Erscheint 9mal jährlich – Paraît 9 fois par an

77. Photochemical Reactions
Part 58 [1]
On the Mechanism of the Rearrangement of the Triplet-excited α,β-Unsaturated δ-Diketone 3,7-Dioxo-4,4-dimethyl-17β-acetoxy-Δ^5-androstene

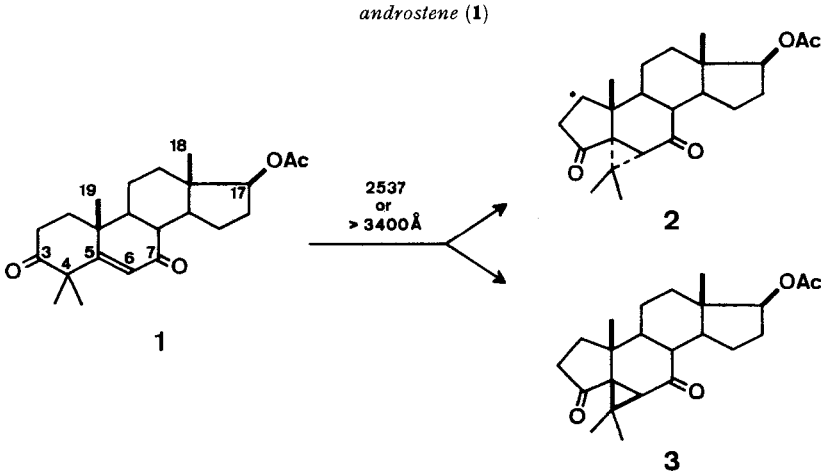
by **S. Domb** and **K. Schaffner**
Laboratorium für Organische Chemie der Eidg. Technischen Hochschule, 8006 Zürich

(3. III. 70)

Zusammenfassung. In einer vorangehenden Arbeit [2] wurde gezeigt, dass sich das triplettangeregte α,β-ungesättigte δ-Diketon **1** in die beiden stereoisomeren Cyclopropyl-diketone **2** und **3** umlagert. Neue Resultate vermitteln nun einen näheren Einblick in die mechanistischen Aspekte dieser Photoreaktion. Die Bestrahlung der 4α-Trideuteromethyl-Verbindung **7** in Dioxan mit 2537 Å lieferte nach einem Umsatz von $\geqq 30\%$ die an C-4 sterisch äquilibrierten Photoisomerenpaare **8a,b** und **9a,b**, während im regenerierten Ausgangsmaterial (**7**) die C(4)-Chiralität erhalten blieb. *Dieser Befund spricht gegen eine konzertierte Umlagerung und ist indikativ für einen schrittweisen Reaktionsablauf.*

In a recent paper [2] we reported the photorearrangement of the triplet-excited α,β-unsaturated δ-diketone **1** to the two stereoisomeric cyclopropyl diketones **2** and **3** (Chart 1). Three pathways are *a priori* possible for this type of transformation: two stepwise mechanisms, each leading to diradical products in the primary photochemical processes, and a concerted $\sigma_a^2(C3,4) + \pi_a^2(\Delta^5)$ cyclo-addition [3]. Each of the stepwise mechanisms is capable of scrambling the diastereotopic geminal methyl groups at C-4, and the concerted reaction should occur with inversion at C-4 [2]. A selective label on one of these methyl groups was therefore considered to serve as a suitable stereo-

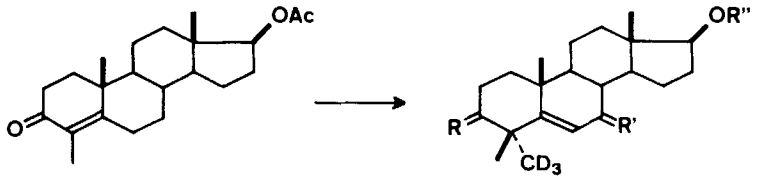
Chart 1. *Previous Results [2]: The Photorearrangement of 3,7-Dioxo-4,4-dimethyl-17β-acetoxy-Δ^5-androstene* (**1**)



chemical test to differentiate between the stepwise and concerted reaction modes in the further pursuit of this work.

