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Linear Steroid Analogues. III.[1] Formation of Abeo-steroids from 3β,20β-Diacetoxy-8,9-seco-5α-pregnane-8,9,11-trione[2]

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A small amount of 3β,20β-diacetoxy-9(8→7)-abeo-5α-pregn-7(9)-ene-8,11-dione (**4**), a compound with a 6-5-7-5 ring system, was formed in the alumina catalyzed cyclization of 3β,20β-diacetoxy-8,9-seco-5α-pregnane-8,9,11-trione (**1**). As it was not at first possible to isolate **4** in a pure state, the structure was deduced from a derivative, the saturated ketone (**10**), the structure of which was confirmed by its synthesis from the known glycol monomesylate (**9b**) with a 6-6-6-5 ring system by means of the pinacolic type rearrangement. Later, the compounds (**4a, b**) were obtained by cyclization of **1** with silica gel followed by alumina treatment and all the features of the reaction were clarified. The stereochemistry of the ketone (**10**) and its derivatives was also discussed.

The preceding paper[2] described the alumina catalyzed condensation of 3β,20β-diacetoxy-8,9-seco-5α-pregnane-8,9,11-trione (**1**). In this reaction, the main product was the diketo-ol(**2**) (90% yield) containing the 6-6-6-5 ring system, and in addition, a small amount of dehydrated by-products (**3a, b** and **4a, b**) (*ca.* 10%) were obtained as a mixture. Two of these by-products (**3a, b**) had previously been obtained from dehydration of the main product (**2**) and characterized as the 14α- and 14β-enediones respectively.[2] On the basis of the mode of cyclization, the remaining components (**4a, b**) were also expected to have enedione structures with a 6-5-7-5 ring system, though at that time this could not be substantiated because of their low yield and difficulty in their isolation. By modification of the compounds however, it has been possible to elucidate their structures and the further work has finally led to the isolation of the compounds in question.

The mixture of dehydrated by-products (**3a, b** and **4a, b**) formed in the reaction of **1** with alumina, was treated with benzyl mercaptan in the presence of *p*-toluenesulfonic acid to afford two products (**5** and **6**). Either of enediones (**3a** or **3b**), on the same treatment gave the identical product (**5**). The structures of **5** and **6** given in Chart 1 are assigned from a consideration of the spectroscopic data of the compounds and in the context of their subsequent reactions. The ultraviolet (UV) spectrum of **5** shows an absorption maximum at 325 mμ (ε 7040) ascribed to an enedione monoenol benzyl thioether and the nuclear magnetic resonance (NMR) spectrum exhibits no olefinic peak around τ 2.0—5.0, only five proton signals due to the phenyl ring. Treatment of **5** with Raney nickel in ethanol led to a mixture of the previously described C_{14}-epimeric enones (**7a, b**). It is interesting to note that a reverse proportion of the product mixture was obtained depending upon the conditions employed, though the reason for this is not obvious,[4] thus, under desulfurization conditions (boiling with Raney nickel in ethanol), the ratio of **7a** to **7b** is 1.7:1 and under hydrogenation conditions (shaking

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1) Part II: S. Aoyama and K. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **18**, 1310 (1970).

2) Part I: S. Aoyama and K. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **18**, 481 (1970).

3) Location: *Fukushima-ku, Osaka.*

4) In hydrogenations of 5,6,7,8-tetrahydro-8-methyl-indan-5-one series, a *cis* fused product almost always predominates over a *trans* fused one except in the case where the compound carries a substituent at the 4 position when a predominant *trans* fused product is obtained (G. Nominé, G. Amiard, and V. Torelli, *Bull. Soc. Chim. France*, **1968**, 3664). In our case, under desulfurization conditions, it might be that the rupture of the C-S bond at 8 position is preceded by a reduction of C_8—C_{14} double bond leading to a similar situation to that of Nominé's giving predominantly the *trans* fused product.

