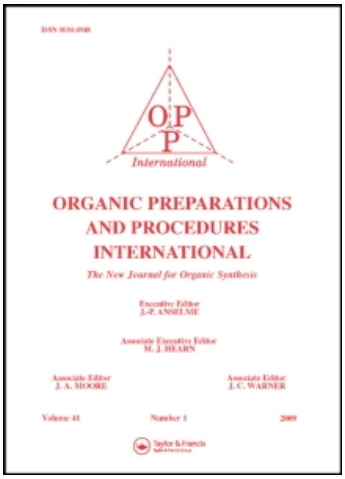

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SYNTHESIS OF PYRAZOLINE AND ISOXAZOLINE DERIVATIVES OF ANDROSTANE SERIES

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SYNTHESIS OF PYRAZOLINE AND ISOXAZOLINE DERIVATIVES OF ANDROSTANE SERIES

Submitted by (10/27/92)

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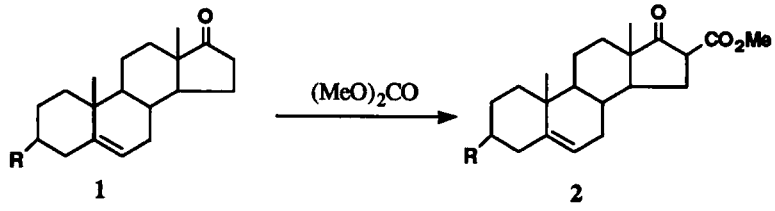
The present work was stimulated by reports of the wide spectrum of pharmacological activities of pyrazoline and isoxazoline derivatives.[1] One of the methods of synthesis of pyrazolines and isoxazolines involves condensation of steroidal ketone with ethyl formate to give an α-formyl ketone, followed by reaction with hydrazines[2] or hydroxylamine.[3] A recent method[4] described the condensation of ketones with ethyl benzoate to give α-benzoyl ketones, followed by formation of pyrazoles and isoxazoles. The present brief describes the condensation of steroidal ketones with dimethyl carbonate and the condensation of the products with hydrazines and hydroxylamines.

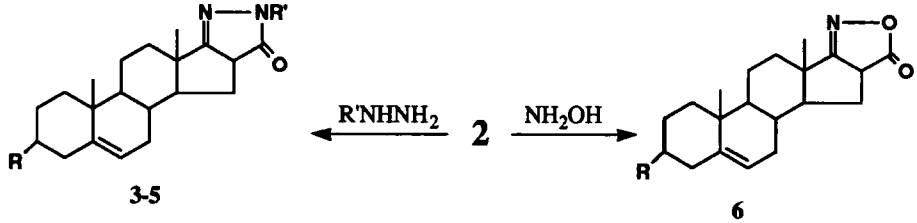
Claisen condensation of 3β-acetoxyandrost-5-en-17-one (**1a**) and 3β–chloroandrost-5-en-17-one (**1b**) with dimethyl carbonate afforded 3β-acetoxy-16-carbomethoxyandrost-5-en-17-one (**2a**) and 3β-chloro-16-carbomethoxyandrost-5-en-17-one (**2b**), respectively. The UV spectra of these



1 **2**

a) R = AcO **b)** R = Cl

compounds showed absorption maxima at 270 nm with log ε 1.3 consistent with the n-π* transition of the carbonyl group. Reaction of **2a** and **2b** with hydrazine hydrate afforded the pyrazolone derivatives



3-5 **6**

a) R = AcO **b)** R = Cl

3) R' = H **4)** R' = CH_3 **5)** R' = C_6H_5

3a and **3b**. With methylhydrazine, **2a** and **2b** gave the methylpyrazolone derivatives **4a** and **4b**. Similarly, reaction of **2a** and **2b** with phenylhydrazine afforded the respective phenylpyrazolone

derivatives **5a** and **5b**. Isoxazoline derivatives **6a** and **6b** were obtained from the reaction of **2a** and **2b** with hydroxylamine hydrochloride.