The 4α-trideuteriomethyl compound **7** was chosen for this purpose. It was obtained by alkylation of O-acetyl-4-methyltestosterone (**4**) [4] with CD_3J and $KOC(CH_3)_3$ in *t*-butanol[1a]), reacetylation of product **5** to **6** and subsequent oxidation of the methylene group C-7 with *t*-butyl chromate solution[1b]) (Chart 2). The comparison of the nmr. spectra of **1** and **7** in C_6D_6 solution[2]) shows that alkylation of **4** with CD_3J had occurred with a stereoselectivity of ~95% (see Fig. 1)[3]).

Chart 2. *Synthesis of 3,7-Dioxo-4α-trideuteriomethyl-4β-methyl-17β-acetoxy-Δ⁵-androstene* (**7**)[3])



4

5 R = O, R' = H_2, R" = H
6 R = O, R' = H_2, R" = Ac
7 R = R' = O, R" = Ac

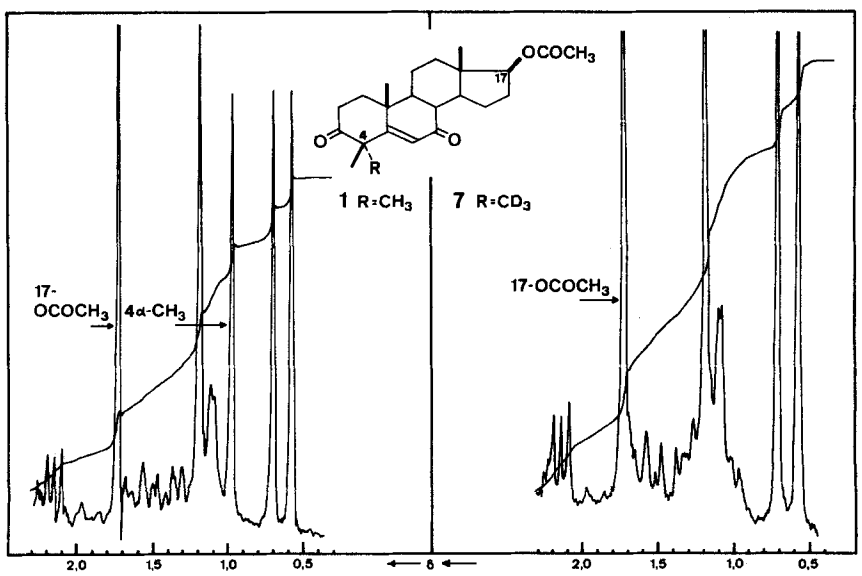


Fig. 1. *Nmr. Spectra* [*100 Mc, C_6D_6 solution*[2])] *of Compounds* **1** [*2*] *and* **7**[3])
[spectra of **7** identical for samples before irradiation and after recovery from the photolyses at 2537 Å in dioxane, and at >3400 Å in dioxane + naphthalene]

[1]) Methods described by (a) *Woodward, Barton & al.* [5]; (b) *Domb & al.* [2], and references therein.

[2]) The nmr. signals of the geminal methyl groups of compound **1** as well as those of the non-deuteriated analogue of **6** are coincidentally isochronous in $CDCl_3$ solution.

[3]) The stereochemical assignment at C-4 in compounds **5**–**7** is based solely on analogy with established results in similar cases, *e.g.* the ethylation of 4-methylcholestenone [6]. We may note here that, while the stereoselective label of C-4 in diketone **7** is essential for the evaluation of the photochemical results reported here, the chirality of this carbon is irrelevant.

