Tetrahedron Vol 32, pp 2997 to 3001. Pergamon Press 1976 Printed in Great Britain

UNUSUAL KNOEVENAGEL CONDENSATIONS OF 16a-SUBSTITUTED-16-METHYLENE-17-KETO-STEROIDS

B. GREEN*, I. S. KHAIDEM, R. I. CRANE and S. S. NEWAZ
Department of Chemistry, University of Maine, Orono, Maine 04473, U.S.A.

(*Received in USA* 7 *April* 1976; *Received in UK for publication* 26 *July* 1976)

Abstract—A Knoevenagel condensation between 3β-acetoxy-16-pyrrolidinylmethylenandrost-5-en-17-one (**8c**) and an excess of malononitrile led unexpectedly to 3β-acetoxyandrost-5-eno-[17,16-c]-1',6'-dicyanoaniline (**12a**) as the major product and 3β-acetoxy-16-pyrrolidinylmethylen-17-dicyanomethylenandrost-5-ene (**11a**) as the minor product. Knoevenagel reactions of other 16a-substituted-16-methylen-17-keto steroids were studied to evaluate the scope and mechanism of the reaction.

With the aim of synthesizing steroidal fused-ring α-pyrones, 5, for biological testing[1] we were attracted by the directness of the plan illustrated in Scheme 1. The key step in this approach is the Knoevenagel condensation of malonic acid or a derivative with a 16-oxymethylene-17-ketoandrostene (**2**). Precedent for this step can be found in the decarboxylative condensation of malonic acid with aldehyde **6** to yield the α-pyrone **7**.[2]

Attempted condensation of the hydroxymethylene compound **2a** with malonic acid in pyridine containing piperidine led to the isolation of the piperidinyl enamine **8a**[3] as the only observable product. When the reaction was repeated with the methoxymethylene derivative **2c**[4] in the presence of morpholine the morpholinyl enamine **8b**[3] was the only product.

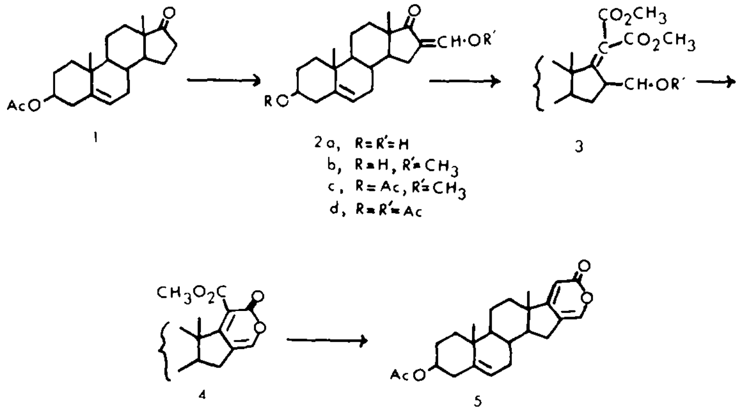
In the absence of a 16-substituent, Knoevenagel condensations occur readily at the 17-keto group.[5] The failure to effect condensation in this instance could be due either to increased steric hindrance by the 16-substituent to approach of the active methylene component or to the modified electronic character of the 17-CO group caused by interaction with the 16a-O atom.

To investigate the question of steric hindrance a methylene component of lower steric requirements, ethyl cyanoacetate, was used. Attempted condensation under the usual Knoevenagel conditions (NH_4OAc, HOAc, benzene, Dean–Stark) of ethyl cyanoacetate with the 16-methoxymethylene compound **2b** and the 16-acetoxymethylene compound **2d**[6] led to recovery of starting material.

Attention was now turned to the use of malononitrile as the active methylene component because of its small size.† There were examples in the literature of the use of malononitrile to produce α-pyrones. Ried[7] condensed *o*-hydroxyacetophenone with this reagent to produce the iminolactone **9a** which was then hydrolyzed by dilute acid to the coumarin **10**. Although the OH group was phenolic the analogy to the enolic form of a β-diketone is reasonably close. A similar case was reported by Sakurai[8] in which *o*-hydroxybenzaldehyde was condensed with malononitrile to form the iminolactone **9b**. A recent paper[9] describes the cyclization of 2-methoxy-α-cyano-β-arylcinnamonitriles to coumarins in sulfuric acid. Such a reaction is formally analogous to the step 3→4 in Scheme 1.

