Synthesis of steroidal pyrimidine *N*-oxides[1]

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Several steroidal pyrimidine *N*-oxides were synthesized by treatment of different *N*-acyl derivatives of steroidal β-amino-α,β-unsaturated ketones with hydroxylamine. This procedure has been applied to obtain steroidal pyrimidine *N*-oxides with the heterocyclic ring condensed with rings A and B of the steroidal moiety. Some chemical and spectral properties of these derivatives are discussed.

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Recently, steroidal pyrimidines with the heterocyclic ring fused to the positions 2,3 or 16,17 have been reported by Ruggieri *et al.* (1, 2). The synthesis of pyrimidine *N*-oxides by cyclization of the adequate amidoximes has also been described (3).

We now wish to describe a procedure for the synthesis of steroidal (3,2-*d*) and (17,16-*d*) pyrimidine *N*-oxides of the androstane and estrane series and of the pyrimidines derived from them.

Treatment of 16-acetyl-17-aminoandrosta-5,16-dien-3β-ol, diacetate (**1***b*) (4) with hydroxylamine hydrochloride and pyridine in methanol solution afforded in good yield the (17,16-*d*) pyrimidine *N*-oxide **2***b*. It analyzed for $C_{25}H_{34}O_3N_2$. In the infrared (i.r.) spectrum **2***b* did not show hydroxyl bands. A carbonyl band at 1740 cm^{-1} corresponds to the 3-acetoxy group. The ultraviolet (u.v.) spectrum of **2***b* exhibited four maxima at 207, 217, 263, and 306 mμ (ε, 19 500, 21 900, 10 200, and 5500, respectively). The maxima at 217 and at 306 mμ are probably attributable to the *N*-oxide function since they disappear when the spectrum of **2***b* is determined in a strong acid medium (5). The nuclear magnetic resonance (n.m.r.) spectrum[2] of **2***b* showed two singlets at δ 2.70 and δ 2.47 corresponding to two aromatic methyl groups. A singlet at δ 2.02 is ascribed to the acetate. The position of the pyrimidine *N*-oxide function as shown in formula **2***b* results from the cyclization of the intermediary oxime.

Alkaline hydrolysis of **2***b* gave the free alcohol **2***a*. The i.r. spectrum of **2***a* showed a hydroxyl band at 3630 cm^{-1} and did not exhibit carbonyl bands. Two aromatic methyl groups are responsible for two singlets at δ 2.71 and δ 2.48 in the n.m.r. spectrum of **2***a*.

Acetylation of **2***a* with acetic anhydride – pyridine did not form **2***b*. Instead the diacetate **3***d* ($C_{27}H_{36}O_4N_2$) was obtained. This reaction is known to occur in heterocyclic rings bearing an *N*-oxide function. It has been previously reported in *N*-oxides of pyrimidine and purine (6–8). The u.v. spectrum of the diacetate **3***d* (λ_{max} 207, 217, and 257 mμ; ε, 7900, 6900, and 5300, respectively) suggested that the pyrimidine *N*-oxide has been transformed into a pyrimidine (9). This was confirmed by the presence of two strong bands in the i.r. spectrum of **3***d* at 1590 and 1570 cm^{-1} which are characteristic of a pyrimidine ring (8, 9). The i.r. spectrum of **3***d* also showed a strong carbonyl band at 1735 cm^{-1} with a shoulder at 1745 cm^{-1}, assigned to two acetoxy groups. One of them substituted at C-3, and the other one formed in the acetylation and attached to the pyrimidine moiety. The singlet corresponding to one of the aromatic methyl groups observed at δ 2.70 in the n.m.r. spectra of **2***a* and **2***b* is absent in the n.m.r. spectrum of the diacetate **3***d*. The singlets at δ 2.48 at δ 2.21 and at δ 2.07 in the n.m.r. spectrum of **3***d* are assigned to an aromatic methyl group and to two acetoxy groups. A sharp singlet (2 H) at δ 5.28 is ascribed to the methylene group bearing the acetoxy function formed in the acetylation. The alternative structure **4** was rejected since the singlet at δ 2.70 present in the n.m.r. spectra of **2***a* and **2***b* corresponds to the methyl group attached to the carbon between the nitrogen atoms of the pyrimidine ring, and this is the signal which is absent in the n.m.r. spectrum of the diacetate **3***d*.

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[2]The n.m.r. spectra were determined by Mr. Eduardo Díaz on a Varian A-60A spectrometer in deuteriochloroform solution using TMS as the internal reference. The chemical shifts are reported in p.p.m. as δ values.

Treatment of the pyrimidine *N*-oxide **2***b* with acetic anhydride yielded two products. One of them was identified as the diacetate **3***d* already described. The second product ($C_{25}H_{34}O_3N_2$) possesses structure **3***c* since it showed a hydroxyl band at 3450 cm^{-1} in the i.r. spectrum and on acetylation produced the diacetate **3***d*.

Reduction of the pyrimidine *N*-oxide (**2***b*) with zinc in acetic acid yielded the pyrimidine **3***b* ($C_{25}H_{34}O_2N_2$) (λ_{max} 207, 215, and 260 mμ; ε, 7900, 7200, and 7100, respectively). Its i.r. spectrum showed the pyrimidine bands at 1595 and 1570 cm^{-1} (8, 9). Alkaline hydrolysis of **3***b* afforded the alcohol **3***a*.

Pyrimidine *N*-oxides of this series with different substituents can be prepared by treatment of the appropriate acyl derivative of **1***a* with hydroxylamine. When the dipropionyl derivative **1***c* was treated with hydroxylamine hydrochloride and pyridine, the pyrimidine *N*-oxide **2***c* was obtained. In the n.m.r. spectrum the latter showed two quadruplets centered at δ 3.13 and at δ 2.32 attributed to the methylene of the ethyl group substituted in the pyrimidine ring and to the methylene of the propionyl ester, respectively. The singlet at δ 2.50 is assigned to the methyl group attached to the aromatic ring. The primary methyl groups are responsible for triplets centered at δ 1.36 and δ 1.15.

Treatment of the pyrimidine *N*-oxide **2***c* with acetic anhydride gave the acetoxy derivative **3***f*. Its i.r. spectrum had a broad carbonyl band at 1735 cm^{-1} (ester groups). The n.m.r. spectrum of **3***f* indicated that the acetoxy group is linked to the methylene of the ethyl group substituted in the pyrimidine ring. It showed a singlet at δ 2.46 corresponding to the aromatic methyl group. A quadruplet (1 H, $J = 6.5$ c.p.s.) at δ 5.89, a doublet (3 H, $J = 6.5$ c.p.s.) at δ 1.63, and a singlet at δ 2.18 (3 H) were attributed to the acetoxyethyl side chain.

