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THE KINETICALLY CONTROLLED METHYLATION OF CONJUGATED POLYCYCLIC KETONES[a]

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Abstract—Addition at very low temperature of potassium t-butoxide to a solution of an α,β-unsaturated ketone and methyl iodide in tetrahydrofuran allows methylation at the methylenic position α', *via* the kinetic enolate. The reaction leads easily to the α'-gem-dimethylated product, but it has been shown, that the reaction can be stopped at the α'-monoalkylated compound.

It is well known that methylation of Δ_4-3-oxosteroids by methyl iodide in alkaline medium leads to the C4-mono and dialkylated products.[1] Thus, when an excess of methyl iodide is added, at room temperature, to a t-butanol solution of 17α-methyl-testosterone, **1b**, which has been previously treated with potassium t-butoxide, the 4,4-dimethyl Δ_5 - 3 - one, **2b**, is isolated in good yield.[2,3] Similar results have been obtained with related compounds and in particular with 19-nortestosterone, **1a**, which gives the deconjugated ketone, **2a**.[4]

The formation of these 4,4-dimethylated derivatives results from the alkylation of the thermodynamic enolate of type B (Chart. 1) which itself is formed at the expense of the kinetic enolate of type A.† Malhotra and Ringold[5] have indeed shown that the action of a strong mineral base on an α,β-unsaturated 3-oxosteroid, such as testosterone, effects, in the first place, the abstraction of the more acidic β axial proton at C-2 with formation of the less stable homoannular dienolate A.

Therefore, it appeared to us that methylation at C-2 on the kinetic sodium or potassium enolate A ought to be possible by modifying the relative rates of alkylation and isomerisation of the enolate A.

This paper reports a study of the kinetic methylation of several tetracycle **1**, **10**, **14** and tricyclic **7** α,β-unsaturated ketones with potassium t-butoxide.‡

In all these examples, we observed that direct methylation in the α' position can be achieved by working at low temperature and with an aprotic solvent.

Our first experiments were carried out with 17α-methyl 19-nortestosterone, **1d**, where the tertiary OH had been previously protected in tetrahydropyranyl ether form (THP) to prevent its partial methylation.

The results are given in Chart 2. Thus, when an excess of methyl iodide (about 14 moles for one mole of product) is added at about $-70°$ to a solution of the enolate prepared by addition of potassium t-butoxide(5,8 moles) to a tetrahydrofuran solution of ketone **3d**, 2,2,17α-trimethyl 19-nortestosterone, **5d**,[7] is isolated in 55% yield after hydrolysis of tetrahydropyranyl ether (Chart 2, exp. 1).

Improved yields may be obtained by reversing the order of introduction of the reagents, i.e. by adding the base to a cold solution of the steroid and

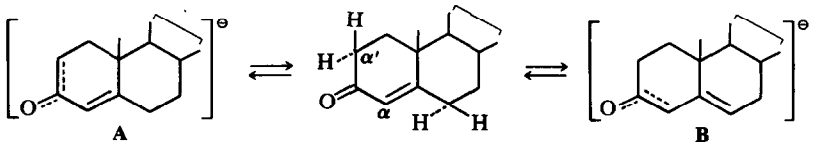


CHART 1

[a]Presented in part at the third International Congress on hormonal steroids, Hamburg, Federal Republic of Germany, September 1970[6]

†That is true for the first alkylation. For the second one, the intermediary 4 - methyl Δ_5 - 3 - oxosteroids are rapidly deprotonated and alkylated at C-4 in the methyl iodide, potassium *t*-butoxide, *t*-butyl alcohol system.[3]

‡After our preliminary communication,[6] a similar kinetic alkylation of a Δ4 - 3 - ketosteroid using lithium enolate was published by W. Reusch *et al.*[10a] and more recently by M. Tanabe *et al.*[10b] We became aware of the first of these two communications after submission of our manuscript to the Editor (note added following referee's report).