Because of its solubility and extreme ease of preparation from 3β-hydroxy-16-hydroxymethylenandrost-5-en-17-one (**2a**) the pyrrolidinyl enamine **8c** was chosen as the starting steroid with the idea that the intermediate condensation product **11a** could be isolated and then hydrolyzed and cyclized to the lactone **5b** by way of the iminolactone.

3β-Acetoxy-16-pyrrolidinylmethylenandrost-5-en-17-one (**8c**) was treated with a 6-fold excess of



Scheme 1.

---

†Impetus was added to our work by the report[10] that certain ylidene-malonitriles showed cytostatic activity.

malononitrile under Knoevenagel conditions (NH_4OAc, HOAc, benzene, Dean-Stark) for 48 hr to give as the major product in 42% yield a colorless compound showing IR peaks (nujol) at 3475, 3350, 3240 and 1640 cm^{-1} attributable to an amino group and at 2225 cm^{-1} assigned to a conjugated cyano group. In the NMR spectrum a broad peak at 5.16 (2 H's) exchanged with deuterium oxide confirming the amino group designation. There was a sharp signal at 7.40 δ (1 H), which was similar to that of the 16a-proton (7.40 δ) in the starting enamine **8c**. This evidence suggested structure **11c** in which the 16a-pyrrolidinyl group has been displaced by an amino group derived from ammonium acetate. The mass spectrum however showed a parent ion at *m/e* 369 (100%) and in the deuterium exchanged product at 371. These values were rationalized in terms of structure **12a**, the parent ion corresponding to a loss of 60 mass units from the unobserved molecular ion.†

After this work had been completed Ducker[11] reported the isolation in very low yield of an analogous product **13** from the condensation of equimolar amounts of 2-acetylcyclohexanone and malononitrile in the presence of ammonium acetate and acetic acid. The UV spectrum of **12a** showed maxima at 229, 237, 252, 265 and 355 nm in reasonable agreement with the values reported by Ducker.

Further transformations were carried out which confirmed the unexpected structure **12a** for the condensation product. Attempted acetylation by heating at 100° for 2 hr with acetic anhydride and pyridine caused no reaction, showing the expected electron deficient nature of the amino N atom. Raising the temperature of the acetylation mixture to 115° yielded a product whose physical properties showed it to be the N,N-diacetyl compound **12b**,[12] which showed in its NMR spectrum a 6-proton singlet at 2.16 corresponding to the N-acetyl hydrogens. Treatment with $Eu(fod)_3$ caused the peak to separate into two equal singlets, presumably by virtue of differential complexation, together with restricted rotation about the bond joining the imide nitrogen to the aromatic ring. An interesting feature of the IR spectrum was the presence of three CO peaks at 1738, 1722 and 1711 cm^{-1}. The last two are attributed to the asymmetric and symmetric stretching modes of the N,N-diacetyl system.[13]

Deamination of **12a** was achieved by treatment with isoamyl nitrite in the presence of hydroquinone and concentrated sulfuric acid[14] to give the dicyanobenzenosteroid **12c** in 23% yield. This showed a parent ion at *m/e* 354, M^+-60 (100%), and an NMR signal at 7.61 δ (2H) attributed to the two aromatic hydrogens. Addition of $Eu(fod)_3$ caused the anticipated separation of this signal into two broad singlets. The UV spectrum of **12c** showed maxima at 232, 238(sh), 244(sh), 288 and 293 nm, which compared well with the values for 1,3-dicyanobenzene itself.

A very minor species isolated from the mother liquors of several condensation reactions after removal of the dicyanoaniline **12a** showed no IR absorption in the N–H region. It had a peak at 2220 cm^{-1} (CCl_4) indicating a conjugated nitrile group. The mass spectrum showed a molecular ion of 459 (100%) and prominent fragment ions at 431, M^+–28 and 399, M^+–60. The latter corresponded to loss of acetic acid from the A-ring and the former suggested loss of ethylene from an N-substituted pyrrolidine.[15] This evidence showed the compound to be the originally desired 3β - acetoxy - 17 - dicyanomethylene - 16 - pyrrolidinylmethylenandrost - 5 - ene (**11a**).

A suggested mechanism for the formation of dicyanoaniline **12a** is given in Scheme 2. An addition/elimination of the activated form of malononitrile at C-16a would lead to intermediate **14** which, upon Knoevenagel condensation of a second molecule of malononitrile at the 17-keto group, would yield intermediate **15**.‡ Intramolecular attack as shown§ would lead to imine **16** which could aromatize by nucleophilic attack on one of the cyano groups. It is likely that a third molecule of malononitrile acts as the nucleophile in this step. An alternative route would comprise initial Knoevenagel condensation at C-17 to yield intermediate **11a** followed by addition/elimination at C-16a to give **15**. This was ruled out by the fact that **11a** was stable to the conditions of the Knoevenagel reaction. It is interesting to note that the pyrrolidinyl residue of **11a** was stable to mild saponification conditions. Despite the fact that the dicyanomethylene group would be expected to provide stabilization of a carbanion generated by nucleophilic attack at C-16a its ability to do so seems to be far less than that of a 17-keto group. Compound **11a** was also stable to refluxing in aqueous acid.