Zinc reduction of the pyrimidine *N*-oxide **2***c* afforded the pyrimidine **3***e*.

Acetylation of 16-acetyl-17-benzoylaminoandrosta-5,16-dien-3β-ol (**1***f*), previously described (4) afforded the acetate **1***e*. Prolonged treatment of **1***e* with hydroxylamine hydrochloride and pyridine afforded in low yield the pyrimidine *N*-oxide **2***h*.

The urethane **1***f* prepared by treatment of **1***a* with ethyl chloroformate gave the hydroxypyrimidine *N*-oxide **2***e* by reaction with hydroxylamine. The n.m.r. spectrum of **2***e* showed a complex signal at δ 7.17 which disappeared on equilibration with deuterium oxide. A singlet at δ 2.48 was assigned to the aromatic methyl group.

Saponification of the hydroxypyrimidine *N*-oxide **2***e* yielded the free alcohol **2***f*. It gave a positive ferric chloride test. Treatment of **2***e* with acetic anhydride and pyridine afforded two products **2***g* and **2***h* in which the *N*-oxide function is still present. The diacetate **2***h* had i.r. bands at 1810 cm^{-1} (acetyl group substituted in the pyrimidine ring) and at 1735 cm^{-1} (C-3 acetyl group).

The monoacetate **2***g* only had a carbonyl i.r. band at 1730 cm^{-1} corresponding to the C-3 acetate. Treatment of **2***g* with acetic anhydride formed the acetate **2***h*.

Reduction of the pyrimidine *N*-oxide gave the hydroxypyrimidine **3***g*.[3] Its i.r. spectrum showed only the C-3 acetyl band at 1730 cm^{-1}. In the n.m.r. spectrum of **3***g* the aromatic methyl group is responsible for a singlet at δ 2.35 showing a displacement to higher field due to the reduction of the *N*-oxide function. It gave a negative ferric chloride test.

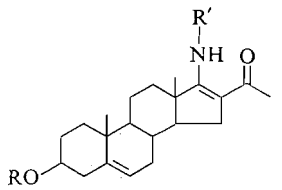
Acetylation of **3***g* with acetic anhydride and pyridine gave **3***h*. It had an i.r. band at 1775 cm^{-1} corresponding to the acetoxy group substituted in the heterocyclic ring.

The facility and good yield with which the pyrimidine *N*-oxides described above are obtained, prompted us to investigate the possibility of obtaining pyrimidine *N*-oxides in which the *N*-oxide function is near the C-18 angular methyl group.

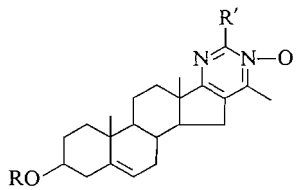
Treatment of the formyl derivatives **5***a* (11) and **9***a* (12) with ammonium hydroxide gave the corresponding ketoamines **5***b* and **9***b*. They gave positive ferric chloride tests. Both products were acetylated to the acetylamino derivatives **5***c* and **9***c*.

Treatment with hydroxylamine hydrochloride and pyridine of the β-amido-α,β-unsaturated ketones described above afforded the corresponding pyrimidine *N*-oxides directly; cyclization occurs very rapidly and the intermediary oximes could not be isolated. A similar treat-

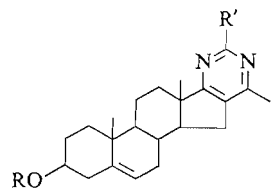
[3]Hydroxypyrimidines have been prepared by condensation of malonic ester derivatives with substituted ureas, see ref. 10.



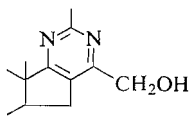
1 *a*, R = R′ = H
b, R = R′ = Ac
c, R = R′ = Et—C=O
d, R = H, R′ = Bz
e, R = Ac, R′ = Bz
f, R = R′ = Et—O—C=O



2 *a*, R = H, R′ = CH_3
b, R = Ac, R′ = CH_3
c, R = Et—C=O, R′ = Et
d, R = Ac, R′ = C_6H_5
e, R = Et—O—C = O, R′ = OH
f, R = H, R′ = OH
g, R = Ac, R′ = OH
h, R = Ac, R′ = AcO



3 *a*, R = H, R′ = CH_3
b, R = Ac, R′ = CH_3
c, R = Ac, R′ = CH_2OH
d, R = Ac, R′ = CH_2OAc
e, R = Et—C=O, R′ = C_2H_5
f, R = Et—C=O, R′ = CH—CH_3
g, R = Ac, R′ = OH
h, R = Ac, R′ = AcO OAc



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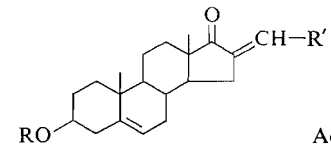
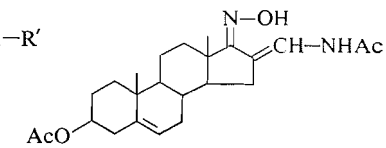
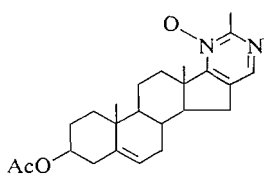


5 *a*, R = H, R′ = OH
b, R = H, R′ = NH_2
c, R = Ac, R′ = NHAc



6 *a*, *b*



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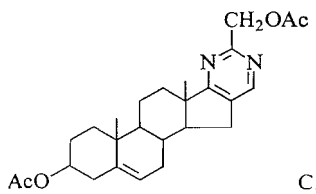

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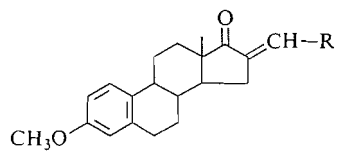


9 *a*, R = OH
b, R = NH_2
c, R = NHAc

ment of the amidoketones **5***c* and **9***c* gave the oximes **6***a* and **10***a*, respectively.

The oxime **6***a* was heated with γ-collidine in order to force the formation of the pyrimidine *N*-oxide; however, the product isolated was an isomer of **6***a*.

Exposure of the isomer **6***b* to acids caused ring closure. The resulting pyrimidine *N*-oxide **7** showed the following singlets in the n.m.r. spectrum: at δ 8.00 (1 H, aromatic proton), at δ 2.75, and at δ 2.05 (aromatic methyl group and C-3 acetyl group, respectively).