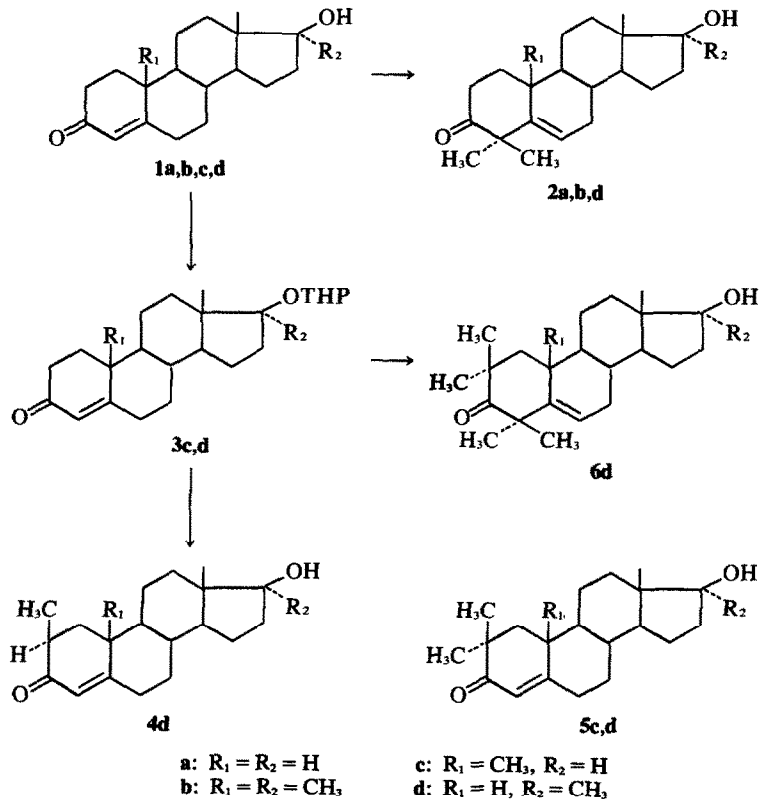


Chart 2. Methylation of 17α - methyl - 19 - nortestosterone - tetrahydropyranyl ether, **3d**

Exp.	Conditions		Product yield %[b]			
	KO*t*Bu[a]	Solvent (t°)	4d	5d	6d	2d
1	5,8 moles	THF (− 70°)[c]	3·5	55·0	—	—
2	5,8 moles	THF (− 70°)[d]	3·2	66·0	6·7	—
3	1,9 moles	THF (− 70°)[d]	67·0	8·6	1·7	—
4	1,9 moles	THF-HMPT (85-15) (− 70°)[d]	71·0	4·6	—	—
5	5,2 moles	THF-HO*t*Bu 1:1 (− 30°)[d]	5·0	—	15[e]	32·5

[a] moles of base for one mole of ketone;
[b] products isolated by chromatography on Silicagel;
[c] methyl iodide dropped into a mixture of ketone-KO*t*Bu and solvent;
[d] solution of KO*t*Bu dropped into a mixture of ketone-methyl iodide and solvent;
[e] in admixture with a trimethylated product;

methyl iodide at − 70° (exp. 2). Using these conditions compound **5d** is isolated in 66% yield. Besides the main product, small amounts of the mono and tetramethylated ketones **4d** and **6d** are produced.

By decreasing the amount of base used (1,9 moles), the monomethylated compound **4d**, already prepared by a different pathway,[7] can be obtained as the main product* (exp. 3). As expected, addition of a small amount of hexamethylphosphoric triamide (HMPT) to the solvent has a favorable effect (exp. 4).

*To achieve the reaction, KO*t*Bu must be used in excess. The reagent is probably partially alkylated by the methyl iodide. We have in fact observed, that the tertiary OH groups could be easily methylated under our working conditions.

As the first Me group introduced has the β configuration uniquely, its introduction agrees with a perpendicular attack of the enolate[8,9] from the β face *via* a prechair transition state having some ketonic character*

A striking solvent effect in this reaction has been demonstrated in experiment 5. Thus, when the methylation is carried out at −30°† in a mixture of THF-HOtBu 1:1, by adding the base to the solution of the steroid and of methyl iodide, only small yields of the C4-methylated deconjugated ketones **2d**[4] and **6d** are obtained. This result can be explained by a diminished rate of alkylation in the presence of HOtBu[16] while proton transfer from the kinetic enolate to the thermodynamic enolate is favoured.