A step corresponding to the postulated transformation **8c** → **14** has recently been described by Junek.[16] Treatment of enamines of cyclohexan-1,3-diones with one equivalent of malononitrile in the presence of potassium hydroxide yielded pyridones by way of initial displacement of the amino function by malononitrile. Also Taurins[3] has described the displacement of the hydroxyl group in 16-hydroxymethylene steroids by cyanoacetamide.

Two further mechanisms must still be considered (Scheme 3). The first would involve condensation of intermediate **14** (Scheme 2) with a second molecule of malononitrile at C-16b to give **17** followed by cyclization of **17** to intermediate **16**. Alternatively condensation of malononitrile dimer[17] with **8c** at C-16a could give **17** directly.

To test the second of these mechanisms it was first demonstrated that malononitrile would indeed dimeriae under the reaction conditions. Next malononitrile dimer was allowed to react with 3β - acetoxy - 16 - pyrrolidinylmethylenandrost - 5 - en - 17 - one (**8c**) under conditions identical to those used earlier with the monomer. In this case the reaction took quite a different course, a highly insoluble compound separating after several hours. This was shown by TLC to be the major product with no more than a trace of dicyanoaniline, **12a**. The elemental analysis and IR data are in accord with structure designation **17** for this product. An NMR spectrum could not be taken because of extreme insolubility. The properties of **17** preclude its involvement in the formation of **12a** and hence rule out the mechanisms outlined in Scheme 3.

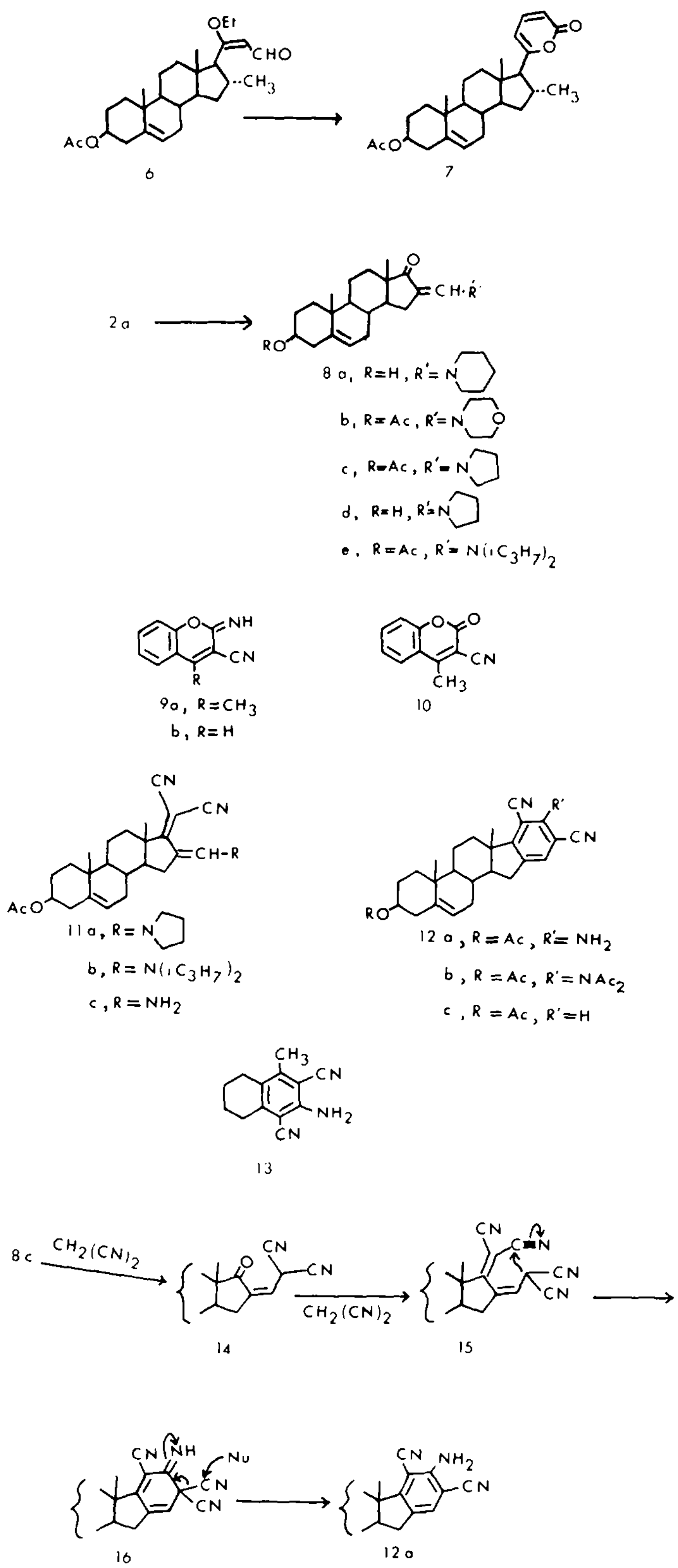
Because the suggested mechanism for formation of the benzenosteroid **12a** requires the participation of at least two and probably three molecules of malononitrile it was decided to carry out a condensation with equimolar amounts of steroid and malononitrile with the aim of changing the product ratio in favor of the 16-