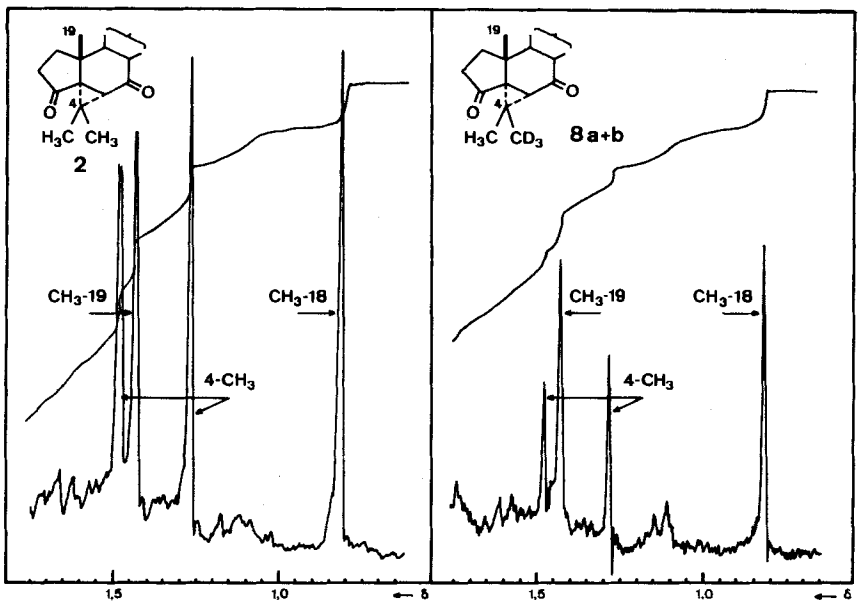


Fig. 2. *Nmr. Spectra (220 Mc, $CDCl_3$ solution) of Compound* **2** *[2]*[4]) *and of the Mixture* **8a + b**

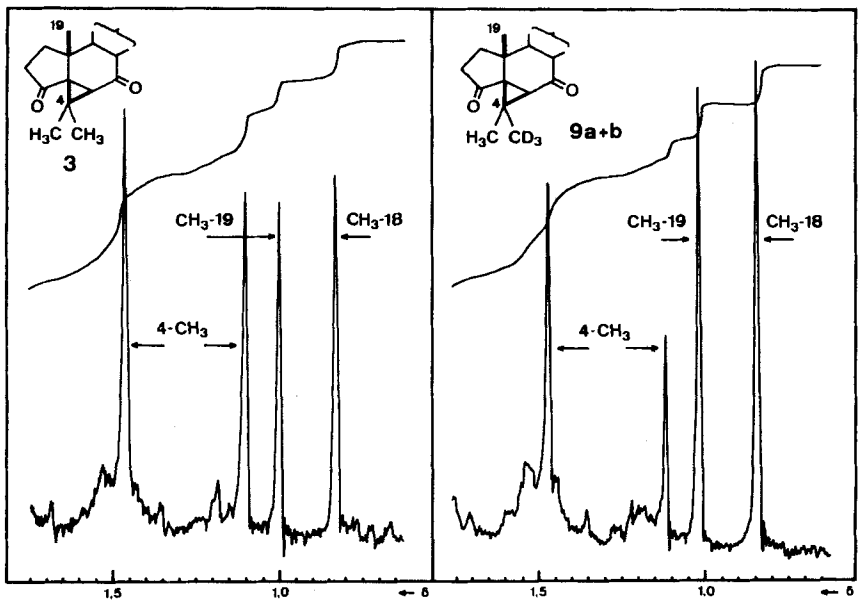
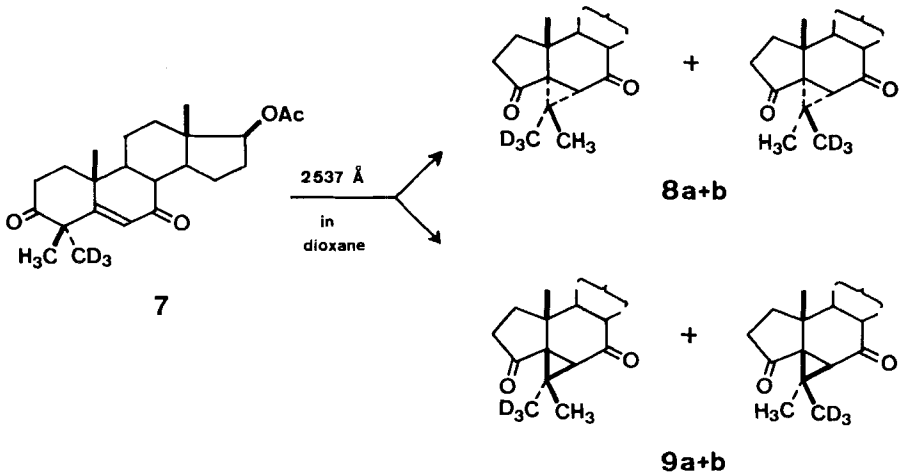


Fig. 3. *Nmr. Spectra (220 Mc, $CDCl_3$ solution) of Compound* **3** *[2] and of the Mixture* **9a + b**

[4]) *Corrigendum:* Two erroneous values for the chemical shifts of methyl groups in photoproduct **2** have been reported in [2]. The correct values are: 1.35 + 1.53 δ/2*s*, 4α- and 4β-CH_3, and 1.46 δ/*s*, CH_3-19.