Although the alkyl group is introduced at C-2 in metadiaxial position with respect to the 10β-hydrogen, the presence of a more bulky group such as the 19-Me does not hinder the kinetic alkylation. This is shown by the experiment carried out with testosterone tetrahydropyranyl ether, **3c**. In this case, the reverse method, just described (exp. 2, Chart 2) affords good yields of the 2,2-dimethyl testosterone **5c** (88% from **1c**). In this series, further work is now in progress and will be published later.

This new method may be applied to other conjugated ketones such as the optically active tricyclic derivative **7a**[11] which, with an excess of base and methyl iodide, gives rise to the dimethylated ketone **9c**. Under the usual conditions, with toluene as solvent and NaOtAm as base, the deconjugated ketone **8b** is the only product from the benzoate **7b**.[12]

The dienic and trienic ketones **10** and **14** give similar results. Under enolate trapping conditions, the dimethylated conjugated ketone **13** can be obtained from the ether **10b**, corresponding to the dienone **10a**[13] *via* the trienic enolate **F**. On the contrary, when the dienic ketone **10a** is enolised with KOtBu in hot HOtBu (before the addition of methyl iodide) the ketone **12** is produced through the intermediacy of the thermodynamic enolate **E**. The same derivative can also be obtained from the deconjugated ketone **11**[14] which results from the acidification of the corresponding enolate by acetic acid.

The trienic ketone **14**[15] represents a special case because enolisation should have been more favorable towards C-2 than towards C-6, since this gives a more conjugated enolate. From this point of view, one would not have expected to find a difference in methylation with respect to the method employed. However, treatment of the ester **14b** in the usual conditions leads only to degradation products. In this case, the reverse method of methylation at low temperature is advantageous and gives the 2,2-dimethylated compound **15**.‡

In conclusion, it has been shown that the simple modification of the calssical procedure of methylation allows mono or dialkylation in α' position of cyclic α,β-unsaturated ketones. Trapping of the less stable enolate was possible because of the great difference between the rate of methylation and the rate of isomerisation of the kinetic enolate when the reaction is carried out in THF at very low temperature.

*Ref 1*d* p 586.

†At −70°, the rate of reaction is very slow.

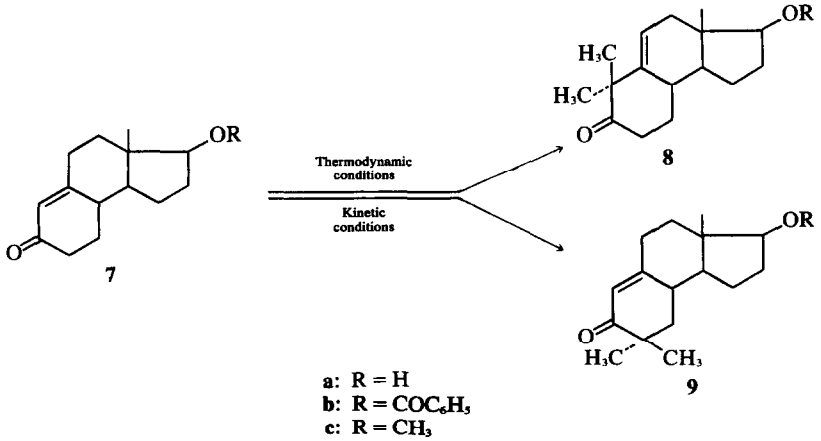
‡This product, of pharmaceutical interest, has already been described by two of us (L. N. and J. C. G.) and R. Bardoneschi.[6]