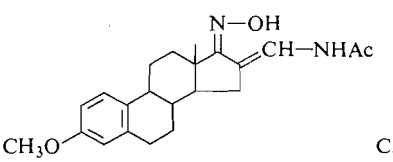
We were not able to produce ring closure by exposure of the oxime **6***a* to acids. Apparently the γ-collidine treatment of the oxime **6***a* affected the C-16 side chain, forming an isomer more prone to undergo cyclization.

Treatment of the pyrimidine *N*-oxide **7** with acetic anhydride resulted in formation of the pyrimidine derivative **8**.

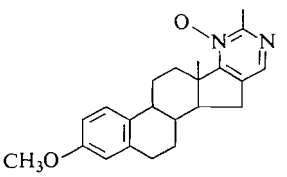
Treatment of the oxime **10***a* with γ-collidine gave the isomer **10***b*. Ring closure of the latter was produced on exposure to acids. The n.m.r. spectrum of the resulting pyrimidine *N*-oxide **11** exhibited singlets at δ 8.00 (1 H) and at δ 2.72 (3 H) corresponding to the hydrogen and methyl group substituted in the heterocyclic ring.

Alkaline hydrolysis of the non-crystalline acetoxy derivative **12***a* obtained by acetic anhydride treatment of **11** gave the pyrimidine **12***b*.

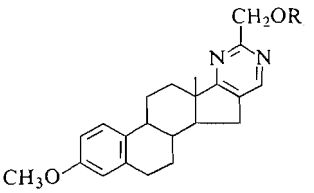
A pyrimidine *N*-oxide (3,2-*d*) was prepared by a similar procedure. The 2-aminomethylene derivative **13***b* was obtained by treatment of 2-formyl-5α-androstan 17β-ol,3-one (13, 14) with ammonium hydroxide. Treatment with hydroxylamine of the acetamido derivative **13***c* prepared by acetylation of the amine **13***b* gave the oxime **14**. When this oxime was heated with γ-collidine the pyrimidine *N*-oxide **15** was obtained. In the n.m.r. spectrum it showed a



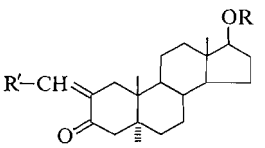
10 *a*, *b*,



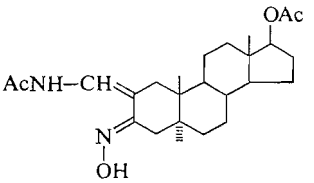
11



12 *a*, R = Ac
b, R = H



13 *a*, R = H, R′ = OH
b, R = H, R′ = NH_2
c, R = Ac, R′ = NHAc



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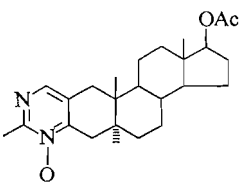

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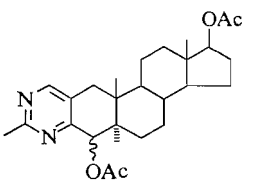

16 *a*, *b*,

singlet at δ 7.90 attributed to the pyrimidine aromatic proton. A triplet centered at δ 4.65 corresponded to the hydrogen substituted at C-17. Two singlets at δ 2.7 and δ 2.03 are assigned to the pyrimidine methyl group and the acetyl group, respectively. Treatment of the pyrimidine *N*-oxide **15** with acetic anhydride yielded two products *a* and *b* (**16**). The i.r. spectra of both products had carbonyl bands at 1735 cm^{-1} (double strength, acetyl groups). The n.m.r. spectra of both derivatives (**16**) had the same signals with very similar chemical shifts as described above for the pyrimidine *N*-oxide **15**. The presence of a singlet at δ 2.68 corresponding to the pyrimidine methyl group in *a* and *b* indicates that the latter remained untouched and that the newly formed acetoxy group is substituted at C-4 in the steroid nucleus. Comparison of the n.m.r. spectra of the products *a* and *b* indicates that these derivatives (**16**) differ in stereochemistry at C-4. The pyrimidine **16***a* exhibited in the n.m.r. spectrum a singlet at δ 2.19 assigned to the C-4 acetyl methyl group. The chemical shift and the coupling constant of a doublet ($J = 10$ c.p.s.) at δ 5.70, attributed to the C-4 proton, corresponds to an axial substituent, therefore the C-4 acetoxy group must be equatorial. The n.m.r. spectrum of **16***b* showed a singlet at δ 2.10 ascribed to the C-4 acetoxy group. The C-4 equatorial hydrogen is responsible for a doublet ($J = 4$ c.p.s.) at δ 6.05 (C-4 axial acetoxy group).

The pyrimidine *N*-oxides **7**, **11**, and **15** showed maxima at 220 and at 265 mμ, in the u.v. spectrum. When the latter was determined in strong acid medium the maximum at 220 mμ decreased in intensity.

Experimental

Melting points are uncorrected; the analyses were performed by Dr. F. Pascher, Bonn, Germany. Infrared (i.r.) spectra and rotations were run in chloroform unless otherwise stated. Ultraviolet (u.v.) spectra were run in 95% ethanol. The chromatograms were run using alumina Alcoa F-20.

Dimethylpyrimidine N-Oxide 2b

A solution of **1***b* (5 g) in methanol (75 ml) and pyridine (7 ml) was treated with hydroxylamine hydrochloride (5 g) and heated under reflux for 1 h. It was then concentrated to a small volume and diluted with water. The precipitate

formed was collected and washed with water. Crystallization from ethyl acetate – ether yielded the pyrimidine **2***b* (4 g) as brilliant plates, m.p. 250–252°. Further crystallizations from ethyl acetate – ether raised the m.p. to 256–258°; negative ferric chloride test; $[\alpha]_D$ −53°; λ_{max}, 207, 217, 263, 306 mμ; ε, 19 500, 21 900, 10 200, and 500; λ_{max} (pH 3)[4] 207, 266 mμ; ε, 19 300, 20 200; i.r. bands at 1740 cm^{-1} (acetyl group), at 1630 cm^{-1} (C=C double bonds), and at 1550 cm^{-1} (C=N double bonds).

Anal. Calcd. for $C_{25}H_{34}O_3N_2$: C, 73.14; H, 8.35; O, 11.69; N, 6.82. Found: C, 73.45; H, 8.47; O, 11.75; N, 6.68.