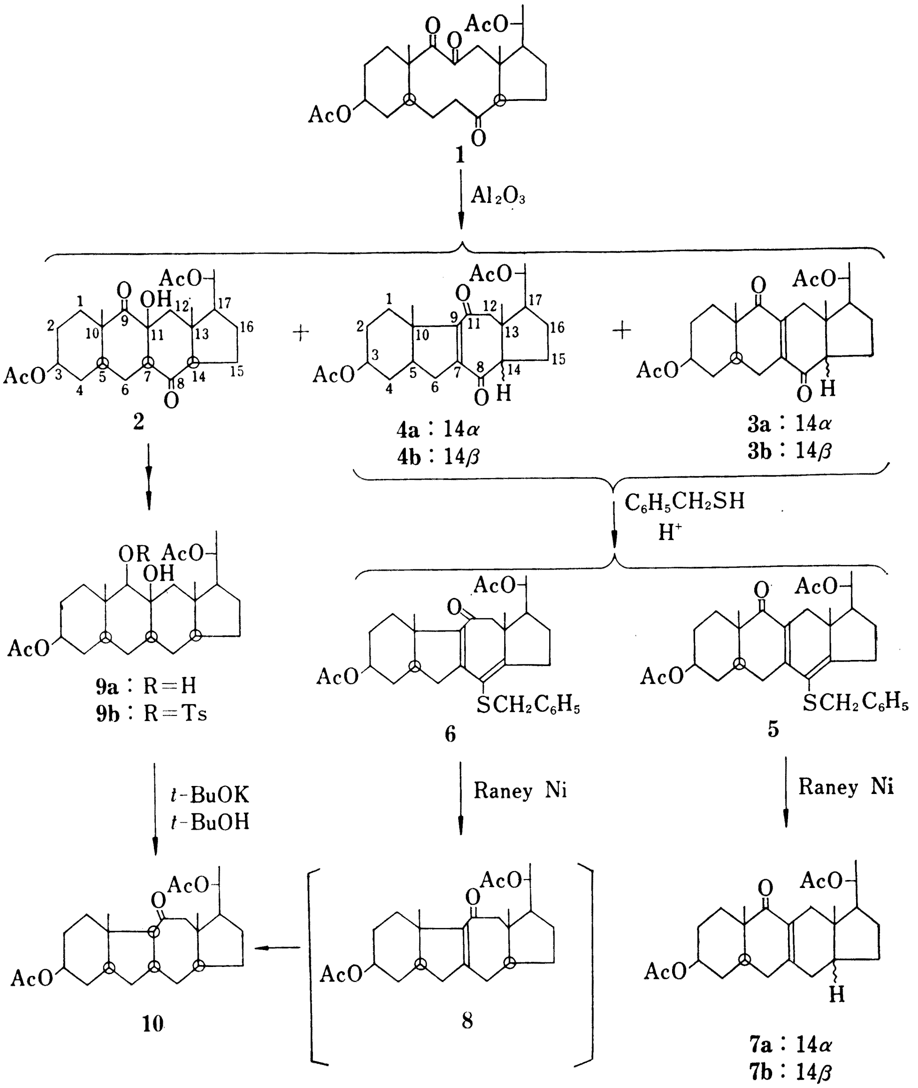


Chart 1

with the catalyst in hydrogen atmosphere at room temperature) it is 1:6.2. The compound (**6**) shows very similar physical properties to those of **5**. It gave the same elemental composition; $C_{33}H_{40}O_5S$ and has an absorption maximum at 317 mμ (ε 5480) in its UV spectrum, due to an enedione monoenol benzyl thioether. The only difference clearly observed is the appearance in its NMR spectrum of AB pattern proton signals in a pair of doublets in the active methylene region. This observation is explicable in terms of the existence of methylene protons adjacent to a carbonyl group, a situation of which is well met by the 11-oxo structure with a 6-5-7-5 ring system. Treatment of compound (**6**) with Raney nickel under either desulfurization or hydrogenation conditions afforded predominantly a saturated ketone (**10**) ($\nu_{C=O}$ 1696 cm^{-1}), accompanied by a small amount of an enone (**8**). The NMR spectrum of the ketone (**10**) also exhibits an AB type quartet and we proposed 3β,20β-diacetoxy-9(8→7)-abeo-5α-pregnan-11-one for the structure. This ketone is thought to have a BC α-*cis* configuration because it is formed under hydrogenation conditions and reagent attack from the

β-side will be hindered by both angular methyl groups. Final and decisive proof for the structure and its stereochemistry was afforded by the fact that the ketone (**10**) could be obtained from the glycol mesylate (**9b**) with potassium *tert*-butoxide in *tert*-butanol. The stereochemistry of the glycol (**9a**) has already been established in the previous paper.[1] It is well known that, in general, the pinacolic type rearrangement[5,6] of a glycol monosulfonate proceeds with retention of configuration at the migration terminus giving a stereospecifically rearranged ketone. In the compound (**9b**), the MsO-C_9 and C_7–C_{11} bonds maintain a *trans*-coplanar relationship and the migration of this C_7–C_{11} bond to the 9 position occurs in a concerted manner to give the ketone (**10**) as depicted in Fig. 1. The 14α-configuration is kept through the rearrangement. This BC α-*cis* configuration should be a stable one since the ketone did not give any isomers on equilibration in methanolic potassium hydroxide.

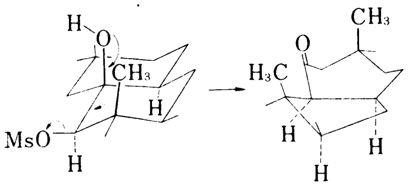
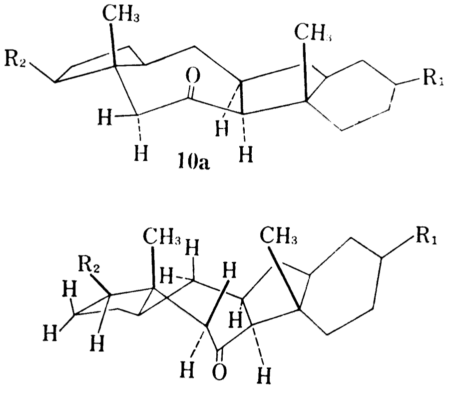


Fig. 1



10a

10b

Fig. 2

A molecular model shows that the ketone (**10**) could have two possible conformers, **10a** and **10b** (see Fig. 2). In the conformer (**10b**), the 19-methyl group comes extremely close to either the 18-methyl group or the 9-hydrogen, giving rise to severe steric congestion. On the other hand, in the conformer (**10a**), the carbonyl group comes between the 18- and 19-methyl groups giving rise to a flat molecule in which no serious non-bonded interaction is expected. Thus, **10a** is thought to be by far the more stable conformer, an assumption supported by the circular dichroism (CD) curves showing a positive Cotton effect ($[\theta]^{295}_{\text{max}}+4500$), a reasonable value for the conformer (**10a**). Conversely, the conformer (**10b**) would show a negative Cotton effect and it can therefore be ruled out.

This ketone shows resistance to reduction with sodium borohydride and to hydrogenation with rhodium–platinum oxide in acetic acid but it is reduced with lithium aluminium hydride to two triols **14a** (70%) and **15a** (30%), a product distribution which was less marked than that obtained by reduction with lithium aluminium deuteride (**14a**:**15a**=6:1). As the mixture of **14a** and **15a** gave the triketone (**16**) in high yield on treatment with Jones reagent, these compounds are thought to be epimeric at C_{11}. Acetylation of these triols (**14a** and **15a**) afforded corresponding triacetates (**14b** and **15b**). The configurations of the **11** substituents (OH and OAc) for these compounds were confirmed by the NMR spectra of the acetates (**14b** and **15b**), the interpretation of which is well understood provided the molecules have the same conformation as **10a**. In the triacetate (**14b**), C_{11}-proton gives a doublet at τ 4.73 (J=7.0 Hz), each line of which is broadened with $W^h/_2 \approx 5$ Hz and a signal ascribed to 12β-proton gives four lines

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5) R.J.W. Cremlyn, D.L. Grarmaise, and C.W. Soppee, *J. Chem. Soc.*, **1953**, 1847.
6) Y. Mazur and M. Nussim, *J. Am. Chem. Soc.*, **83**, 3911 (1961).