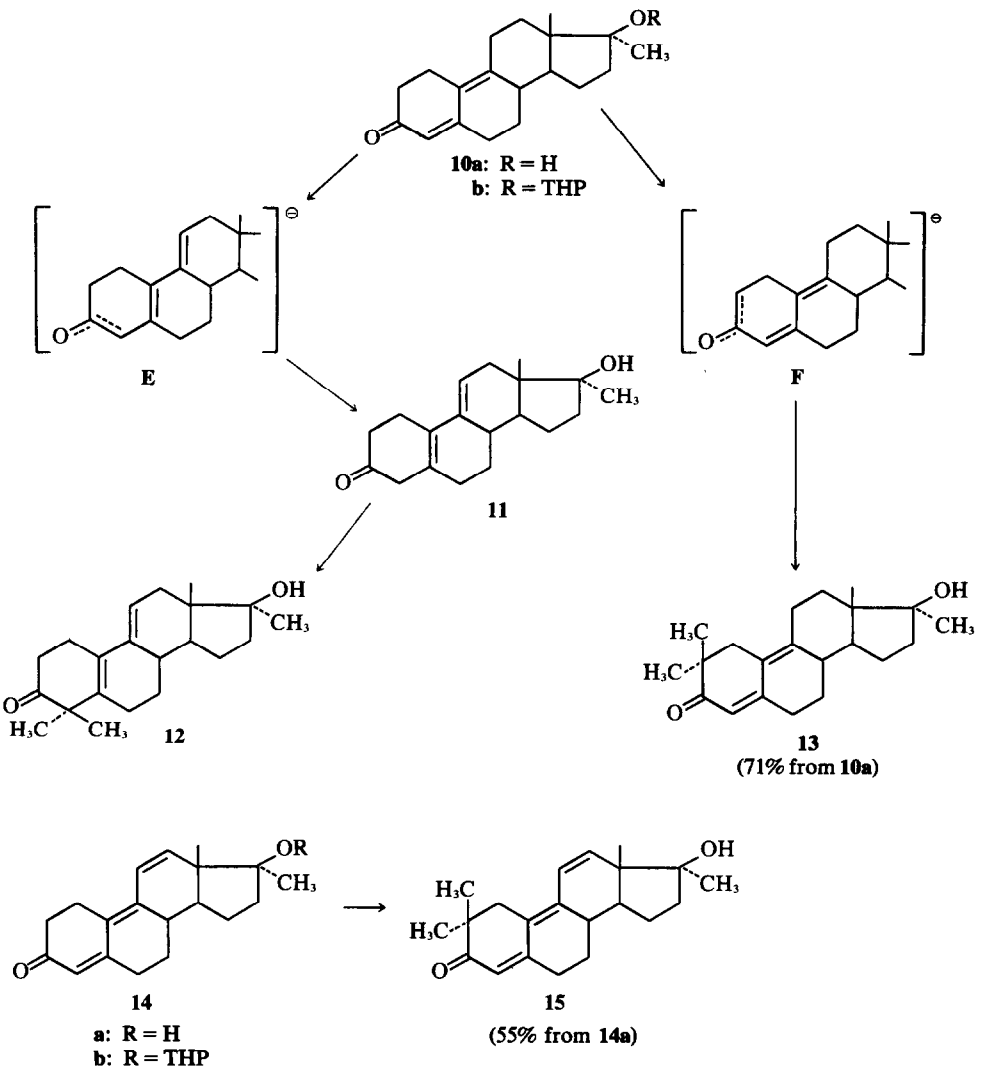
‡M.ps were determined on a Kofler block. IR spectra were determined in $CHCl_3$ and UV spectra in EtOH solution. NMR spectra were recorded on a Varian 60 A spectrometer in $CDCl_3$ containing tetramethyl silane as an internal standard. Dichroism circular curves were recorded on a "Dichrographe Roussel-Jouan". Specific rotations were measured at room temperature.

EXPERIMENTAL§

General procedure of methylation

Trapping method. To a 0·8, 0·9 molar soln of α,β-unsaturated ketone in anhyd THF was added MeI in the





molar ratio ICH_3/ketone ~ 14. After cooling to −65°, −70°, a 20% t-BuOK* soln in THF (2 moles or more) was added slowly while the low temp was maintained. After the reaction was complete, according to tlc, (0·5 hr or more), the mixture was diluted with water and extracted with ether or methylene chloride. After subsequent treatment (drying and removal of the solvent and eventual hydrolysis of tetrahydropyranyl ether) the residue was crystallized or chromatographed on silicagel.†