Compound **7** was irradiated at 2537 Å in dioxane solution until a conversion of $\geqq 30\%$ was reached. The components (**7**, **8** and **9**) of the resulting mixture were separated by chromatography and crystallization and investigated by nmr. spectroscopy. The spectrum of the recovered starting material (**7**, Fig. 1) shows that the chirality of C-4 had been fully preserved during the irradiation. The spectra (Fig. 2 and 3) of the fractions which correspond in their appropriate data to the photoproducts **2** and **3**, however, prove that both of these samples consist of *ca.* 1:1 mixtures of C(4)-diastereoisomeric products (**8a** + **b** and **9a** + **b**, Chart 3).

Chart 3. *The Photorearrangement of Compound* **7**[3])



7

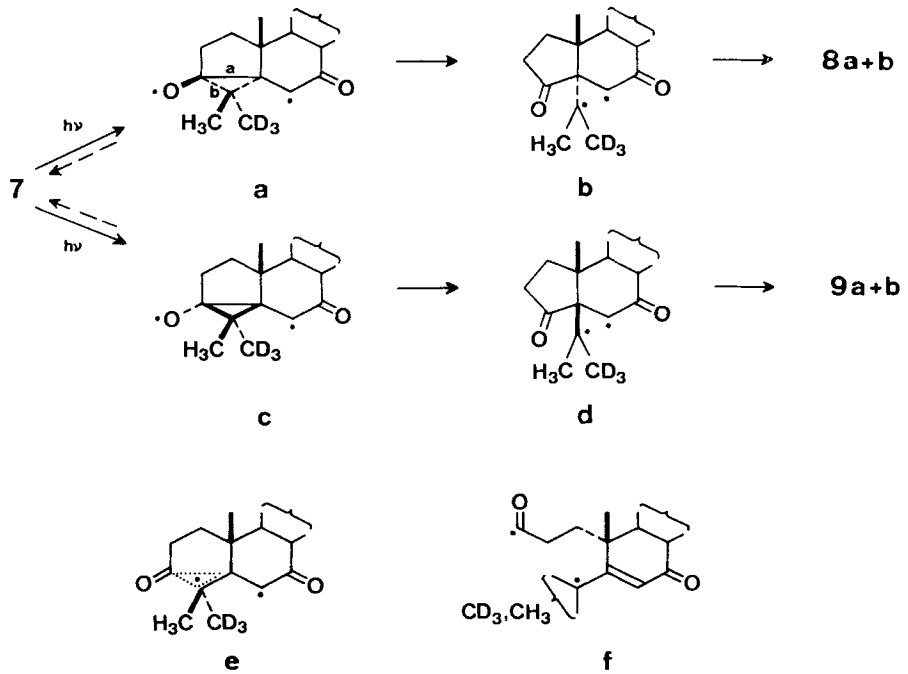
The *cis*-fusion of the three- and six-membered rings in the products **2** and **3** demands that in a photochemically allowed concerted mechanism [3] the 3,4-single bond of **1** adds in an *antara-antara*-facial fashion to the Δ^5-bond. While such pathways with inversion at C-4 appear feasible structurally for the rearrangement to both **2** and **3** (cf. [2]), the molecular geometry is extremely unfavorable for the alternative with retention at C-4, even if one allows for maximum non-planar distortion of the triplet-excited enone group. The stereochemical scrambling at C-4 during the rearrangements **7** → **8** and **7** → **9** would demand a fortuitous 1:1 partitioning between $\sigma_a^2 + \pi_a^2$ additions with inversion and with retention at C-4, respectively. Barring this unlikely coincidence, *the experimental result is not compatible with a rearrangement mechanism which is subject to orbital symmetry conservation rules, but it is acceptable as evidence for a stepwise rearrangement sequence.*