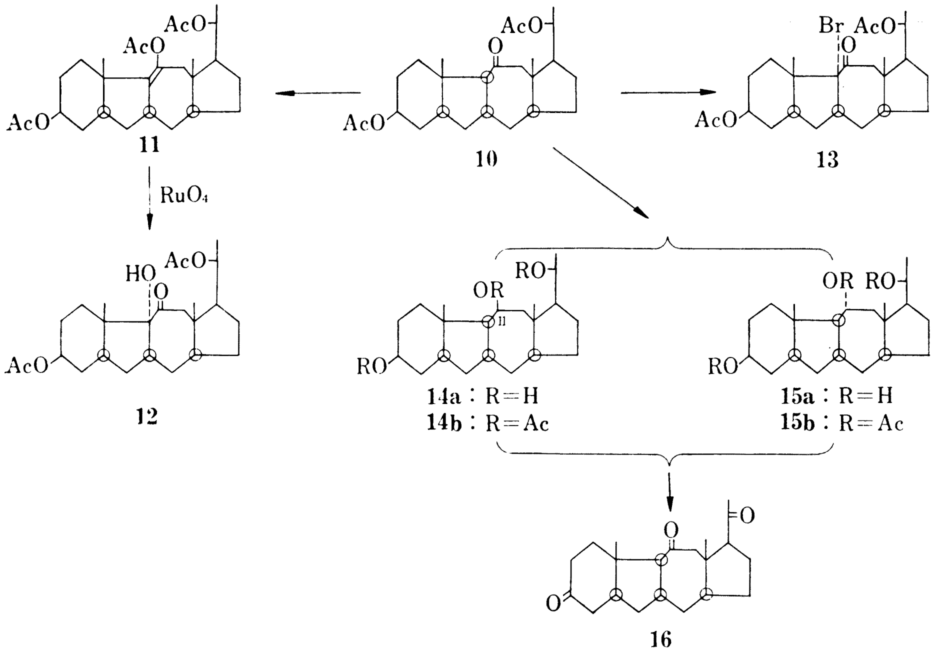

Chart 2

at τ 7.60, 7.48, 7.35, and 7.23 (J_{vic}=7.0 Hz, $|J_{gem}|$=15.0 Hz), which in the deuteriated compound (**14b**, C_{11}-D), appears as a doublet at τ 7.42 ($|J_{gem}|$=15.0 Hz), indicating that the 11-proton is α-equatorial. Alternatively in the triacetate (**15b**), the 11-proton gives a triplet at τ 4.87 (J=11.0 Hz), each line of which further splits with 1.5 Hz and a signal due to 12β-proton apears as a doublet at τ 7.79 (J=14.0 Hz), each line of which also splits with 1.5 Hz. In the deuteriated compound (**15b**, C_{11}-D) this small splitting (1.5 Hz) disappears. Thus, the 11-proton of the triacetate (**15b**) was assigned as β-axial. A model shows that the dihedral angle between C_{11}-proton and $C_{12\beta}$-proton is about 30° for **14b** and 90° for **15b**. This is in good agreement with the observed coupling constants.

Enol acetylation of **10** with isopropenyl acetate gave an enol acetate (**11**) ($\nu_{C=O}$ 1750 cm^{-1}). The appearance of the 12-methylene protons at τ 7.57 as a singlet and the lack of signal due to a vinyl proton in the NMR spectrum of **11** proved the location of the double bond at C_9–C_{11}. Treatment of this enol acetate (**11**) with RuO_4 afforded the ketol (**12**). Bromination of **10** with **1** equimolar amount of phenyl trimethyl ammonium perbromide gave the monobromoketone (**13**). In the NMR spectra of both compound (**12**) and (**13**), AB type proton signals due to the 12-methylene came out clearer than those in **10** and no signals ascribable to protons on the carbon bearing hydroxyl or bromine were found. This observation confirms the position of the hydroxyl and the bromine at C-9. And further, the α configurations for these substituents could reasonably be assigned from the physical data shown in Table I. In this series of compounds listed in the Table, the effects of the α-substituents on the carbonyl group are typical of the axial property.

Later in the course of our studies on this series, we found that the cyclodecatrione (**1**), on cyclization with silica gel instead of alumina afforded an unexpectedly high proportion of a new diketo-ol (**17**) (40%) as well as the known diketo-ol (**2**) (60%). The structure of the compound (**17**) was confirmed by its NMR spectrum showing the 12-methylene proton signals in four AB lines and by chemical conversion into **6** *via* the enedione (**4a**). Treatment of **17** with thionyl chloride in pyridine gave, as a major product, the enedione (**4a**) (55%) as well as

Table I

Compd.	IR $\nu_{C=O}^{CCl_4}$	UV λ_{max}^{MeOH} mμ (ε)	CD (MeOH) [θ](mμ)
10	1696	294 (35)	+4498 (295)
13	1700	306 (32)	+9104 (310)
14	1697	314 (106)	+18445 (320)