Alkaline Hydrolysis of the Dimethylpyrimidine N-Oxide 2b

A solution of **2***b* (3.2 g) in methanol (50 ml) was mixed with potassium hydroxide (3 g) in water (6 ml), heated under reflux for 1 h, concentrated to a small volume, poured in water, and the precipitate collected. Crystallization from methanol–acetone yielded **2***a* (2.6 g), m.p. 275–278°. Further crystallizations from methanol–acetone raised the m.p. to 279–281°, $[\alpha]_D$ −41°; λ_{max}, 205, 216, 262, and 304 mμ; ε, 20 000, 21 100, 10 500, 6100; i.r. bands at 3640 cm^{-1} (hydroxyl group), at 1625 cm^{-1} (C=C double bonds), and at 1550 cm^{-1} (C=N double bonds).

Anal. Calcd. for $C_{23}H_{32}O_2N_2$: C, 74.96; H, 8.75; O, 8.68; N, 7.60. Found: C, 74.92; H, 8.88; O, 8.91; N, 7.67.

Treatment of the Dimethylpyrimidine N-Oxide 2a with Acetic Anhydride and Pyridine

A solution of **2***a* (100 mg) in acetic anhydride (5 ml) and pyridine (5 ml) was heated on the steam bath for 1 h and then poured into water. The precipitate formed was extracted with ethyl acetate. The organic extract was washed with dilute hydrochloric acid, aqueous sodium bicarbonate, dried on anhydrous sodium sulfate, and evaporated. The solid residue (60 mg) was crystallized from acetone–hexane. This yielded **3***d* as needles, m.p. 144–147°; $[\alpha]_D$ −57°; λ_{max}, 207, 217 (shoulder), and 257 mμ; ε, 7900, 6900, 5300; i.r. bands at 1735 cm^{-1} with a shoulder at 1745 cm^{-1} (acetyl groups), and at 1590 and 1570 cm^{-1} (pyrimidine ring).

Anal. Calcd. for $C_{27}H_{36}O_4N_2$: C, 71.65; H, 8.02; O, 14.14; N, 6.19. Found: C, 71.94; H, 8.03; O, 13.63; N, 6.45.

Treatment of the Dimethylpyrimidine N-Oxide 2b with Acetic Anhydride

A solution of **2***b* (750 mg) in acetic anhydride (5 ml) was heated on the steam bath for 1 h, poured in water, and the precipitate extracted with ethyl acetate. The organic extract was washed with aqueous sodium bicarbonate, evaporated to dryness, and the gummy residue chromatographed on alumina. The crystalline fractions, eluted with benzene–hexane 1:1, were combined and recrystallized from acetone–hexane. This yielded the diacetate **3***d* (175 mg), m.p. 142–146°, which was identified by the standard methods with the product obtained in the above acetylation with acetic anhydride and pyridine.

The crystalline fractions eluted with benzene and increasing proportions of ethyl acetate were combined. Crystallization from ethyl acetate afforded **3***c* (150 mg) as needles, m.p. 245–248°; $[\alpha]_D$ −56° (dioxane); λ_{max}, 207, 217 (shoulder), and 258 mμ; ε, 8400, 7100, 5600; i.r. bands at 3450 cm^{-1} (hydroxyl group), at 1740 cm^{-1} (acetyl group), and at 1595 and 1570 cm^{-1} (pyrimidine ring).

Anal. Calcd. for $C_{25}H_{34}O_3N_2$: C, 73.14; H, 8.35; O, 11.69; N, 6.82. Found: C, 72.97; H, 8.30; O, 11.83; N, 6.78.

Acetylation of the derivative **3***c* with acetic anhydride–pyridine afforded the diacetate **3***d*, m.p. 142–146°.

Zinc Reduction of the Pyrimidine N-Oxide (2b)

A solution of the pyrimidine oxide **2***b* (5 g) in acetic acid (50 ml) was treated with zinc dust (10 g), heated under reflux for 1 h, filtered, evaporated to a small volume *in vacuo*, and diluted with water. The precipitate was extracted with ethyl acetate, the organic solution washed with aqueous sodium bicarbonate, dried with anhydrous sodium sulfate, concentrated, and cooled. The crystalline precipitate of **3***b* was collected and washed with ether, yield 1.3 g, m.p. 236–238°. Further crystallizations from ethyl acetate raised the m.p. to 239–241°; $[\alpha]_D$ −53°; λ_{max}, 207, 215 (shoulder), and 260 mμ; ε, 7900, 7200, 7100; i.r. bands at 1730 cm^{-1} (acetyl group), and at 1595 and 1570 cm^{-1} (pyrimidine ring).

Anal. Calcd. for $C_{25}H_{34}O_2N_2$: C, 76.10; H, 8.69; O, 8.11; N, 7.10. Found: C, 76.30; H, 8.77; O, 8.20; N, 7.09.

Alkaline Hydrolysis of the Dimethylpyrimidine 3b

A solution of **3***b* (500 mg) in methanol (20 mg) was mixed with potassium hydroxide (500 mg) in water (2 ml), heated under reflux for 1 h, concentrated, poured in water, and the precipitate collected and washed with water. Crystallization from methanol – ethyl acetate yielded **3***a* (410 mg) as prisms, m.p. 243–245°. Further crystallizations from the same solvents raised the m.p. to 248–250°; $[\alpha]_D$ −47° (dioxane); λ_{max}, 208, 215 (shoulder), and 259 mμ; ε, 7900, 7700, 7000; λ_{max} (pH 3) 208, 267 mμ; ε, 9400, 7200; i.r. bands at 3610 cm^{-1} (hydroxyl group), and at 1590 and 1570 cm^{-1} (pyrimidine ring).

Anal. Calcd. for $C_{23}H_{32}ON_2$: C, 78.36; H, 9.15; O, 4.54; N, 7.95. Found: C, 78.15; H, 9.12; O, 4.74; N, 8.03.

Acetylation of **3***a* with acetic anhydride – pyridine on the steam bath for 1 h afforded the acetate **3***b*.

16-Acetyl-17-aminoandrosta-5-16-dien-3β-ol Dipropionate (1c)

The amino derivative **1***a* (4) (1 g), in pyridine (5 ml) and propionic anhydride (5 ml), was heated on the steam bath for 1 h, poured in water, and the precipitate collected and washed with water. Crystallization from methanol yielded **1***c* (1.165 g) as brilliant plates, m.p. 181–183°; $[\alpha]_D$ −204°; λ_{max}, 207 and 313 mμ; ε, 10 000, 14 300; i.r. bands at 1740 cm^{-1} (ester group), 1640 cm^{-1} (hydrogen bonded, α,β-unsaturated ketone), and at 1580 cm^{-1} (C=C double bonds).

Anal. Calcd. for $C_{27}H_{39}O_4N$: C, 73.43; H, 8.90; O, 14.49; N, 3.17. Found: C, 73.20; H, 8.84; O, 14.68; N, 3.25.