EXPERIMENTAL SECTION

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin-Elmer 137 spectrophotometer. The ^1H NMR spectra were obtained in $CDCl_3$ on a JEOL FX-90 Q FT instrument with TMS as internal standard. Chemical shifts are given in ppm (δ). Petroleum ether refers to the fraction of bp. 60-80°. 3β-chloroandrost-5-en-17-one **1** was prepared by a known procedure.[5]

3β-Acetoxy-16-carbomethoxyandrost-5-en-17-one (2a).- To a suspension of sodium methoxide (0.5 g) in dry pyridine (30 mL) was added a solution dimethyl carbonate (2 mL; 24 mmol) in dry pyridine (20 mL) and then a solution of 3β-acetoxyandrost-5-en-17-one (**1a**) (2 g, 6 mmol) in dry pyridine (25 mL) dropwise at room temperature, and the mixture was stirred under nitrogen for 6 hrs. The mixture was diluted with ice water (50 mL) and neutralized with 1M HCl. The precipitate was collected and recrystallized from methanol to give 1.4 g (60%) of **2a**, mp. 138-140°. IR: 1730 (carbomethoxy C=O), 1710 (C=O), 1600 (C=C), 1240 (C-O) cm^{-1}; ^1H NMR: δ 5.4 (m, 1H, C_6-H), 4.24 (m, 1H, $W_{1/2}$=12 Hz, H-3α),[6] 3.2 (m, 3H, OCH_3), 2.10 (s, 3H, CH_3COO).

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.11; H, 8.30. Found: C, 71.10; H, 8.20

3β-Chloro-16-carbomethoxyandrost-5-en-17-one (2b).- To a suspension of sodium methoxide (0.5 g) in dry pyridine (30 mL) was added a solution dimethyl carbonate (2.2 mL; 25.6 mmol) in dry pyridine (20 mL) and then a solution of 3β-chloroandrost-5-en-17-one (**1a**) (2 g, 6.4 mmol) in dry pyridine (30 mL) dropwise at room temperature, and the mixture was stirred under nitrogen for 6 hrs. The mixture was diluted with ice water (50 ml) and neutralized with 1M HCl. The precipitate was collected and recrystallized from methanol to give 1.36 g (59%) of **2b**, mp. 123-125°. IR: 1730 (carbomethoxy C=O), 1710 (C=O), 1610 (C=C), 1240 (C-O), 680 (C-Cl)[7] cm^{-1}; ^1H NMR: δ 5.38 (m, 1H, C_6-H), 4.26 (m, 1H, $W_{1/2}$=12 Hz, H-3α),[6] 3.24 (m, 3H, OCH_3).

Anal. Calcd. for $C_{21}H_{29}ClO_3$: C, 69.13; H, 8.01. Found: C, 69.20; H, 7.90

3β-Acetoxy-5-androsteno[17,16-c]pyrazolin-5'-one (3a).-To a solution of 3β-acetoxy-16-carbomethoxyandrost-5-en-17-one (**2a**) (0.5 g, 1.28 mmol) in methanol (25 mL) was added acetic acid (2 mL) and 99% hydrazine hydrate (0.25 mL, 5.12 mmol) and the mixture was refluxed for 2 hrs. The mixture was concentrated and poured onto ice. The precipitate was collected and recrystallized from ethanol-acetic acid to give 0.3 g (63%) of **3a** as a colorless solid, mp. 155-157°. IR: 3350 (NH), 1720 (acetate C=O), 1670 (pyrazolone C=O), 1620 (C=N), 1550 (C=C), 1240 (C-O) cm^{-1}; ^1H NMR: δ 8.0 (br s, 1H, NH exchangeable), 5.38 (m, 1H, C_6-H), 4.25 (m, 1H, $W_{1/2}$=12 Hz, H-3α), 2.10 (s, 3H, CH_3COO).

Anal. Calcd. for $C_{22}H_{30}N_2O_3$: C, 71.32; H, 8.16; N, 7.56. Found: C, 71.30; H, 8.10; N, 7.60

3β-Chloro-5-androsteno[17,16-c]pyrazolin-5'-one (3b).- A mixture of 3β-chloro-16-carbomethoxyandrost-5-en-17-one (**2b**) (1 g, 2.74 mmol), methanol (25 mL), acetic acid (2 ml) and 99% hydrazine

hydrate (0.55 mL, 10.9 mmol) was refluxed for 2 hrs. The mixture was concentrated and poured onto ice. The precipitate was collected and recrystallized from ethanol-acetic acid to give 0.55 g (58%) of **3b** as a colorless solid, mp. 168-170°. IR: 3360 (NH), 1670 (pyrazolone C=O), 1640 (C=N), 1560 (C=C), 680 (C-Cl) cm^{-1}; ^1H NMR: δ 8.1 (br s, 1H, NH exchangeable), 5.48 (m, 1H, C_6-H), 4.25 (m, 1H, $W_{1/2}$=12 Hz, H-3α).