---

†Such behavior is common in 3β-acetoxy-Δ^5-steroids.

‡The carbonyl group of intermediate **15** would now possess normal ketonic properties so enhancing its susceptibility to attack by malononitrile.

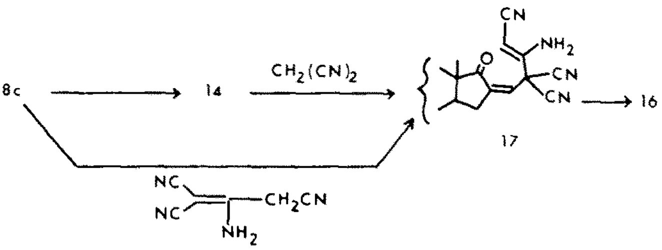
§The exact nature of the attacking species can only be surmized but under acidic conditions the enimine form (CN)C=C=NH is a reasonable assumption.



Scheme 2.

pyrrolidinylmethylene compound **11a**. In addition the reaction was carried out with pyrrolidinium acetate in place of ammonium acetate with the idea that reversibility of the first steps, **8c** ⇄ **14** ⇄ **15**, would allow regeneration of **8c** and hence favor formation of **11a**. Under these conditions the product ratio of **12a** to **11a** was found to be 1/1 with each compound being formed in 15% yield.

A further condensation was carried out using a slight molar excess of malononitrile but replacing the pyrrolidine by diisopropylamine as the basic catalyst. The



Scheme 3.

purpose was to see whether any base exchange took place at C-16a in a manner similar to that observed earlier when oxygen containing groups at C-16a in 16-oxymethylen-17-keto-steroids had been displaced by secondary amines. No exchange was observed and the products were 3β - acetoxy - 16 - pyrrolidinylmethylen - 17 - dicyano - methylenandrost - 5 - ene(**11a**, 18%) and 3β - acetoxyandrost - 5 - eno - [17,16 - c] - 2′,6′ - dicyano - aniline (**12a**, 28%).

To find out whether a bulky nitrogen function at C-16a would affect the product ratio by virtue of its steric effect at C-17 the diisopropylamino compound **8e**, was prepared and subjected to Knoevenagel condensation employing two equivalents of malononitrile and diisopropylamine as basic catalyst. In this case the benzenosteroid, **12a**, was the sole product in 19% yield, showing that a bulky substituent at C-16a does indeed hinder initial attack at the 17-CO group.

To ascertain whether other 16a-substituted-16-methylene-17-keto steroids would react under Knoevenagel conditions to yield the benzenosteroid, **12a**, the 16-acetoxymethylene, **2d**,[6] and the 16-methoxymethylene analog, **2c**,[4] were subjected to the same reaction conditions which had produced a 42% yield of **12a** from the 16-pyrrolidinylmethylene compound. The 16-acetoxy compound was converted to **12a**, in 10% yield, whereas the 16a-OMe compound was recovered unchanged. This suggests that in the addition/elimination sequence at C-16a the nucleofugality of the initially attached group is of prime importance. The greater nucleofugality[18] of a pyrrolidinyl group relative to a OMe group probably reflects the fact that the former will exist to some extent in the protonated form under the reaction conditions employed. The far greater nucleofugality of an acetate group relative to a OMe group is well known.