Methylethylpyrimidine N-Oxide 2c

A solution of the dipropionate **1***c* (900 mg) in methanol (25 ml) and pyridine (3 ml) was treated with hydroxylamine hydrochloride (1 g), heated under reflux for 1 h,

[4]The ethanol solution was acidified with hydrochloric acid to pH 3 and the spectrum determined immediately.

concentrated, poured in water, and the precipitate collected and washed with water. Crystallization from ethyl acetate yielded **2***c* (670 mg) as small needles, m.p. 183–185°. Further crystallizations from the same solvents raised the m.p. to 193–195°; $[\alpha]_D$ −52°; λ_{max}, 207, 218, 265, and 306 mμ; ε, 19 300, 21 900, 10 200, 5900; λ_{max} (pH 3) 207, 268 mμ; ε, 18 600, 9800; i.r. bands at 1740 cm^{-1} (ester group), at 1620 (C=C double bonds), and at 1535 cm^{-1} (C=N double bonds).

Anal. Calcd. for $C_{27}H_{38}O_3N_2$: C, 73.94; H, 8.73; O, 10.94; N, 6.39. Found: C, 74.09; H, 8.69; O, 11.18; N, 6.27.

Treatment of the Methylethylpyrimidine N-Oxide 2c with Zinc Dust

A solution of the pyrimidine *N*-oxide **2***c* (500 mg) in acetic acid (5 ml) was treated with zinc dust (1 g) and the method used was the same as that described for the preparation of **3***b*. Chromatography of the crude product on alumina yielded the methylethylpyrimidine **3***e* (360 mg), m.p. 154–156° (needles from hexane–pentane); $[\alpha]_D$ −59°; λ_{max}, 207, 214 (shoulder), and 259 mμ; ε, 9000, 8500, 6600; i.r. bands at 1730 cm^{-1} (ester group), and at 1585 and 1560 cm^{-1} (pyrimidine ring).

Anal. Calcd. for $C_{27}H_{32}O_2N_2$: C, 76.73; H, 9.06; O, 7.57; N, 6.63. Found: C, 77.20; H, 9.16; O, 7.31; N, 6.77.

Treatment of the Methylethylpyrimidine N-Oxide 2c with Acetic Anhydride

A solution of **2***c* (500 mg) in acetic anhydride (5 ml) was treated as described before. The crude product was purified by chromatography on alumina. Crystallization from hexane–pentane furnished **3***f* as needles, (310 mg), m.p. 183–185°; $[\alpha]_D$ −8°; λ_{max}, 206, 217 (shoulder), and 257 mμ; ε, 8300, 7000, 6900; i.r. bands at 1735 cm^{-1} with a shoulder at 1745 cm^{-1} (ester groups), and at 1590 and 1570 cm^{-1} (pyrimidine ring).

Anal. Calcd. for $C_{29}H_{40}O_4N_2$: C, 72.47; H, 8.39; O, 13.32; N, 5.83. Found: C, 72.60; H, 8.67; O, 12.69; N, 5.90.

16-Acetyl-17-benzoylaminoandrosta-5,16-dien-3β-ol Acetate (1e)

Acetylation of **1***d* (4) (1.25 g) with acetic anhydride – pyridine on the steam bath for 1 h yielded the acetate **1***e* (600 mg) as pale-yellow prisms, m.p. 196–198°; $[\alpha]_D$ −68°; λ_{max}, 205, 241, and 331 mμ; ε, 16 100, 12 900, 12 500; i.r. bands at 1730 cm^{-1} (ester group), at 1700 cm^{-1} (benzamide group), 1630 cm^{-1} (hydrogen bonded, α,β-unsaturated ketone), and 1610 and 1580 cm^{-1} (C=C double bonds).

Anal. Calcd. for $C_{30}H_{37}O_4N$: C, 75.76; H, 7.84; O, 13.46; N, 2.95. Found: C, 75.29; H, 7.98; O, 14.14; N, 2.81.

Methylphenylpyrimidine N-Oxide 2d

A solution of **1***e* (600 mg) in methanol (25 ml) and pyridine (1 ml) was treated with hydroxylamine hydrochloride (600 mg), heated under reflux for 15 h, concentrated, diluted with water, and the precipitate collected and washed with water. The crude product was chromatographed on alumina. Crystallization from ethyl acetate – ether yielded **2***e* (100 mg) as pale-yellow needles, m.p. 240–242°; $[\alpha]_D$ −27°; λ_{max}, 206, 250, and 286 mμ; ε, 21 500, 26 200, 900; i.r. bands at 1740 cm^{-1} (acetyl group), at 1680 and 1630 cm^{-1} (C=C double bonds), and at 1580 cm^{-1} (C=N double bonds).

Anal. Calcd. for $C_{30}H_{36}O_3N_2$: C, 76.24; H, 7.68; O, 10.16; N, 5.93. Found: C, 76.27; H, 7.77; O, 10.25; N, 5.76.

Urethane 1f

Ethyl chloroformate (5 ml) was added slowly to a cooled solution of the amine **1***a* (900 mg) in pyridine (10 ml). After the addition was complete the reaction mixture was left at room temperature for 2 h, heated on a steam bath for 30 min, and poured into water. The solid product obtained was collected, washed with water, and crystallized from chloroform–methanol. This yielded **1***f* (1.040 g), m.p. 188–190°. Further crystallizations from the same pair of solvents gave an analytical sample, m.p. 193–195°; $[\alpha]_D$ −135°; λ_{max}, 306 mμ; ε, 23 500; i.r. bands at 1740 cm^{-1} (ester group), at 1630 cm^{-1} (hydrogen bonded α,β-unsaturated ketone), and at 1575 cm^{-1} (C=C double bond).

Anal. Calcd. for $C_{27}H_{39}O_6N$: C, 68.47; H, 8.30; O, 20.27; N, 2.96. Found: C, 68.70; H, 8.24; O, 20.08; N, 2.86.

Hydroxypyrimidine N-Oxide 2e

A solution of **1***f* (1 g) in methanol (25 ml) and pyridine (5 ml) was treated with hydroxylamine hydrochloride (1.3 g) and heated under reflux for 1 h. The solution was concentrated, diluted with water, and the solid precipitate collected and washed with water. Crystallization from chloroform–methanol gave small needles (810 mg), m.p. 284–285°; positive ferric chloride test (red color); λ_{max}, 209, 222, 318 mμ; ε, 12 600, 10 500, 7000; λ_{max} (pH 3) 210, 334 mμ; ε, 12 800, 8200; i.r. bands at 1745 cm^{-1} (ester group), 1650, 1620, and 1575 cm^{-1}.