Anal. Calcd. for $C_{20}H_{27}ClN_2O$: C, 69.25.; H, 7.85; N, 8.08. Found: C, 69.34; H, 7.80; N, 8.10

3β-Acetoxy-5-androsteno-1'-methyl [17,16-c]pyrazolin-5'-one (4a).- To a solution of **2a** (1 g, 2.57 mmol) in methanol (25 mL) was added acetic acid (2 mL) and methylhydrazine (0.55 mL, 10.24 mmol) and the mixture was refluxed for 2 hrs. The mixture was concentrated and poured onto ice. The solid was collected and recrystallized from petroleum ether-methanol to give 0.63 g (55%) of **4a** as a colorless solid, mp. 128-130°. IR: 1725 (acetate C=O), 1665 (pyrazolone C=O), 1630 (C=N), 1550 (C=C), 1240 (C-O) cm^{-1}; ^1H NMR: δ 5.32 (m, 1H, C_6-H), 4.25 (m, 1H, $W_{1/2}$=12 Hz, H-3α), 2.80 (s, 3H, N-CH_3), 2.10 (s, 3H, CH_3COO); ^{13}C NMR: δ 175.4 (pyrazolone C=O), 172.0 (CH_3COO), 155.2 (C=N), 68.2 (C_3), 140.5 (C_5), 121.4 (C_6).

Anal. Calcd. for $C_{23}H_{32}N_2O_3$: C, 71.84; H, 8.39; N, 7.29. Found: C, 71.90; H, 8.30; N, 7.30

3β-Chloro-5-androsteno-1'-methyl [17,16-c]pyrazolin-5'-one (4b).- A mixture of **2b** (0.5 g, 1.37 mmol), methanol (15 mL), acetic acid (1 mL) and methylhydrazine (0.3 mL, 5.48 mmol) was refluxed for 2 hrs. The mixture was concentrated and poured onto ice. The solid was collected and recrystallized from petroleum ether-methanol to give 0.28 g (50%) of **4b** as a colorless solid, mp. 150-152°. IR: 1670 (pyrazolone C=O), 1640 (C=N), 1560 (C=C), 680 (C-Cl) cm^{-1}; ^1H NMR: δ 5.38 (m, 1H, C_6-H), 4.30 (m, 1H, $W_{1/2}$=12 Hz, H-3α), 2.86 (s, 3H, N-CH_3); ^{13}C NMR: δ 175.2 (pyrazolone C=O), 155.6 (C=N), 68.4 (C_3), 140.2 (C_5), 121.1 (C_6).

Anal. Calcd. for $C_{21}H_{29}ClN_2O$: C,69.88; H, 8.10; N, 7.76. Found: C, 70.0; H, 8.05; N, 7.80

3β-Acetoxy-5-androsteno-1'-phenyl [17,16-c]pyrazolin-5'-one (5a).- To a solution of **2a** (1 g, 2.57 mmol) in methanol (25 mL) was added phenylhydrazine hydrochloride (1.48 g, 10.28 mmol) and sodium acetate (0.42 g, 5.14 mmol) and the mixture was refluxed for 2 hrs. The mixture was concentrated and poured onto ice. The pale yellow solid was collected and recrystallized from petroleum ether-methanol to give 0.80 g (60%) of **5a** as a colorless solid, mp. 178-180°. IR: 1730 (acetate C=O), 1670 (pyrazolone C=O), 1630 (C=N), 1610 (C=C), 1245 (C-O) cm^{-1}; ^1H NMR: δ 7.3-7.8 (m, 5H, aromatic), 5.35 (m, 1H, C_6-H), 4.28 (m, 1H, $W_{1/2}$=11 Hz, H-3α), 2.15 (s, 3H, CH_3COO); ^{13}C NMR: δ 178.2 (pyrazolone C=O), 171.8 (CH_3COO), 156.2 (C=N), 68.4 (C_3), 139.4 (C_5), 132.8-127.6 (C=C; Ar), 121.2 (C_6).