EXPERIMENTAL

M.ps (Thomas-Hoover unit) are uncorrected. IR spectra were obtained on a Perkin-Elmer 457 instrument. UV spectra were run on a Perkin-Elmer 202 spectrophotometer. NMR spectra were recorded on a Varian A-60 spectrometer; chemical shifts (δ) are given in ppm downfield from internal TMS. Mass spectra were taken on a Dupont 491 instrument equipped with a direct inlet. Silicagel HF_{254} (E. Merck) was used for TLC analysis. Microanalyses were performed by Alfred Bernhardt Laboratories, Elbach über Engelskirchen, W. Germany and by Analytical Chemical Services, Lowell, Mass.

3β - *Hydroxy* - 16 - *pyrrolidinylmethylenandrost* - 5 - *en* - 17 - *one* (**8d**). Compound **2a**[19] (3.2 g, 10 mmole) dissolved in hot pyridine (30 ml) was treated with pyrrolidine (4.15 ml, 50 mmole). The soln was heated to boiling, cooled, the crystals collected, washed with pyridine (10 ml), water and then dried. The yield of **8d** was 3.68 g. (100%), m.p. 253–4°; IR (Nujol) 3370, 1680, 1572 cm^{-1}. (Found: C, 77.91; H, 9.63; N, 3.82; O, 8.74. Calcd for $C_{24}H_{35}NO_2$: C, 78.00; H, 9.55; N, 3.79; O, 8.66%.) The 3β-acetate **8c** (Ac_2o/pyridine, 100°/1 hr) had m.p. 235°; IR (Nujol) 1730, 1675, 1585, 1570, 1245, 1220, 1030, 1007 cm^{-1}; NMR ($CDCl_3$) δ 0.99 (s, 3), 1.06 (s, 3), 2.03 (s, 3), 1.90 (m, 4), 3.54 (m, 4), 5.43 (m, 1), 7.40 (br.s, 1); *m/e* (%) M$^+$ 411 (55), 396 (26), 138 (47), 109 (100), 108 (44), 84 (23), 81 (37), 70 (29). (Found: C, 75.85; H, 9.15; N, 3.38; O, 11.77. Calcd for $C_{26}H_{37}NO_3$: C, 75.87; H, 9.06; N, 3.40; O, 11.66%.)

3β - *Acetoxy* - 16 - *diisopropylaminomethylenandrost* - 5 - *en* - 17 - *one* (**8e**). The title compound was prepared from **2a**[19] (25 g, 79.2 mmole) exactly as described for **8c**. The crude product (14.7 g) was recrystallized from hexane (impurities less soluble) to give the pure product as prisms, m.p. 157–158°, IR (CCl_4) 1738, 1689, 1250, 1030 cm^{-1}; NMR ($CDCl_3$) 0.98 (s, 3), 1.04 (s, 3), 1.21 (d, 12), 2.00 (s, 3), 3.87 (hep., 2), 4.5 (br, 1), 5.32 (br, 1), 7.32 (s, 1) δ; *m/e* (%) 441 (17, M$^+$), 426 (31), 398 (100), 381 (13), 366 (20), 338 (65), 139 (35), 124 (22), 96 (29), 44 (59), 43 (39), 40 (89). (Found: C, 76.00; H, 9.72; N, 3.14; O, 10.87. Calcd for $C_{28}H_{43}NO_3$: C, 76.15; H, 9.81; N, 3.17, O, 10.92%.)

Attempted Knoevenagel condensation of 3β - hydroxy - 16 - hydroxymethylenandrost - 5 - en - 17 - one (**2a**) *with malonic acid.* Compound[19] **2a** (633 mg, 2 mmole) in a mixture of dry pyridine (6 ml) and dry piperidine (5 ml) was treated with malonic acid (420 mg, 4 mmole) and the temp. maintained at 100° for 18 hr. The cooled mixture was poured into water (100 ml) and acidified with 2N HCl. The ppt was recrystallized from EtOH/water to give **8a** (400 mg, 52%), m.p. 231° (d), needles from EtOH–water (lit.[3] m.p. 218–24°); IR (Nujol) 3600, 1670, 1570 cm^{-1}; NMR ($CDCl_3$), δ 0.86 (s, 3), 1.03 (s, 3), 3.38 (m, 5), 5.40 (m, 1), 7.22 (br.s, 1).