Anal. Calcd. for $C_{25}H_{34}O_5N_2$: C, 67.85; H, 7.75; O, 18.08; N, 6.33. Found: C, 67.69; H, 7.64; O, 17.90; N, 6.16.

Saponification of the Hydroxypyrimidine N-Oxide 2e

A solution of **2***e* (800 mg) in methanol (50 ml) was mixed with potassium hydroxide (1 g) in water (2 ml) and heated under reflux for 1 h. The solution was concentrated, diluted with water, and acidified with diluted hydrochloric acid. The precipitate was collected and washed with water. Crystallization from methanol–ether gave **2***f* (530 mg), m.p. 278–280°; positive ferric chloride test (red color); $[\alpha]_D$ −59° (ethanol); λ_{max}, 222, 316 mμ; ε, 9550, 6300; i.r. bands (Nujol) at 3200 cm^{-1} (hydroxyl group), at 1650, 1625, and 1545 cm^{-1}.

Anal. Calcd. for $C_{22}H_{30}O_3N_2$: C, 71.32; H, 8.16; O, 12.96; N, 7.56. Found: C, 71.18; H, 8.11; O, 13.26; N, 7.33.

Acetylation of the Hydroxypyrimidine N-Oxide 2f

A solution of **2***f* (500 mg) in pyridine (5 ml) and acetic anhydride (5 ml) was heated on the steam bath for 1 h, poured into water, and the solid precipitate collected and washed with water. Fractional crystallization from chloroform–hexane gave the diacetate **2***h* (300 mg), m.p. 230–232°; $[\alpha]_D$ −81°; λ_{max}, 316 mμ; ε, 6300; i.r. bands at 1810 cm^{-1} (acetyl group substituted in the pyrimidine *N*-oxide ring); at 1735 cm^{-1} (C-3 acetate), at 1685, 1650, and 1550 cm^{-1}.

Anal. Calcd. for $C_{26}H_{34}O_5N_2$: C, 68.70; H, 7.54; O,

17.60; N, 6.16. Found: C, 68.91; H, 7.46; O, 17.41; N, 6.19.

From the mother liquors of the diacetate **2*h*** crystallized the monoacetate **2*g*** (50 mg). The analytical sample had m.p. 247–250° (needles from chloroform–hexane); λ_{max}, 222, 317 mμ; ε, 11 000, 7400; i.r. bands at 1730 cm^{-1} (acetate), 1650, 1615, and 1575 cm^{-1}.

Anal. Calcd. for $C_{24}H_{32}O_4N_2$: C, 69.88; H, 7.82; O, 15.51; N, 6.79. Found: C, 69.64; H, 8.06; O, 15.74; N, 6.85.

Treatment of **2*g*** (250 mg) with acetic anhydride under reflux for 15 min, gave **2*h*** (200 mg).

Zinc Reduction of the Hydroxypyrimidine N-Oxide 2h

A solution of **2*h*** (200 mg) in acetic acid (3 ml) was heated on the steam bath with zinc dust (500 mg) for 1 h. The mixture was treated as previously described. The resulting product (**3*g***) (150 mg) had m.p. 315–317° (decomposed) (needles from chloroform–methanol); negative ferric chloride test; $[\alpha]_D$ −80°; λ_{max}, 308 mμ; ε, 4600; i.r. bands at 1730 cm^{-1} (C-3 acetate), 1660, 1645, and 1570 cm^{-1}.

Anal. Calcd. for $C_{24}H_{32}O_3N_2$: C, 72.69; H, 8.13; O, 12.11; N, 7.07. Found: C, 72.40; H, 8.19; O, 12.37; N, 7.21.

Acetylation of **3*g*** (50 mg) with acetic anhydride – pyridine gave **3*h***. The analytical sample (needles from ethyl acetate) had m.p. 308° (decomposed); i.r. bands at 1775 cm^{-1} (acetate substituted in the pyrimidine ring), 1730 cm^{-1} (C-3 acetate), and 1650, 1595, 1570 (pyrimidine ring).

Anal. Calcd. for $C_{26}H_{34}O_4N_2$: C, 71.20; H, 7.82; O, 14.59; N, 6.39. Found: C, 71.03; H, 7.61; O, 14.66; N, 6.28.

16-Aminomethylene-5-androst-5-en-3β-ol-17-one (5b)

A solution of 16-formyl-androst-5-en-3β-ol-17-one (**5*a***) (11) (4.83 g) in ethanol (25 ml) and concentrated ammonium hydroxide (25 ml) was heated under reflux for 1 h. After 15 min a precipitate began to form. The mixture was diluted with water, filtered, and the precipitate washed with water and crystallized from methanol. This yielded the amine **5*b***, m.p. 269–273°. Further crystallizations from ethanol raised the m.p. to 276–278°; positive ferric chloride test (dark green color); $[\alpha]_D$ −96° (ethanol), λ_{max}, 302 mμ; ε, 18 000; i.r. bands (Nujol) at 3300 cm^{-1} (broad, hydroxyl and amino groups), at 1655 cm^{-1} (hydrogen bonded α,β-unsaturated ketone), and at 1575 cm^{-1} (C = C double bond).

Anal. Calcd. for $C_{20}H_{29}O_2N$: C, 76.15; H, 9.27; O, 10.14; N, 4.44. Found: C, 76.07; H, 9.19; O, 10.39; N, 4.24.

16-Acetylaminomethylene-androst-5-en-17-one-3β-ol Acetate (5c)

The enamine **5*b*** (1.2 g) dissolved in acetic anhydride (5 ml) and pyridine (5 ml) was heated on the steam bath for 3 h, poured into water, and the precipitate collected and washed with water. Crystallization from chloroform–ether yielded the acetylaminoketone **5*c*** (630 mg), m.p. 236–238°. Further crystallizations from the same pair of solvents raised the m.p. to 247°, $[\alpha]_D$ −101°; λ_{max}, 290 mμ; ε, 22 900; i.r. bands at 1725 cm^{-1} (acetyl groups), at 1645 cm^{-1} (hydrogen bonded α,β-unsaturated ketone).

Anal. Calcd. for $C_{24}H_{33}O_4N$: C, 72.25; H, 8.33; O, 16.02; N, 3.51. Found: C, 72.22; H, 8.16; O, 16.10; N, 3.49.

The oxime (**6*a***) had m.p. 184–185°; (needles from methanol–ether) $[\alpha]_D$ −113°; λ_{max}, 280 mμ; ε, 17 400; i.r. bands at 3450 and 3580 cm^{-1} (hydroxyl group), at 1725 and 1700 cm^{-1} (acetyl groups), and at 1650 and 1625 cm^{-1}.