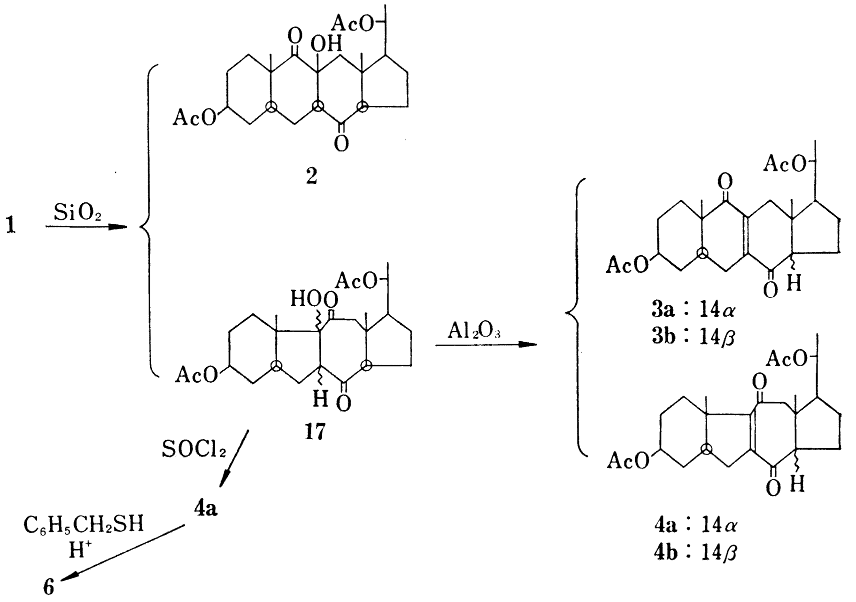

Chart 3

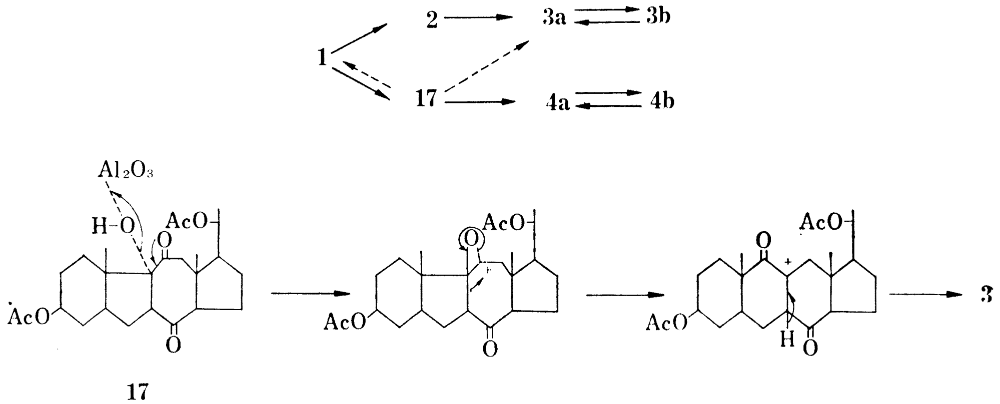

Chart 4

two minor products.[7] This enedione, showing an absorption maximum at 262.5 mμ (ε 18000) in the UV spectrum, was treated with benzyl mercaptan in a manner similar to that described before and furnished **6**, identical with that obtained above. Unexpectedly, treatment of **17** with alumina in benzene afforded a considerable amount of the enediones (**3a** and **b**, *ca.* 50%)

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[7] The structures of these minor products will be elucidated elsewhere.

as well as the expected enediones (**4a** and **b**, *ca.* 50%) all as a mixture. These enediones were very difficult to separate into each component since they behave similarly on thin-layer chromatography (TLC), on recrystallization and on column chromatography, however, by means of an elaborated TLC technique (5—8 times repetition of the development), two enediones (**3a**) and (**4a**) among the four isomers could be separated in pure state, the other two (**3b** and **4b**) still remaining inseparable. The proportion of the inseparable mixture was estimated as **3b**/**4b**=1/2 from the NMR and infrared (IR) spectra. This fact suggests that while half of the starting diketo-ol (**17**) on the alumina treatment gives the normal dehydration products (**4a**) and (**4b**), the other half gives the enediones with a 6-6-6-5 ring system (**3a**) and (**3b**) either through the reopening of C_7-C_9 bond according to the reverse aldol type or by direct dehydration accompanied by rearrangement. The direct path (see Chart 4) is thought to be more likely because the diketo-ol (**17**) is dehydrated more than twenty times faster than the diketo-ol (**2**). This means that if the reaction took the reverse aldol path, a certain amount of the diketo-ol (**2**) should survive in the work-up, whereas in the actual case not even a trace of the spot corresponding to the diketo-ol (**2**) could be detected on its TLC. The observed difference of the properties between alumina and silica gel in the cyclization of **1** will be the subject of future studies.

Experimental

General Methods——All melting points were determined on Yanagimoto Micromelting apparatus and are uncorrected. Optical rotations were measured in 1% EtOH–$CHCl_3$ with a Perkin Elmer Polarimeter type 141 (c=1.0—0.3, l=1 cm). Unless otherwise stated, UV spectra were recorded in 95% EtOH with a Hitachi EPE-2 spectrophotometer and IR spectra in CCl_4 by a Koken DS-201B spectrophotometer and partly by a Hitachi grating IR spectrophotometer Model EPI-G3. CD and ORD were taken with Jasco Model ORD/UV-5 equipped with CD. NMR spectra were taken in $CDCl_3$ solution with a Varian A-60 spectrometer, TMS as internal standard. Chemical shifts are reported in τ value and apparent coupling constants and bandwidths at half heights were obtained from the lst order analysis in Hz. For preparative and analytical TLC, Silica gel G or GF (E. Merck Co.) was used as adsorbent.

Enedione Monoenol Benzyl Thioether (5) and (6) from a Mixture of Dehydration Product——A mixture of the dehydration products was obtained in the mother liquor from the crystallization of **2** in the Al_2O_3 catalyzed cyclization of **1** in benzene. This mixture (860 mg), benzyl mercaptan (2.2 ml) and *p*-TsOH (110 mg) were dissolved in benzene (22 ml) and the solution was refluxed for 18 hr in a flask equipped with a water separator. The reaction mixture was then poured into ice–water. The product was extracted with ether and the ethereal solution washed several times with 10% aq. NaOH and with water. After evaporation of the dried extract, the residue, showing 2 spots on TLC, was separated by preparative TLC (*n*-hexane–AcOEt, 3:1). On crystallization from MeOH, the upper fraction (222 mg) afforded **5** (150 mg) mp 156—158°, $[\alpha]_D^{22}+2.7°$. IR ν_{max} cm^{-1}: 3030, 1735, 1656, 1560, 697. UV λ_{max} mμ (ε): 325 (7040). NMR τ: 9.33 (3H, s, 18-Me), 9.05 (3H, s, 19-Me), 8.80 (3H, d, J=6.0, 21-Me), 7.94 (OAc), 7.87 (OAc), 6.36, 6.46 (2H, AB type d of d, $|J|$=13.0, C_6H_5–$\underline{CH}_2$-S-), 5.53—4.91 (2H, m, $C_{3,20}$-H), 2.67—3.00 (Phenyl 5H). *Anal.* Calcd. for $C_{32}H_{40}O_5S$: C, 71.59; H, 7.52; S, 5.98. Found: C, 71.65; H, 7.64; S, 6.35.

The lower fraction (430 mg) was crystallized from MeOH to give **6** (325 mg) mp 171—173°. $[\alpha]_D^{22}-92.0°$. IR ν_{max} cm^{-1}: 3040, 1735, 1649, 695. UV λ_{max} mμ (ε): 317 (5480). NMR τ: 9.25 (3H, s, 18–Me), 8.98 (3H, s, 19–Me), 8.82 (3H, d, J=6.0, 21-Me), 7.95 (OAc), 7.90 (OAc), 7.73, 6.96 (2H, AB type d of d, $|J|$=15.0, C_{12}-H), 6.30, 6.17 (2H, AB type d of d, $|J|$=13.0, C_6H_5–$\underline{CH}_2$–S–), 5.37—4.91 (2H, m, $C_{3,20}$-H), 2.70 (5H, br, s, Phenyl-H). *Anal.* Calcd. for $C_{32}H_{40}O_5S$: C, 71.59; H, 7.52; S, 5.98. Found: C, 71.74; H, 7.41; S, 6.20.