Methylation of 17α - *methyl* - 17 - *tetrahydropyranyloxy*-*estr* - 4 - *en* 3 - *one* **3d** (Chart 2)

The tetrahydropyranyl ether **3d** was prepared from 17α-methyl 17 - hydroxy - estr 4 - en 3 - one.[18] Compound **1d** (3 g) in ethyl ether (150 ml) dihydropyran (3·3 ml) and *p*-toluenesulfonic acid (70 mg) were stirred for 20 hr at room temp. The crude product was chromatographed on silicagel (yield 80%). The resulting oily material was homogeneous in TLC, ν_{max} 1 640 cm^{-1} (C=O), 1 605 cm^{-1} (C=C).

Exp. 1. To a soln cooled to −60°/70°, **3d** (1·17 g; 3·14 mmoles) in THF (4 ml) was added a soln of *t*-BuOK (1·995 g, 18 mmoles) in THF (10 ml(1). At −65°, a mixture of MeI (0·5 ml, 80 mmoles) and THF (0·5 ml) was added dropwise during 5 min. After stirring for 30 min, the mixture was treated as usual. The crude product was chromatographed on silicagel. Elution with benzene-EtOAc gave 2,2,17α - *trimethyl* - 17 - *hydroxyester* 4 *en* 3 - *one* **5d**, (0·55 g; yield 55%) m.p. 144° − 155° which was crystallized from hexane-ethylether, m.p. 159°, $[\alpha]_D + 21°$ in $CHCl_3$ [lit.[7] m.p. 150° − 153°, $[\alpha]_D + 34°$ in $CHCl_3$], λ_{max} 239 − 240 nm (ε 15,300) ν_{max} about 1 665 cm^{-1} broad (C=O) and 1 605 cm^{-1} (C=C), NMR: 0·92 ppm (18-H), 1·04 and 1·08 ppm (2-CH_3), 1·21 ppm (17-CH_3) and 5·72 ppm (4-H). CD in EtOH, $\Delta\epsilon = -2·05$ at 322 nm, + 1·3 at 240 nm, + 9·8 at 210 nm. (Found: C, 79·9; H, 10·5; $C_{21}H_{32}O_2$ requires: C, 79·70; H, 10·19%).

*Supplier: Dynamit-Nobel

†Supplier: E. Merck, A. G. Darmstadt grade H.

Exp. 2. To a soln of **3d** (1·15 g; 3·09 mmoles) in THF (3·5 ml and MeI (2·7 ml; 43·4 mmoles) cooled to −65°/−70°, a soln of *t*-BuOK (2 g; 17·8 mmoles) in THF (11 ml) was added dropwise (~ 1 hr). After isolation and hydrolysis of the THP ether in aqueous ACOH at 70°, the crude product was chromatographed on silicagel. Elution with benzene-EtOAc (7:3) afforded 2,2,4,4, 17α - *pentamethyl* - 17 - *hydroxyestr* - 5 - *en* 3 - *one*, **6d**, (70 mg, 6·6%) m.p. 135°−140°, which was crystallized from hexane m.p. 140−142°, ν_{max} ~ 1696 cm^{-1} (C=O), NMR: 0·92 ppm (18-H), 1·07 and 1·12 ppm (2-CH_3), 1·20 and 1·24 ppm (4-CH_3), 1·24 ppm (17-CH_3) and 5·61 ppm (6-H).

Further elution with the same solvent gave **5d** (645 mg; yield 66%) m.p. 145°−159° and 2β, 17α - *dimethyl* - 17 - *hydroxyestr* - 4 - *en* 3 - *one*, **4d**, (30 mg, 3·2%) m.p. 140° $[\alpha]_D$: −55° in $CHCl_3$ [lit.[7] m.p. 138°−140°, $[\alpha]_D = -72°$ in $CHCl_3$], λ_{max} = 241 nm (ε = 14,800), ν_{max} broad about 1662 cm^{-1} (C=O) 1632 and 1622 cm^{-1} (C=C); NMR: 0·94 ppm (18-H), 1·10 ppm, J ≃ 7 hz (2-CH_3), 1·22 ppm (17-CH_3) and 5·73 ppm (4-H), in C_6D_6: 1·08 ppm, J ≃ 7 hz (2-CH_3); CD in EtOH, Δε = −0·94 at 322 nm, −5·3 at 243 nm and +5·4 at 210 nm (Found: C, 79·5; H, 10·0; $C_{20}H_{30}O_2$ requires: C, 79·42; H, 10·00%).