Anal. Calcd. for $C_{24}H_{34}O_4N_2$: C, 69.53; H, 8.27; O, 15.44; N, 6.76. Found: C, 69.45; H, 8.18; O, 15.46; N, 6.67.

Treatment of the Oxime 6a with γ-Collidine

The oxime **6*a*** (200 mg) in γ-collidine (4 ml) was heated under reflux for 15 min. Ethyl acetate was added, and the organic solution was washed with dilute hydrochloric acid and water, dried, and evaporated. Crystallization of the residue from methanol–ether yielded the oxime **6*b*** (85 mg), m.p. 255–256°; $[\alpha]_D$ −153° (dioxane); i.r. bands (Nujol) at 3250 cm^{-1} (hydroxyl group), at 1735 cm^{-1} (acetyl group), and at 1655 cm^{-1} (broad), 1600 cm^{-1}.

Anal. Calcd. for $C_{24}H_{34}O_4N_2$: C, 69.53; H, 8.27; O, 15.44; N, 6.76. Found: C, 69.79; H, 8.33; O, 15.46; N, 6.73.

Treatment of the Oxime 6b with Trifluoroacetic Acid

A solution of the oxime **6*b*** (350 mg) in trifluoroacetic acid (2 ml) was left at room temperature for 15 min, diluted with water, and the precipitate extracted with chloroform. The organic layer was washed with water, dried, and evaporated. Crystallization of the residue from chloroform–ether gave the pyrimidine *N*-oxide **7** (200 mg) as small leaflets, m.p. 230–232°; λ_{max} 223, 265 mμ; ε, 23 400, 7760; λ_{max} (pH 3) 223, 265 mμ; ε, 10 200, 7700; i.r. bands at 1730 cm^{-1} (acetyl group), and at 1575 cm^{-1} (pyrimidine nucleus).

Anal. Calcd. for $C_{24}H_{32}O_3N_2$: C, 72.69; H, 8.13; O, 12.11; N, 7.07. Found: C, 72.47; H, 8.00; O, 12.11; N, 7.05.

A solution of **6*b*** (230 mg) in acetic acid (5 ml) was treated with concentrated hydrochloric acid (0.5 ml) at room temperature for 15 min. Crystallization from chloroform–ether yielded **7** (90 mg), m.p. 234–236° (decomposed).

Treatment of the Pyrimidine N-Oxide 7 with Acetic Anhydride

A solution of **7** (200 mg) in acetic anhydride (2 ml) was heated on the steam bath for 30 min, diluted with water, and the precipitate extracted with chloroform. The organic solution was washed with aqueous sodium bicarbonate, water, dried, and evaporated. The crude solid product obtained was dissolved in benzene and passed through alumina (2 g). Crystallization from ether–hexane yielded **8** (100 mg), m.p. 122–124°; $[\alpha]_D$ −47°; λ_{max}, 220, 260 mμ; ε, 11 000, 5750; i.r. bands at 1745 and 1735 cm^{-1} (acetyl groups), and at 1590 and 1560 cm^{-1} (pyrimidine nucleus).

Anal. Calcd. for $C_{26}H_{34}O_4N_2$: C, 71.20; H, 7.82; O, 14.59; N, 6.39. Found: C, 71.45; H, 7.91; O, 14.37; N, 6.44.

16-Aminomethylene-estrone Methyl Ether 9b

A solution of 16-formyl-estrone methyl ether **9*a*** (12) (4.64 g) in ethanol (25 ml) and concentrated ammonium hydroxide (15 ml) was heated under reflux for 1 h, diluted

with water, and the precipitate collected and washed with water. Crystallization of the amine **9***b* from methanol–ether afforded pale-yellow prisms (3.42 g), m.p. 217–219°; positive ferric chloride test (dark-green color); $[\alpha]_D$ +108°; λ_{max}, 301 mμ; ε, 20 000; i.r. bands (Nujol) at 3470 and 3360 cm^{-1} (hydroxy and amine groups), at 1680 cm^{-1} (hydrogen bonded α,β-unsaturated ketone), at 1660 cm^{-1} (C═C double bonds), and at 1600 cm^{-1} (aromatic ring).

Anal. Calcd. for $C_{20}H_{25}O_2N$: C, 77.13; H, 8.09; O, 10.28; N, 4.50. Found: C, 76.84; H, 7.99; O, 10.51; N, 4.52.

16-Acetylaminomethylene-estrone Methyl Ether 9c

The amine **9***b* was acetylated as described for previous cases. Crystallization from methanol–ether yielded **9***c* (760 mg), m.p. 205–206°. The analytical sample had m.p. 211–213° (needles from methanol – isopropyl ether); $[\alpha]_D$ +102°; λ_{max}, 288 mμ; ε, 24 000; i.r. bands at 3450 cm^{-1} (NH group), at 1715 cm^{-1} (acetyl group), and at 1640 cm^{-1} (hydrogen bonded, α,β-unsaturated ketone).

Anal. Calcd. for $C_{22}H_{27}O_3N$: C, 74.75; H, 7.70; O, 13.58; N, 3.96. Found: C, 75.07; H, 7.79; O, 13.71; N, 4.05.

The oxime **10***a* had m.p. 227–228° (needles from methanol); $[\alpha]_D$ +76°; λ_{max}, 282; ε, 21 400; i.r. bands (Nujol) at 3300 cm^{-1} (hydroxyl group), at 1690 cm^{-1} (acetyl group), at 1650, and 1615 cm^{-1}.

Anal. Calcd. for $C_{22}H_{28}O_3N_2$: C, 71.71; H, 7.66; O, 13.03; N, 7.60. Found: C, 71.87; H, 7.56; O, 13.12; N, 7.55.

Treatment of the Oxime 10a with γ-Collidine

A solution of the oxime **10***a* (1.15 mg) was treated with γ-collidine as described previously for **6***a*. Crystallization from methanol–ether yielded the oxime **10***b*, m.p. 248° (decomposed) (small needles from methanol–ether; $[\alpha]_D$ +4° (dioxane); λ_{max}, 288 mμ; ε, 17 800; i.r. bands (KBr) at 3300 cm^{-1} (hydroxyl group), at 1650 and 1610 cm^{-1}.

Anal. Calcd. for $C_{22}H_{28}O_3N_2$: C, 71.71; H, 7.66; O, 13.03; N, 7.60. Found: C, 71.75; H, 7.77; O, 13.29; N, 7.57.