Enedione Monoenol Benzyl Thioether (5) from Pure 3*β*, 20*β*-Diacetoxy-9(8→7), 8(9→11)-diabeo-5*α*, 14*α*-pregn-7(11)-ene-8,9-dione (3a)——A mixture of **3a** (60 mg), benzyl mercaptan (0.5 ml) and *p*-TsOH (10 mg) in benzene (12 ml) was treated in a manner similar to that described above. Work-up gave a product (73 mg) as a single component, which was recrystallized from MeOH to afford **5** mp 156—157.5°. This was shown to be identical with the product obtained above by mixed melting point and IR spectrum.

Enedione Monoenol Benzyl Thioether (5) from Pure 3*β*,20*β*-Diacetoxy-9(8→7), 8(9→11)-diabeo-5*α*, 14*β*-pregn-7(11)-ene-8,9-dione (3b)——Treatment of **3b** (60 mg) in the same way as above afforded a single product (**5**) (72 mg), which was recrystallized to give a sample with mp 156—157°. Identification was by mixed melting point and IR spectrum.

Reduction of 5 with Raney Nickel——a) Under Desulfurization Conditions: A mixture of **5** (90 mg) and Raney nickel (W-2, 4 ml) in EtOH (12 ml) was stirred under reflux for 30 min. The catalyst was filtered off and washed several times with MeOH. The combined filtrate was evaporated to dryness and the residue was taken up in ether. The ethereal solution was filtered free of undissolved material and the solvent was evaporated to afford a crude product (78 mg). This product showed one spot with the same *Rf* value as that of authentic **7a**[8] on TLC however, the IR spectrum of the product was slightly different from that of **7a**. Therefore, an aliquot of the crude product was subjected to NMR analysis which revealed that the product was a mixture of **7a** and **7b** in a ratio of 1.7:1. Careful recrystallization of the product from MeOH three times gave **7a** (15 mg) mp 152—155°, identical with authentic **7a** by mixed melting point and comparison of IR and NMR spectra.

b) Under Hydrogenation Conditions: Raney nickel (W-2, 4 ml) in abs. EtOH (6 ml) was shaken for 30 min in hydrogen gas. Into the suspension was added **5** (90 mg) in AcOEt (2 ml) and the mixture was hydrogenated at room temperature for 20 min under hydrogen, absorbing 3.3 ml of hydrogen. Usual work-up afforded a product (75 mg) showing one spot on TLC. The NMR analysis showed that the product was a mixture of **7a** and **7b** in a ratio of 1:6.2. Recrystallization of the product from MeOH gave **7b**, mp 145—149°, identical with authentic **7b** by mixed melting point and comparison of IR and NMR spectra.

Reduction of Enedione Monoenol Benzyl Thioether (6) with Raney Nickel——A mixture of **6** (180 mg) and Raney nickel (W-2, 1.7 ml) in abs. EtOH (10 ml) was stirred for 1 hr under reflux. The catalyst was removed by filtration and washed with MeOH. The combined filtrate was evaporated to dryness. The residue (132 mg) was taken up in ether and the ethereal solution was filtered free of undissolved material. After evaporation of the solvent, the product (128 mg) showed, on TLC, one spot which under UV light gave faint absorption. The IR spectrum of the crude product indicated contamination by a small amount of an enone (assumed to be **8** $\nu_{C=O}$ 1647, $\nu_{C=C}$ 1598) in addition to the main saturated ketone ($\nu_{C=O}$ 1696). This crude product was crystallized free from the contaminant enone to afford 3β,20β-diacetoxy-9(8→7αH)-abeo-5α,9α,14α-pregnan-11-one (**10**) (101 mg) double mp 150—160°, 167—170°, $[\alpha]_D^{25}+14.6°$. IR ν_{max} cm^{-1}: 1737, 1696, 1234, 1028. NMR τ: 9.42 (3H, s, 18–Me), 9.02 (3H, s, 19–Me), 8.85 (3H, d, $J=6.0$, 21–Me), 7.98 (OAc), 7.93 (OAc), 7.59, 7.16 (2H, AB type d of d, $|J|=10.5$, C_{12}–H), 5.50—5.00 (2H, m, $C_{3,20}$–H). CD ($c=0.384$, MeOH) $[\theta]$ (mμ): +4498 (245) (max). *Anal.* Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.94; H, 9.33.

Under Hydrogenation Conditions; a mixture of **6** (100 mg) and Raney nickel (W-2, 1 ml) in abs. EtOH (4 ml) was shaken for 30 min in a current of hydrogen at room temperature. Work-up gave the ketone (**10**) (75 mg) with double mp 150—158°, 165—167°, the homogeneity and the identity of which was supported by NMR and IR spectra.

Pinacolic Rearrangement of 3*β*,20*β*-Diacetoxy-9*β*,11*β*-dihydroxy-9(8→7*α*H),8(9→11)-diabeo-5*α*,14*α*-pregnane-9-monomesylate (9b)——A mixture of **9a** (1.0 g) and CH_3SO_2Cl (300 mg) in pyridine (10 ml) was stored for two days at room temperature, then taken up in CH_2Cl_2. The CH_2Cl_2 solution was washed with 10% HCl, 5% Na_2CO_3 and water. After evaporation of the solvent, the product (1.15 g) showed one spot on TLC and exhibited absorption bands at 3600, 3520, 1730, 1240, 1177, 1028, 912 cm^{-1} in its IR spectrum. The product, without further purification, was used for the following reaction.

A mixture of the above product (1.15 g) and potassium *t*-butoxide (800 mg) in *t*-butanol (50 ml) was stirred at reflux for 3 hr under N_2. The reaction mixture was poured into cold 15% HCl. The product was extracted with CH_2Cl_2 and the CH_2Cl_2 solution washed with 5% Na_2CO_3 and water and dried. Evaporation of the solvent gave foams which were acetylated with Ac_2O– pyridine affording an oily material (950 mg). Chromatography of the product over silica gel with ether–petr. ether (4:1) as an eluant afforded **10** as crystals (673 mg, 70% yield) double mp 149—160°, 165—170°. The IR and the NMR spectra of the compound were identical with those obtained above.