Exp. 3, *Chart* 2. To a soln of **3d** (1·11 g; 2·99 mmoles) in THF (3·5 ml) and MeI (2·7 ml; 43·4 mmoles) cooled to −65°/−70°, a soln of *t*-BuOK (0·628 g, 5·6 mmoles) in THF (3·25 ml) was added dropwise for 30 min. The crude product isolated in the usual way was chromatographed on silicagel. Elution with benzene-EtOAc (7:3) afforded **4d** 0·61 g, 67·5%) m.p. 139°.

Exp. 4. To a soln of **3d** (1·19 g; 3·2 mmoles) in THF (3 ml), HMPT (0·5 ml) and MeI (2·7 ml; 43·4 mmoles) cooled to −65°, was added dropwise for 40 min, *t*-BuOK (0·684 g, 6·1 mmoles) in THF (2·75 ml) and HMPT (0·5 ml). Then, the mixture was stirred for 1 hr 30 min at −65°. After usual treatment the crude product was chromatographed on silicagel. Elution with benzene-EtOAc (7:3) gave **5d** (47 mg 4·6%) and **4d** (0·684 g, 71%) m.p. 139°.

Exp. 5. To a cooled mixture (−50°) of **3d** (1·2 g; 3·32 mmoles) in THF (5 ml), *t*-BuOH (4 ml) and MeI (3 ml), a soln of *t*-BuOK was added during 50 mins. (1·9 g 17 mmoles) in *t*-BuOH (6 ml) and THF (4 ml). According to TLC the reaction did not progress at this temp. In 1 hr, the temp was raised to −45° and the reaction slowly started. In the following hours, the temp was allowed to reach −30°, then the methylation was clearly progressing. The mixture was treated as usual after stirring for 5 hr 30 min. The crude product was chromatographed on silicagel. Elution with benzene-EtOAc (7:3) gave a first fraction of surmethylated product **6d** (0·17 g) in admixture with the corresponding C2 monomethylated C4 dimethylated product. Further elution afforded 4,4, 17α-*trimethyl*-17-*hydroxyestr* - 5 - *en* 3 - *one*, **2d**, (0·33 g, 32·5%) m.p. 158°−160°, $[\alpha]_D$ = −10° in $CHCl_3$ [lit.[4] m.p. 160°−162° needles and 168°−170° rhom. $[\alpha]_D$ = −15° in $CHCl_3$]. ν_{max} = 1711 cm^{-1} (C=O); NMR: 0·92 ppm (18-H), 1·22 ppm (two-CH_3) and 1·27 ppm (one-CH_3) (methyls in C4 and C17).

The following fraction was a monomethylated product (yield 5%).

In addition, 19·5% of the starting ketone **4d** were recovered.

17β - *Tetrahydropyranyloxyandrost* - 4 - *en* 3 - *one*, **3c**

A soln of **1c** (2 g; 6·95 mmoles) in ethylether (100 ml), dihydropyran (2·2 ml) and *p*-toluenesulfonic acid (50 ml) was stirred for 15 hr at room temp. The mixture was poured into $NaHCO_3$ aq., and extracted with ethylether. The resulting crude oil (**3c**; 2·82 g) did not exhibit hydroxylic IR absorption.