Knoevenagel condensation of 3β - acetoxy - 16 - pyrrolidinylmethylenandrost - 5 - en - 17 - one (8c) *with malononitrile*

Method A (6-equivalents malononitrile). To a solution of **8c** (8.095 g, 19.6 mmole), malononitrile (6.52 ml, 117.6 mmole) and AcOH (70 ml) in dry benzene (250 ml) was added ammonium acetate (1.0 g, 13 mmole) and the soln refluxed for 48 hr using a Dean–Stark adapter. The cooled mixture was diluted with ether (200 ml) and the resulting soln washed with water (4 × 100 ml). The organic layer was dried ($MgSO_4$) and the solvent evaporated to yield a brown oil, which was crystallized first from EtOH–water and then from dioxane–methanol to yield prisms of **12a** (3.53 g, 42%), m.p. 210–13°; IR ($CDCl_3$) 3500, 3400, 2200, 1725, 1625, 1255, 1030 cm^{-1}; (Nujol) 3475, 3350, 3240 cm^{-1}; NMR ($CDCl_3$) 1.08 (s, 3), 1.01 (s, 3), 2.05 (s, 3), 4.52 (broad, 2, exchanged with D_2O), 5.30 (broad, 1H), 7.31 (s, 1); *m/e* (%) 369 (100, M$^+$-60), 354 (28), 261 (30), 208 (29), 145 (24), 121 (36), 107 (30), 105 (27), 91 (28), 43 (80); UV (CH_3CN), 229 sh (23,387), 237 (27,150), 252 (8,064), 265 (5,645), 355 (8,333) nm. (Found: C, 75.63; H, 7.32; N, 9.69; O, 7.30. Calcd for $C_{27}H_{31}N_3O_2$: C, 75.49; H, 7.27; N, 9.78; O, 7.45%.)

The mother liquors from the crystallization of **12a** showed a TLC spot at slightly higher R_f value. Repeated chromatography on basic alumina of the residual material from several Knoevenagel condensations led to the isolation of a small quantity of **11a**, m.p. 208–209 (d); IR ($CDCl_4$) 2218, 1728, 1612, 1540, 1422, 1252, 1030 cm^{-1}, (CCl_4) 2218, 1742 cm^{-1}; NMR ($CDCl_3$) 0.95 (s, 3), 1.10 (s, 3), 2.03 (s, 3), 3.80 (filled in triplet, 4), 4.5 (br, 1), 5.4 (br, 1), 7.48 (s, 1) δ; *m/e* (%) 459 (100, M$^+$), 431 (15), 417 (19), 404 (22), 399 (31), 370 (61), 357 (15), 344 (20), 91 (23), 70 (95), 43 (100). (Found: C, 75.78; H, 7.92; N, 9.13; O, 7.14. Calcd for $C_{29}H_{37}N_3O_2$: C, 75.78; H, 8.11; N, 9.14; O, 6.95%.)

Method B (1.4 equivalents malononitrile). To a soln of **8c** (3.60 g, 8.76 mmole), malononitrile (792 mg, 12.4 mmole) in dry benzene (250 ml) was added pyrrolidine (124 mg, 1.75 mmole) and AcOH (1.5 ml, 250 mmole). The mixture was refluxed for 48 hr through a Soxhlet thimble containing 3A molecular seives.

Work-up was carried out as in method A and the crude product then chromatographed on silicagel 60 (E. Merck). Compound **11a** (531 mg, 13%) eluted in a solvent mixture of 4% ether/benzene. Compound **12a** (482 mg, 13%) eluted in a solvent mixture of 75% ether/benzene.

Method C (use of diisopropylamine: 1.2 equivats malononitrile). The reaction was carried out using **8c** (2.334 g, 5.68 mmole), malononitrile (423 mg, 6.4 mmole), diisopropylamine (630 mg, 6.25 mmole) and AcOH (830 mg, 13.8 mmole). The mixture was refluxed through a Soxhlet extractor containing 3A molecular seives for 37 hr and then worked up as described in method A. The crude product was chromatographed on silicagel to yield **11a** (360 mg, 14%) and **12a** (670 mg, 28%) as the only isolable products.

Knoevenagel condensation of 3β - acetoxy - 16 - diisopropylaminomethylenandrost - 5 - en - 17 - one (**8e**) *with malononitrile.* To **8e** (5 g, 11 mmole) in dry benzene (200 ml) was added malononitrile (1.49 g, 22.6 mmole), diisopropylamine (228 mg, 2.26 mmole) and AcOH (1.2 ml, 200 mmole). Refluxing was carried out for 40 hr using a Dean–Stark adapter and work up achieved as previously described.

Chromatography on silicagel 60 (140 g, E. Merck) yielded in mixtures of 2%–5% ether/benzene **12a** (931 mg, 19%) with physical properties as listed above.