Equilibration of the Ketone (10)——A mixture of **10** (50 mg) and KOH (500 mg) in MeOH (10 ml) was refluxed for 1 hr under N_2, then worked up as usual. The product, after acetylation with Ac_2O–pyridine, was examined by NMR and IR spectra and found to be identical with the starting ketone (**10**). Recrystallization from MeOH gave crystals with double mp 145—155°, 164—168°.

Attempted Reduction of the Ketone (10)——a) With $NaBH_4$: Treatment of **10** (100 mg) with $NaBH_4$ (50 mg) under three different sets of conditions, i) 4 hr at 5°, ii) 2 hr at 22°, iii) 1 hr at 50°, all resulted in recovery of the starting ketone, identified by mixed melting point and IR spectrum.

b) Hydrogenation: A solution of **10** (50 mg) in AcOH (3 ml) was shaken with Rh-Pt oxide (25 mg) in an atmosphere of hydrogen for 10 hr. TLC analysis of the product indicated only starting ketone. Work-up and crystallized from MeOH gave crystals with double mp 150—158°, 166—168°, identical with the ketone (**10**) by mixed melting point and IR spectrum.

c) With $LiAlH_4$ ($LiAlD_4$): A solution of **10** (200 mg) in abs. ether (16 ml) was added dropwise into a suspension of $LiAlH_4$ (180 mg) in abs. ether (24 ml) under effective stirring. The solution was stirred for 1 hr under reflux. AcOEt (2 ml) was added to the solution under cooling then a few drops of water were added. The solution was poured into cold 10% HCl and the product was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried and evaporated. The residue, showing two spots in addition to a

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8) **7a** and **7b** have the same *Rf* value on TLC in a variety of solvent systems and can not be distinguished from each other.

trace of the starting ketone (hydrolysed) on TLC, was separated by preparative TLC (CH_2Cl_2–MeOH, 10:1, duplicated development). The upper fraction (8 mg) was identified as the 3β,20β-dihydroxy compound of the ketone (**10**) by acetylation. The middle fraction (106 mg, 70%) on crystallization from CH_2Cl_2–MeOH gave **14a** mp 207—209°, $[\alpha]_{\mathrm{D}}^{25}+11.8^{\circ}$. IR $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 3614, 3250 (br), 1035. The lower fraction (46 mg, 30%) on crystallization from $CHCl_3$ gave **15a** mp 228—229°, $[\alpha]_{\mathrm{D}}^{25}$ -12.2°. IR $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 3420, 1036. *Anal.* Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 75.01; H, 10.68.

When $LiAlD_4$ was used for the reduction instead of $LiAlH_4$, the corresponding triols **14a** and **15a** in which the C_{11}–H was substituted by deuterium were obtained in a ratio of 6:1, confirmed by IR and NMR spectra of the acetylated compounds later.

Oxidation of a Mixture of Triols (14a) and (15a) to the Triketone (16)——A portion (30 mg) of the mixture of the reduction products (**14a**) and (**15a**) was treated with Jones reagent (30 mg) in acetone at 20° for 30 min. Usual work-up gave 9(8→7αH)-abeo-5α,9α,14α-pregnane-3,11,20-trione (**16**), homogeneous on TLC. Recrystallization from ether–petr. ether gave a sample with mp 168.5—172°. IR $\nu_{\max}$ cm^{-1}: 1715, 1701. NMR τ: 9.33 (3H, s, 18-Me), 8.84 (3H, s, 19–Me), 7.87 (3H, d, $J=6.0$, 21–Me), 7.65, 7.18 (2H, AB type d of d, $|J|=10.0$, C_{12}–H). *Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.41; H, 9.04.

Acetylation of the Triols (14a) and (15a)——Triol (14a) (50 mg) was treated with Ac_2O–pyridine at room temperature over night. Work-up gave the product (**14b**) as a gum which failed to crystallize from a variety of solvents but the homogeneity of which was supported by analytical TLC with several kinds of the solvent system. Mass Spectrum *m/e*: 462 (M^+). IR $\nu_{\max}$ cm^{-1}: 1735, 1235, 1025. In the 11-deuteriated compound, weak bands due to C–D stretching were observed at 2158, 2134 and 2093 cm^{-1}. NMR τ: 9.26 (3H, s, ⟩C–Me), 9.20 (3H, s, ⟩C–Me), 8.88 (3H, d, $J=6.0$, 21–Me), 8.02 (OAc), 8.00 (OAc), 7.98 (OAc), 7.60, 7.48, 7.35, 7.23 (1H, q, $J_{\mathrm{vic}}=7.0$, $|J_{\mathrm{gem}}|=15.0$, C_{12}-βH) (In the 11-deuteriated compound, this quartet, collapsed to a doublet at τ 7.54 and 7.29 $|J_{\mathrm{gem}}|=15.0$), 7.45—5.05 (2H, m, $C_{3,20}$ –H), 4.73 (1H, br, d, $J=7$, $W^{h}/_{2}=5$, $C_{11}-\alpha$H (this signal disappeared in the 11-deuteriated compound)).

Triol (**15a**) (50 mg) was treated in the same way as described above and gave triacetate (**15b**) (60 mg). Recrystallization from ether–petr. ether gave a sample with mp 200—203°, $[\alpha]_{\mathrm{D}}^{25}-23.6^{\circ}$. IR $\nu_{\max}$ cm^{-1}: 1735, 1235, 1025. Besides these bands, weak bands due to C–D stretching were observed at 2174, 2136 and 2089 cm^{-1} in the 11-deuteriated compound. NMR τ: 9.22 (3H, s, ⟩C–Me), 9.14 (3H, s, ⟩C-Me), 8.87 (3H, d, $J=6.0$, 21-Me), 8.07 (OAc), 8.05 (OAc), 8.00 (OAc), 7.90, 7.67 (1H, d of d, $J_{\mathrm{vic}}=1.5$ $|J_{\mathrm{gem}}|=14.0$) (In the 11-deuteriated compound this doublet of doublets became a single doublet at τ 7.90 and 7.67.), 5.42—5.05 (2H, m, $C_{3,20}$ -H), 4.87 (1H, t of d, $J=1.5$, $J=11.0$ (this signal disappeared in the 11-deuteriated compound)). *Anal.* Calcd. for $C_{27}H_{42}O_6$: C, 70.10; H, 9.15. Found; C, 70.38; H. 9.18.