2,2 - *Dimethyl* - 17β - *hydroxyandrost* - 4 - *en* 3 - *one*, **5c**

To a cooled soln (−65°) of **3c** (1·4 g; 3·45 mmoles) in THF (3·9 ml) and MeI (3 ml), a soln of *t*-BuOK (2·3 g; 20·5 mmoles) in THF (11 ml) was added during 1 hr. After isolation in the usual way, the crude product was chromatographed on silicagel. Elution with benzene-EtOAc (8:2) afforded **5c** (0·96 g, 88%), m.p. 190° (Kofler), $[\alpha]_D$ = +49° in EtOH, λ_{max} (EtOH) = 241 nm (ε = 15,650), ν_{max} ($CHCl_3$) broad about 1 661 cm^{-1} (C=O), 1 627 cm^{-1} (C=C); NMR ($CDCl_3$): 0·81 ppm (18-H) 1·12, 1·19 and 1·3 ppm (19-H and 2-CH_3), 5·73 ppm (4-H). (Found: C, 79·7; H, 10·4; $C_{21}H_{32}O_2$ requires: C, 79·70; H, 10·19%).

(3*S*, 3a*S*, 9a*S*, 9b*S*) 3-*Methoxy* - 3a, 8, 8 - *trimethyl* - 1, 2, 3, 3a, 4, 5, 8, 9, 9a, 9b - *decahydro* [7*H*] *benz* [*e*] *inden* - 7-*one*, **9c**.

To a soln of **7a** (1 g; 4·55 mmoles) in THF (60 ml) and MeI (5 ml) cooled at −70°, was added in 1 hr, *t*-BuOK (5·3 g; 47·3 mmoles) in THF (20 ml). The mixture was stirred for an another hr, and poured into water. The crude product was chromatographed on silicagel. Elution with benzene-EtOAc (7:3) gave (0·37 g; yield 28% an oily product) identified as (3*S*, 3a*S*, 9a*S*, 9b*S*) 3 - *methoxy* - 3a, 6, 6, 8, 8 - *pentamethyl* - 1, 2, 3, 3a, 4, 6, 9, 9a, 9b - *decahydro* [7*H*] *benz* [*e*] *inden* - 7 - *one*, ν_{max} = 1703 cm^{-1} (C=O), NMR: 0·77 ppm (3a-CH_3), 1·08 ppm, 1·14, 1·22 and 1·27 ppm (four methyls in C6 and C8), 3·38 ppm (3-OCH_3) and 5·55 ppm (5-H). Further elution afforded 0·613 g of compound **9c** (51·5%), m.p. 63°, λ_{max} = 239 nm (ε = 14900), ν_{max} = 1662 cm^{-1} (C=O), 1 626 cm^{-1} (C=C), NMR: 0·93 ppm (3a-CH_3), 1·07 ppm (8-CH_3), 3·35 ppm (3-OCH_3) and 5·75 ppm (6-H). (Found: C, 77·5; H, 10·0; $C_{17}H_{26}O_2$ requires: C, 77·82; H, 9·99%).

(3*S*, 3a*S*, 9a*S*, 9*S*) 3 - *Benzoyloxy* - 3a, 6, 6 - *trimethyl* - 1, 2, 3, 3a, 4, 6, 8, 9, 9a, 9b - *decahydro* [7*H*] *benz* [*e*] *inden* - 7 - *one*, **8b**.

To a soln of **7b** (25 g, 77 mmoles) in toluene (713 ml) heated at 100°, was added a soln of 1·46 N NaOtAm (111·5 ml) in toluene (0·163 mmole). The mixture was kept at this temp for 10 min, then MeI (38·5 ml; 0·6 mole) was added; 10 min later, MeI (28·5 ml; 0·445 mole) was added. After 15 min at 95°, the mixture was poured into water and isolated in the usual way. The crude **8b**, crystallized from isopropylic ether gave 15·75 g (58%) of ketone m.p. 124°−128°, λ_{max} = 229 nm (ε = 13,000), ν_{max} = 1709 cm^{-1} (C=O), NMR: 0·96 ppm (3a-CH_3), 1·29 and 1·32 ppm (6-CH_3) and 5·59 ppm (5-H).

17α - *Methyl* 17 - *tetrahydropyranyloxy* - *estr* - 4,9 - *dien* 3 - *one*, **10b**

The THP ether was prepared in usual way from **10a**[13] (5 g; 17·5 mmoles), ethyl ether (200 ml) and *p*-toluenesulfonic acid (0, 1 g). The crude **10b**, did not exhibit hydroxylic IR absorption.