Acetylation of 3β - acetoxyandrost - 5 - eno - [17,16-c] - 2′,6′ - dicyanoaniline (**12a**)

Method A (100°). Heating the steroid at 100° with Ac_2O pyridine led to quantitative recovery of starting material.

Method B (115°). Steroid **12a** (205 mg, 0.47 mmole) was dissolved in pyridine (5 ml) and Ac_2O (1 ml) and the soln heated at reflux for 2 hr. The deep brown soln was cooled to room temp. and poured into ice water to yield a brown solid, which was recrystallized from EtOH/water (Norit) to give a microcrystalline solid, **12b**, 193 mg (79%), m.p. 205–206.5°; IR (Nujol), 2230, 1738, 1722, 1711, 1250, 1222, 1031 cm^{-1}; NMR ($CDCl_3$), 7.66 (br. s, 1H), 2.16 (s, 6H), 2.00 (s, 3H), 1.10 (s, 6H); NMR spectrum after addition of 10 μmole $Eu(fod)_3$/mmole steroid, 6.15 (s, 3H, 3β-OAc), 2.81, 2.75 (s, 3H each, N-Ac_2); *m/e* (%) 453 (43, M^+–60), 414 (40), 411 (100), 396 (17), 373 (M*), 369 (17), 354 (27), 321 (60), 307 (25), 303 (16). (Found: C, 71.95; H, 6.87; N, 8.51; O, 12.78. Calcd for $C_{31}H_{35}O_4N_3$: C, 72.49; H, 6.87; N, 8.18; O, 12.46%.)

Deamination of 3β - acetoxyandrost - 5 - eno - [17,16-c] - 2′,6′ - dicyanoaniline (**12a**). To a stirred soln of **12a** (1.5 g, 3.49 mmole) and hydroquinone (5.75 g, 52.3 mmole) in dry dioxan (500 ml) containing H_2SO_4 (0.7 ml) was added dropwise isoamyl nitrite (3.66 ml, 27.3 mmole, freshly prepared) in dry dioxan (100 ml). The addition was continued for 1 hr at room temp. after which the pink soln was stirred at room temp. for an additional 90 min. The mixture was then poured into water (700 ml) and the aqueous mixture extracted with ether. After washing the ethereal layer successively with sat $NaHSO_3$ aq, satd $NaHCO_3$ aq and water, it was dried (Na_2SO_4) and evaporated to yield a red oil, which was crystallized from EtOH/water to give a red solid. This was chromatographed on silicagel 60 (E. Merck) to yield in 9/1 hexane/EtOAc the dicyanobenzene **12c**. Later fractions containing mixtures of **12c** and starting material were subjected to rechromatography to give further amounts of **12c**. The complete recovery of **12c** could not be achieved. Recrystallization from EtOH/water gave **12c** (328 mg, 23%), m.p. 217.5–218°; IR ($CDCl_3$) 2230, 1720, 1030 cm^{-1}; NMR ($CDCl_3$) 7.61 (broad, 2H), 5.35 (m, 1H), 4.35–4.61 (broad, 1H), 2.00 (s, 3H), 1.08 (s, 6H) δ; NMR after addition of 8.4 μ. mole $Eu(fod)_3$/0.12 mmole steroid 7.70 (s, w/2 3.5 Hz) 7.63 (s, w/2 3.5 Hz); UV (CH_3CN) 232 (12,953), 238 (sh., 12,564), 244 (sh., 11,010) nm; *m/e* (%) 354 (100, M^+–60), 339 (37), 283 (20), 246 (10), 193 (29), 145 (31), 121 (34). (Found: C, 78.10; H, 7.39; N, 6.72; O, 7.80. Calcd for $C_{27}H_{30}N_2O_2$: C, 78.26; H, 7.25; N, 6.76; O, 7.73%.)

Condensation of 3β - acetoxy - 16 - pyrrolidinylmethylenandrost - 5 - en - 17 - one (**8c**) *with malononitrile dimer.* To a soln of **8c** (500 mg, 1.216 mmole) in benzene (15 ml) and AcOH (3 ml) containing ammonium acetate (195 mg, 2.53 mmole) was added malononitrile dimer (350 mg, 2.65 mmole). The soln turned orange during reflux under a Dean–Stark trap.