3β,20β-Diacetoxy-9α-bromo-9(8→7αH)-abeo-5α,14α-pregnan-11-one (13)——To a stirred solution of **10**(100 mg) in CH_2Cl_2 (4 ml) was added phenyl trimethyl ammonium tribromide (1.1 mole eq. 100 mg) at room temperature and the mixture was stirred for 15 min, then poured into water. The product was extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with 5% HCl, 5% Na_2CO_3 and water, dried and evaporated under reduced pressure at room temperature. The residue was crystallized from ether–petr. ether to give **13** mp 159—163°, $[\alpha]_{\mathrm{D}}^{23}+127.3^{\circ}$. IR $\nu_{\max}$ cm^{-1}: 1735, 1700, 1235. UV $\nu_{\max}^{\mathrm{MeOH}}$ mμ (ε): 314 (106). NMR τ: 9.40 (3H, s, 18-Me), 8.90 (3H, s, 19-Me), 8.83 (3H, d, $J=6.0$, 21-Me), 7.98 (OAc), 7.92 (OAc), 7.88, 7.46 (2H, AB type d of d, $|J|=11.0$), 5.47—5.00 (2H, m, $C_{3,20}$–H). *Anal.* Calcd. for $C_{25}H_{37}O_5Br$: C, 60.36; H, 7.50; Br, 16.06. Found: C, 60.09; H, 7.69; Br, 16.10.

3β,11,20β-Triacetoxy-9(8→7αH)-abeo-5α,14α-pregn-9(11)-ene (11)——A mixture of **10** (160 mg) and *p*-TsOH (40 mg) in isopropenyl acetate (10 ml) was gently refluxed for 1 hr, then about 5 ml of the distilate was removed over 1 hr. Additional fresh isopropenyl acetate (6 ml) was added to the reaction mixture, which was again condensed to half volume. After repetition of this procedure one more time, the reaction mixture was taken up in ether and washed with 5% Na_2CO_3 and water. After evaporation of the solvent, the product was separated by preparative TLC (CH_2Cl_2–AcOEt,20:1). On crystallization from ether–petr. ether, the main fraction (144 mg) gave **11** mp 182—183°, $[\alpha]_{\mathrm{D}}^{24}-33.6^{\circ}$. IR $\nu_{\max}$ cm^{-1}: 1750 (sh), 1735, 1237, 1220 (sh). NMR τ: 9.33 (3H, s, 18–Me), 9.02 (3H, s, 19–Me), 8.87 (3H, d, $J=6.0$, 21–Me), 8.05 (OAc), 8.02 (OAc), 7.98 (OAc), 7.57 (2H, s, C_{12}-H), 5.50—4.95 (2H, m, $C_{3,20}$-H). *Anal.* Calcd. for $C_{27}H_{40}O_6$: C, 70.40; H, 8.75. Found: C, 70.14; H, 8.91.

3β,20β-Diacetoxy-9α-hydroxy-9(8→7αH)-abeo-5α,14α-pregnan-11-one (12)——$NaIO_4$ (300 mg), CCl_4 (10 ml) and water (50 ml) were taken in a separatory funnel. RuO_2 (160 mg) was added and the mixture shaken. RuO_4 (yellow) formed transferred to CCl_4 layer. The yellow solution of CCl_4 containing RuO_4 was added to a solution of **11** (116 mg) in CCl_4 (6 ml) under stirring at 10°. The mixture was stirred for 15 min at the temperature and poured into water containing a small amount of $NaHSO_3$. The product was extracted with $CHCl_3$ washed with water and dried. The solvent was evaporated and the product crystallized from ether–petr. ether to afford **12** (70 mg) mp 174—177°, $[\alpha]_{\mathrm{D}}^{22}+50.7^{\circ}$. IR $\nu_{\max}$ cm^{-1}: 3560, 3470, 1733, 1696, 1240. NMR τ: 9.40 (3H, s, 18-Me), 9.02 (3H, s, 19–Me), 8.83 (3H, d, $J=6.0$, 21-Me), 8.32 (1H, OH), 7.99 (OAc), 7.95 (OAc), 7.28, 7.03 (2H, AB type d of d, $|J|=11.0$, C_{12}-H), 5.50—5.07 (2H, m, $C_{3,20}$-H). *Anal.* Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.31; H, 8.82.

Condensation of 1 with Silica Gel Formation of 3β,20β-Diacetoxy-9ξ-hydroxy-9(8→7ξH)-abeo-5α,14α-pregnane-8,11-dione (17)——A solution of **1** (500 mg) in benzene (20 ml) was added to a suspension of SiO_2

(5 g) in benzne (30 ml) under stirring and the mixture stirred for 1.5 hr at room temperature. SiO_2 was removed by filtration, washed several times with $CHCl_3$ containing 5% MeOH. The filtrates were combined and evaporated to dryness. The residue (502 mg), showing two spots on TLC, was separated by preparative TLC (CH_2Cl_2–AcOEt, 25:1 duplicate development). The lower fraction (295 mg, 60%) on crystallization from MeOH gave 2 double mp 149—158°, 196—205°. This was shown to be identical with the authentic sample in its IR spectrum and on analytical TLC. The upper fraction (200 mg, 40%) was crystallized from ether to afford the diketo-ol (**17**) mp 200—206°, $[\alpha]_D^{22}+20.0°$. IR ν_{max} cm^{-1}: 3451, 1736, 1710, 1240, 1026. UV $\lambda_{max}^{CHCl_3}$ mμ (ε): 299 (57). CD (c=0.137, $CHCl_3$) [θ] (mμ): 0 (356), +4310 (324) (max), 0 (304.5), −3524 (286) (max). NMR τ: 9.44 (3H, s, 18–Me), 9.26 (3H, s, 19–Me), 8.82 (3H, d, J=6.0, 21–Me), 7.99 (OAc), 7.95 (OAc), 7.22 (1H, br, s, OH), 7.00, 6.85 (2H, AB type d of d, $|J|$=12.0, C_{12}-H), 5.42—5.07 (2H, m, $C_{3,20}$-H). *Anal.* Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 66.77; H, 8.09.