Anal. Calcd. for $C_{28}H_{34}N_2O_3$: C, 75.31; H, 7.67; N, 6.25. Found: C, 75.30; H, 7.60; N, 6.30

3β-Chloro-5-androsteno-1'-phenyl [17,16-c]pyrazolin-5'-one (5b).- A mixture of **2b** (0.5 g, 1.37 mmol), methanol (25 mL), phenylhydrazine hydrochloride (0.97 g, 5.48 mmol) and sodium acetate (0.22 g, 2.74 mmol) was refluxed for 2 hrs. The mixture was concentrated and poured onto ice. The pale yellow solid was collected and recrystallized from petroleum ether-methanol to give 0.40 g (60%) of **5b** as a colorless solid, mp. 132-134°. IR: 1670 (pyrazolone C=O), 1630 (C=N), 1610

(C=C), 670 (C-Cl) cm^{-1}; ^1H NMR: δ 7.3-7.8 (m, 5H, aromatic), 5.35 (m, 1H, C_6-H), 4.30 (m, 1H, $W_{1/2}$=11 Hz, H-3α); ^{13}C NMR: δ 178.4 (pyrazolone C=O), 156.5 (C=N), 68.5 (C_3), 139.7 (C_5), 132.9-127.8 (C=C; Ar), 121.5 (C_6).

Anal. Calcd. for $C_{26}H_{31}ClN_2O$: C, 73.83; H, 7.39; N, 6.62. Found: C, 73.90; H, 7.30; N, 6.60

3β-Acetoxy-5-androsteno[17,16-c]isoxazolin-5'-one (6a).- A mixture **2a** (1 g, 2.57 mmol) hydroxylamine hydrochloride (0.71 g, 10.28 mmol) and sodium acetate (0.42 g, 5.14 mmol) in methanol (30 mL) was refluxed for 3 hrs. The mixture was concentrated and poured onto ice. The precipitate was collected and recrystallized from methanol-acetic acid to give 0.57 g (52%) of **6a** as a colorless solid, mp. 190-192°. IR: 1730 (acetate C=O), 1725 (isoxazoline C=O), 1625 (C=N), 1590 (C=C), 680 (N-O) cm^{-1}; ^1H NMR: δ 7.3-7.8 (m, 5H, aromatic), 5.35 (m, 1H, C_6-H), 4.28 (m, 1H, $W_{1/2}$=11 Hz, H-3α), 2.35 (m, 2H, C_{15}-H), 2.15 (s, 3H, CH_3COO).

Anal. Calcd. for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77. Found: C, 71.20; H, 7.80; N, 3.80

3β-Chloro-5-androsteno[17,16-c]isoxazolin-5'-one (6b).- A mixture **2b** (1 g, 2.74 mmol) hydroxylamine hydrochloride (0.76 g, 10.97 mmol) and sodium acetate (0.45 g, 5.48 mmol) in methanol (30 mL) was refluxed for 3 hrs. The mixture was concentrated and poured onto ice. The precipitate was collected and recrystallized from methanol-acetic acid to give 0.57 g (51%) of **6b** as a colorless solid, mp. 190-192°. IR: 1720 (isoxazoline C=O), 1630 (C=N), 1600 (C=C), 690 (N-O), 670 (C-Cl) cm^{-1}; ^1H NMR: δ 7.3-7.8 (m, 5H, aromatic), 5.30 (m, 1H, C_6-H), 4.32 (m, 1H, $W_{1/2}$=12 Hz, H-3α), 2.38 (m, 2H, C_{15}-H).

Anal. Calcd. for $C_{20}H_{26}ClNO_2$: C, 69.05; H, 7.53; N, 4.03. Found: C, 69.12; H, 7.50; N, 4.10

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ASYMMETRIC INDUCTIVE SYNTHESIS OF α-AMINOARYLACETIC ACIDS IN THE PRESENCE OF β-CYCLODEXTRIN

Submitted by (06/15/92)

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Landini[1] has reported the synthesis of α-aminoarylacetic acids in the presence of a quaternary salt TEBA as phase transfer catalyst from the reaction of chloroform with corresponding aldehydes. Optically active α-aminoarylacetic acids could be obtained in chiral micellar systems by a similar scheme[2,3]. We now report that asymmetric induction in this reaction occurs in the presence of β–cyclodextrin (β-CD).

The highest yield of pure products is 85% for α-amino(4-bromophenyl)acetic acid ($[\alpha]_D^{25}$ +9.08). The value of e.e. % is about 2.6% for α-aminophenylacetic acid and about 28.2% for phenylalanine. All of the amino acids obtained are optically active. Moreover, some yields of pure products are higher than those obtained from the phase-transfer or the chiral micellar conditions (Table 1). In particular, the synthesis of phenylalanine from phenylacetaldehyde in the presence of β-CD has not