After 2 hr a crystalline solid had separated. Heating was continued for a further 12 hr and then the mixture cooled and filtered. The yield of yellow crystalline material was 383 mg. A portion of this solid was recrystallized three times from THF to yield cream-colored needles, m.p. > 400°; IR (KBr) 3500, 3350, 3170 (br. m), 2200 (m), 1710 (m), 1670 (sh), 1600 (v.s.), 1560 (s), 1230–1280 (m), 1025 (m), 800 (m). (Found: C, 71.08; H, 7.04; N, 11.39. Calcd for $C_{28}H_{32}N_4O_3$: C, 71.16; H, 6.83; N, 11.86%.)

Knoevenagel condensation of 3β - acetoxy - 16 - acetoxymethylenandrost - 5 - en - 17 - one[6] (**2d**) *with malononitrile.* A mixture containing **2d**[6] (1.0 g, 2.5 mmole), malononitrile (0.9 ml, 16.2 mmole), AcOH (15 ml) and ammonium acetate (200 mg) in benzene (70 ml) was refluxed for 48 hr using a Dean–Stark trap. The cooled soln was diluted with ether, washed with water, and dried ($MgSO_4$). Evaporation yielded a yellow solid which was recrystallized twice to yield heavy prisms of **12a** (110 mg, 10%).

Attempted Knoevenagel condensation of 3β - acetoxy - 16 - methoxymethylenandrost - 5 - en - 17 - one[4] (**2c**) *with malononitrile.* Using conditions identical to those used for **2d** only starting material could be isolated. TLC and spectral analysis showed the dicyanoaniline **12a** to be completely absent.

Acknowledgement—This work was supported by grant MA 2 R01 CA 11020 from the National Institute of Health.

REFERENCES

[1] For leading refs to the biological activity of steroidal α-pyrones see G. R. Pettit, B. Green and G. L. Dunn, *J. Org. Chem.* **35**, 1367 (1970); R. Ode, Y. Kamano and G. R. Pettit, *MIP International Review of Science, Organic Chemistry Series One* (Edited by W. D. Johns), Vol. 8. Butterworths, London (1972).

[2] T. Nambara, K. Shimada, S. Goya and J. Goto, *Chem. Pharm. Bull. Tokyo* **16**, 2236 (1968).

[3] B. G. Ketcheson and A. Taurins, *Can. J. Chem.* **38**, 972 (1960).

[4] J. Fajkos and F. Sorm, *Chem. Listy* **47**, 712 (1953).

[5] D. Bertin and L. Nedelec, *Bull. Soc. Chim. Fra.* 1555 (1962).

[6] G. Gerali, A. Ius, C. Parini and G. C. Sportoletti, *Farmaco, Ed. Sci.* **24**(2), 221 (1969); *Chem. Absts.*, **70**, 88044W (1969).

[7] W. Reid and E. Nyiondi-Bonguen, *Ann. Chem.* 134 (1973).

[8] A. Sakurai, Y. Motomura and H. Midorikawa, *J. Org. Chem.* **37**, 1523 (1972).

[9] E. Campaigne and D. E. Mais, *J. Hetero. Chem.* **12**, 267 (1975).

[10] N. Latif, I. F. Zeid and F. Assad, *Chem. & Ind.* 1539 (1970).

[11] J. W. Ducker and M. J. Gunter, *Austr. J. Chem.* **28**, 581 (1975).

[12] Diacetylation of electron deficient anilines has been reported by L. C. Raiford, R. Taft and H. P. Lankelma, *J. Am. Chem. Soc.* **46**, 2051 (1924).

[13] T. Uno and K. Machida, *Bull. Chem. Soc. Japan* **34**, 545 (1961); *Cf.* also R. B. Boar, J. F. McGhie, M. Robinson and D. H. R. Barton, *J. Chem. Soc.* Perkin I, 1242 (1975).

[14] R. N. McDonald and J. M. Richmond, *Ibid.* Chem. Comm., 605 (1973).

[15] A. M. Duffield, H. Budzikiewicz and C. Djerassi, *J. Am. Chem. Soc.* **87**, 2913 (1965).

[16] G. Zacharias, O. S. Wolfbeis and H. Junek, *Monatsh für Chemie* **105**, 1283 (1974).

[17] E. C. Taylor and K. S. Hartke, *J. Am. Chem. Soc.* **81**, 2452 (1959).

[18] The term nucleofugality is derived from the term nucleofuge used by Grob to describe a group which leaves with the bonding electron pair. Nucleofugality seems to us more concise and preferable to the cumbersome term "leaving group ability". C. A. Grob and P. W. Schiess, *Angew. Chem. Int.* **6**, 1 (1967).

[19] L. Ruzicka, V. Prelog and J. Battegay, *Helv. Chim. Acta* **31**, 1296 (1948).