Dehydration of 17 with $SOCl_2$ Formation of 3*β*,20*β*-Diacetoxy-9(8→7)-abeo-5*α*,14*α*-pregn-7(9)-ene-8,11-dione (4a)——A solution of **17** (100 mg) in pyridine was stirred under cooling with ice–water. $SOCl_2$ (0.1 ml) was added dropwise into the solution then the mixture was stirred at room temperature for 15 min. After usual work-up, the product (96 mg), showing three sports on TLC, was separated by preparative TLC (*n*-hexane–AcOEt, 2:1, duplicate development). On crystallization from ether–petr. ether, the upper fraction (57 mg, 58%) gave the enedione (**4a**) mp 176—179°, $[\alpha]_D^{23}$ −8.8°. UV λ_{max} mμ (ε): 262.5 (8833). IR ν_{max} cm^{-1}: 1738, 1665, 1577, 1230. NMR τ: 9.28 (3H, s, 18–Me), 8.94 (3H, s, 19–Me), 8.82 (3H, d, J=6.0, 21–Me), 7.98 (OAc), 7.92 (OAc), 7.18, 6.72 (2H, AB type d of d, $|J|$=15.0, C_{12}–H), 5.47—4.97 (2H, m, $C_{3,20}$–H). *Anal.* Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 70.02; H, 7.98. The middle fraction (30 mg, 31%) and the lower fraction (10 mg, 11%) were found to contain non-conjugated ketone systems from their IR spectra but further characterizations were not done because of insufficient sample.

Formation of the Enedione Monoenol Benzyl Thioether (6) from 4a——A mixture of **4a** (20 mg), benzyl mercaptan (0.3 ml) and *p*-TsOH (5 mg) in benzene (8 ml) was refluxed for 15 hr in a flask equipped with water separation. Work-up gave a single product. Recrystallization from MeOH gave **6**, mp 169—171°, identical with the authentic sample previously made by mixed melting point and IR spectrum.

Equilibration of 3 with Al_2O_3 in Benzene——A mixture of **3a** (30 mg) and Al_2O_3 (Woelm grade I, 300 mg) in benzene (3 ml) was stirred for 2 days at room temperature. The catalyst was filtered off and the product mixture, after treatment with Ac_2O–pyridine, was separated by preparative TLC (ether–petr. ether, 1:3, 3 times development). The upper fraction (**3b**) weighed to 19 mg (64%) and the lower fraction (**3a**) weighed to 11 mg (36%). These IR and NMR spectra were samples. Treatment of **3b** (20 mg) in the same way as before gave a mixture of a similar composition (**3a**:**3b**=33%: 67%).

Equilibration of 4a with Al_2O_3 in Benzene Formation of 3*β*,20*β*-Diacetoxy-9(8→7)-abeo-5*α*,14*β*-pregn-7(9)-ene-8,11-dione (4b)——A mixture of **4a** (60 mg) and Al_2O_3 (600 mg) in benzene (5 ml) was stirred for 2 days at room temperature. After work-up and acetylation with Ac_2O–pyridine, the product (59 mg) showed apparently one spot on TLC but further examination using a variety of solvent systems showed there to be two spots with heavy overlapping. It was found that the repetition of the development of TLC with ether–petr. ether (1:3) gradually effected separation of the spots. Preparative TLC of the product mixture (ether–petr. ether 1:3, 8 times development) gave two separate fractions. The lower fraction (25 mg, 43%) was crystallized from ether–petr. ether to give **4a** mp 175—178°, identical with the authentic sample by mixed melting point and IR spectrum. The upper fraction (33 mg, 57%), on crystallization from ether–petr. ether, gave **4b** mp 138—139°, $[\alpha]_D^{27}$ 0°. UV λ_{max} mμ (ε): 267.5 (6483). IR ν_{max} cm^{-1}: 1738, 1671, 1592, 1240, 1026. NMR τ: 8.97 (3H, s, 18–Me), 8.92 (3H, s, 19–Me), 8.81 (3H, d, J=6.0, 21–Me), 7.98 (OAc), 7.97 (OAc), 7.32 (2H, s, C_{12}–H), 5.45—4.97 (2H, m, $C_{3,20}$-H). *Anal.* Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.69; H, 8.15. The homogeneities of the crude separated products (**4a**) and (**4b**) were supported by examination of their NMR spectra. The assignment of **4b** as the 14*β*-epimer of **4a** was also supported by the spectral data. Especially, the NMR spectrum of **4b** shows its 18-methyl protons signal at τ 8.97, a 0.31 ppm down field shift compared with that of **4a** and this shift value is in accord with the general tendency observed in steroids field⁹⁾ and also in this series.¹⁾

Treatment of 17 with Al_2O_3 in Benzene——A mixture of **17** (66 mg) and Al_2O_3 (1 g) in benzene (10 ml) was stirred for 2 days at room temperature. Work-up gave a product mixture (64 mg), which showed three separate spots on TLC (ether–petr. ether, 1:2, 5 times development). Preparative TLC of the mixture (ether–petr. ether, 1:3, 8 times development) gave three fractions. The lower fraction (11 mg, 17%), on crystallization from ether–petr. ether, gave crystals (**3a**), mp 185—198°, identical with the authentic sample by IR spectrum. The middle fraction (19 mg, 30%) was crystallized from ether–petr. ether to give **4a** mp 175—178° identical with the authentic sample with mixed melting point and IR spectrum. The upper fraction (34 mg, 53%) failed to give crystals. Examination of the NMR and IR spectra of this fraction revealed it to be a mixture of **3b** and **4b** in about a ratio of 1:2.

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9) N.S. Bhacca and D. H.Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, 1964, p 13.

Attempted Dehydration of 2 with Al_2O_3 in Benzene——A mixture of 2 (100 mg) and Al_2O_3 (2 g) in benzene (10 ml) was stirred for 2 days at room temperature. After usual work-up, the product showed a considerable amount of the starting material besides the enone (**3a**) and (**3b**) on TLC, which were separated by preparative TLC (ether–petr. ether, 1:3, 3 times development). The fraction corresponding to the starting material weighed to 48 mg (48%), shown to be identical with 2 by IR spectrum. The upper fraction in the less polar region gave **3b** (31 mg), identical with the authentic sample in IR and NMR spectra. The lower fraction in the less polar region gave **3a** (17 mg), identical with the authentic sample in IR and NMR spectra. From this experiment it was found that the rate of the dehydration of 2 with Al_2O_3 was very slow and neither the enedione (**4a**) nor (**4b**) could be detected.

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