Methylation of dienone **10b**

(a) *Under kinetic conditions.* The crude **10b**, was dissolved in THF (140 ml) and MeI (29 ml). To this soln cooled to −35°, a soln of *t*-BuOK (14 g; 0·1 mole) in THF (140 ml) and HMPT (35 ml) was added during 1 hr

30 min. Then, this mixture was stirred for 1 hr. After the usual treatment, the crude product was crystallized from isopropylic ether, and **13** (3·92 g, 71%) was obtained, m.p. 138°, $[\alpha]_D = -291°$ in EtOH, $\lambda_{max} = 303$ nm ($\epsilon = 20{,}900$), $\nu_{max} = 1661 - 1644\ cm^{-1}$ (C = O), $\sim 1605\ cm^{-1}$ (C=C); NMR: 1·03 ppm (18-H), 1·08 and 1·12 ppm (2-CH_3), 1·22 ppm (17-CH_3), 5·58 ppm (4-H) (Found: C, 80·4; H, 9·4; $C_{21}H_{30}O_2$ requires: C, 80·21; H, 9·62%).

(b) *Under thermodynamic conditions.* A soln of **10a** (2·86 g; 10 mmoles) in 0·95 M *t*-BuOK in *t*-BuOH (22 ml, 21 mmoles) was refluxed for 5 min. Then, under reflux, a molar soln of MeI in *t*-BuOH (25 ml) was added in 30 min. The mixture was acidified with 2 N HCl (1 ml) poured into water and extracted with methylene chloride. The crude product was chromatographed on silicagel. Elution with benzene-EtOAc gave **12** (1·86 g; 60%) m.p. 172°, $[\alpha]_D = +93·5°$ in $CHCl_3$, $\lambda_{max} = 240$ nm, (ϵ 20,000) $\nu_{max} = 1710\ cm^{-1}$ (C=O), NMR: 0·87 ppm (18-H), 1·18 ppm (one CH_3) and 1·22 ppm (two-CH_3) (three methyls at C_4 and C_{17}) and 5·69 ppm (4-H). (Found: C 79·9; H 9·7; $C_{21}H_{30}O_2$ requires: C 80·21; H 9·61).

17α - *Methyl* - 17 - *tetrahydropyranyloxyestr* - 4, 9, 11 - *trien* - 3 - *one*, **14b**

A soln of **14a** (2 g; 7·05 mmoles) in ethylether (100 ml), dihydropyran (2·2 ml) and *p*-toluenesulfonic acid (50 ml) was stirred for 17 hr at room temp. The crude **14b**, was isolated in usual way and did not exhibit hydroxylic IR absorption.

2, 2, 17α - *Trimethyl* - 17 - *hydroxyestr* - 4, 9, 11 - *trien* 3 - *one*, **15**

The crude **14b**, was dissolved in THF (8 ml) and MeI (6·15 ml; ~ 0·1 mole). To this soln cooled to − 65°, a soln of *t*-BuOK (3·1 g; 27·6 mmoles) in THF (15 ml) was added in 30 min. After isolation in the usual way, the crude product was chromatographed on magnesium silicate (Florisil).* Elution with methylene chloride gave crude **15**, (2·1 g) which on crystallisation from isopropyl ether furnished **15** (1·2 g; 55%), m.p. 137°. An analytical sample was obtained after recrystallization from EtOAc or isopropylic ether, m.p. 139°, $[\alpha]_D = -54°$ in EtOH, ν_{max} between $1657\ cm^{-1}$ and $1640\ cm^{-1}$ (C=O), $\sim 1578\ cm^{-1}$ (C=C), $\lambda_{max} = 342$ nm ($\epsilon = 30{,}100$), NMR: 1·02 ppm (18-H), 1·08 and 1·12 ppm (2-CH_3), 1·26 ppm (17-CH_3), 5·69 ppm (4-H) 6·33 and 6·52 ppm (two coupled olefinic protons at C_{11} and C_{12} with J = 10 hz). (Found: C, 80·6; H, 9·0; $C_{21}H_{28}O_2$ requires: C, 80·73; H, 9·03).

*Supplier: Floridin Corp.

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