Treatment of the Oxime 10b with Trifluoroacetic Acid

A solution of the oxime **10***b* (650 mg) in trifluoroacetic acid (2 ml) was treated as described previously for **6***b*. Crystallization from chloroform–acetone yielded the pyrimidine *N*-oxide **11** (530 mg), m.p. 235–237°; $[\alpha]_D$ +54°; λ_{max}, 224, 268 mμ; ε, 31 630, 8100; λ_{max} (pH 3) 224, 264 mμ: ε, 23 200, 7900; i.r. bands at 1600 cm^{-1} (aromatic C═C double bonds) and at 1570 cm^{-1} (pyrimidine nucleus).

Anal. Calcd. for $C_{22}H_{26}O_2N_2$: C, 75.40; H, 7.48; O, 9.13; N, 7.99. Found: C, 75.51; H, 7.47; O, 9.19; N, 8.13.

Treatment of an acetic acid solution of **10***b* (200 mg) with hydrochloric acid afforded **11** (60 mg), m.p. 233–235°.

Treatment of the Pyrimidine N-Oxide 11 with Acetic Anhydride

The *N*-oxide (200 mg) was treated with acetic anhydride as described above for a similar case. The gummy product did not crystallize even after chromatography on alumina. It was dissolved in methanol (25 ml), mixed with a solution of potassium bicarbonate (250 mg) in water (5 ml), heated under reflux for 1 h, concentrated, diluted with water, and the precipitate collected and washed with water. Crystallization from acetone–ether yielded plates (80 mg), m.p. 172–175°; i.r. bands at 3450 cm^{-1} (hydroxyl group), and at 1590, 1575, 1545 cm^{-1} (pyrimidine nucleus).

Anal. Calcd. for $C_{22}H_{26}O_2N_2$: C, 75.40; H, 7.48; O, 9.13; N, 7.99. Found: C, 75.62; H, 7.64; O, 9.36; N, 8.13.

Aminoketone 13b

Treatment of **13***a* (13) (9 g) with ammonium hydroxide yielded **13***b* (5.4 g), m.p. 240–242°; positive ferric chloride test (purple color); $[\alpha]_D$ +48° (ethanol); λ_{max}, 316 mμ; ε, 15 850; i.r. bands (Nujol) at 3300 cm^{-1} (hydroxyl group) and at 1660 cm^{-1} (hydrogen bonded α,β-unsaturated ketone).

Anal. Calcd. for $C_{20}H_{31}O_2N$: C, 75.67; H, 9.84; O, 10.08; N, 4.41. Found: C, 75.55; H, 9 77; O, 10.13; N, 4.54.

Acetylaminoketone 13c

Acetylation of **13***b* with acetic anhydride – pyridine gave **13***c*. It had m.p. 156–158° (prisms from ethyl acetate – isopropyl ether); $[\alpha]_D$ +81°; λ_{max}, 300 mμ; ε, 15 850; i.r. bands at 1725 cm^{-1} (double strength, acetyl groups); at 1660 cm^{-1} (hydrogen bonded α,β-unsaturated ketone), and at 1590 cm^{-1} (C═C double bond).

Anal. Calcd. for $C_{24}H_{35}O_4N$: C, 71.79; H, 8.79; O, 15.94; N, 3.49. Found: C, 71.87; H, 8.88; O, 16.04; N, 3.61.

The oxime **14** had m.p. 191–192° (prisms from chloroform–hexane) $[\alpha]_D$ +56°; λ_{max}, 290 mμ; ε, 11 750; i.r. bands at 1720 cm^{-1} (acetyl group), at 1680, 1650, and 1560 cm^{-1}.

Anal. Calcd. for $C_{24}H_{36}O_4N_2$: C, 69.20; H, 8.71; O, 15.36; N, 6.73. Found: C, 69.07; H, 8.82; O, 15.37; N, 6.81.

Treatment of the Oxime 14 with γ-Collidine

A solution of the oxime **14** (500 mg) in γ-collidine (5 ml) was heated under reflux for 3 h. The method was then as described previously. The crude material obtained was chromatographed on alumina (10 g). Elution with benzene and with benzene – ethyl acetate (9:1) gave the pyrimidine *N*-oxide **15** (200 mg), m.p. 165–170° (prisms from ether–hexane). Further crystallizations from the same pair of solvents raised the m.p. to 187–188°; $[\alpha]_D$ +46°; λ_{max}, 220, 264, 298 mμ; ε, 23 400, 7400, 3300; λ_{max} (pH 3) 220, 265 mμ; ε, 20 500, 7300; i.r. bands at 1735 cm^{-1} (acetyl group) and at 1590 and 1560 cm^{-1} (pyrimidine nucleus).

Anal. Calcd. for $C_{24}H_{34}O_3N_2$: C, 72.33; H, 8.60; O, 12.04; N, 7.03. Found: C, 72.07; H, 8.59; O, 12.18; N, 7.20.

The mother liquors of the amine **13***b* were subjected to the same process as that followed in the preparation of the crystalline amine. A yield of 1.5 g of the pyrimidine *N*-oxide **15**, m.p. 184–187° was obtained in this way.

Treatment of the Pyrimidine N-Oxide 15 with Acetic Anhydride

The *N*-oxide **15** (400 mg) in acetic anhydride (5 ml) was heated under reflux for 30 min. The solution was

worked up as previously described for similar cases. The crude gummy product obtained, was chromatographed on alumina (5 g). Elution with benzene–hexane 1:1 and benzene gave a solid product **16***a* (100 mg), m.p. 173–174°; (leaflets from ether–hexane); $[\alpha]_D$ −20°; λ_{max}, 261 mμ; ε, 4570; i.r. bands at 1735 cm^{-1} (broad, acetyl groups) and at 1580 and 1555 cm^{-1} (pyrimidine nucleus).

Anal. Calcd. for $C_{26}H_{36}O_4N_2$: C, 70.88; H, 8.24; O, 14.53; N, 6.36. Found: C, 71.22; H, 7.98; O, 14.64; N, 6.46.

Elution with benzene – ethyl acetate (9:1) gave **16***b* (75 mg), m.p. 202–203°; (plates from ether–hexane); $[\alpha]_D$ +59°; λ_{max}, 261; ε, 4570; i.r. bands at 1730 and 1720 cm^{-1} (acetyl groups) and at 1575 and 1555 cm^{-1} (pyrimidine nucleus).

Anal. Calcd. for $C_{26}H_{36}O_4N_2$: C, 70.88; H, 8.24; O, 14.53; N, 6.36. Found: C, 70.68; H, 8.29; O, 14.61; N, 6.16.

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