) R. Adams and W. P. Samuels, *ibid.*, **77**, 5383 (1955).