One possibility is C(5) → C(3) bonding to form the stereoisomeric diradicals **a** and **c** (Chart 4)[5]). Thermal reversal to starting material (**7**) by the cleavage of bonds *a* in **a** and **c** would maintain the stereochemistry at C-4, and the cleavage of bonds *b* would permit stereochemical equilibration of the 4-CH_3 and 4-CD_3 groups in the intermediates

[5]) The preparation of a 4,4-dimethyl-3α,5α-cyclo-cholestane (an *i*-steroid, corresponding to the ring system of **c**) has been achieved by a base-catalyzed internal displacement of the tosyloxy group in the 3β-tosyloxy-6-ketone precursor [7]. The formation of the hitherto unknown 3β,5β-cyclo system of **a** could be anticipated here as a consequence of the considerable steric interaction between the 4β-CH_3 and CH_3-19 groups, which is introduced upon formation of **c**.

b and **d** prior to the ring closure to products. An analogous bridging mechanism has been considered previously for the similar photorearrangement of the triplet-excited α,β-unsaturated γ-aldehydoketone 3,19-dioxo-17β-acetoxy-Δ^4-androstene [8].

Chart 4. *Stepwise Mechanisms for the Rearrangements* **7** → **8a** + **b** *and* **7** → **9a** + **b**[3])



A direct (4 → 5) acyl shift *via* the two corresponding stereoisomeric species **e**[6]) as another pathway to the intermediates **b** and **d** remains an alternative possibility[7]).

Homolytic fission of the 3,4-bond and total release of the acyl radical, leading to intermediate **f**[7]), appears less likely. Molecular models of **f** show that cyclization to **8a** + **b**, the major photoproducts, is clearly less favorable for structural reasons than cyclization to **9a** + **b**, which represent the minor part of the mixture of photo-isomers. Moreover, recombination of **f** to **7** would be expected to scramble the geminal methyl groups at C-4, an effect which could not be detected experimentally (see Fig. 1)[8]).

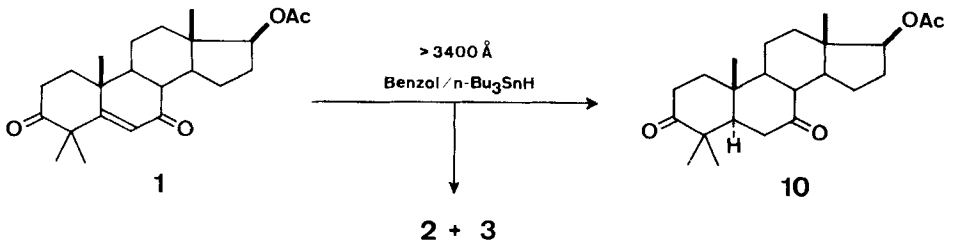
[6]) A species of type **e** has been proposed for a non-concerted variant of the cyclohexenone-bicyclo[3.1.0]hexanone rearrangement of, *e.g.*, the ring-A-enone testosterone; see [9].

[7]) Note that more than one conformation of ring A has to participate at the excited state reaction of **7** in order to account for two stereochemical paths of the (3 → 5) bonding (→ **a** + **c**) and the acyl migration (→ **e**) mechanisms: boat-like form of ring A → **b**, chair-like form → **d**. A similar condition is required for the C(4)-methyl scrambling in the mechanism *via* **f**.

[8]) In search for a reversible cleavage involving stereochemical equilibration at C-4 in the singlet-excited compound **7**, a photolysis of **7** in dioxane at > 3400 Å was carried out in the presence of 1.0 M naphthalene, which is known to quench the photorearrangement completely [2]. After an irradiation time which corresponded to the 2.5-fold period required for complete conversion of **1** in a parallel run without naphthalene, the stereochemistry of C-4 was unaltered in the regenerated starting material **7** (Fig. 1).

Attempts to intercept free radical intermediates of the photorearrangements of **1**, *e.g.* in the form of cyclopropanol derivatives of the diradicals **a** and **c**, have not been successful so far. In one series of such experiments (irradiation of 0.018 M **1** in benzene at > 3400 Å) various concentrations of tri-*n*-butyl-stannane were added. At 0.15 M stannane, only reduction to the saturated diketone **10** was observed, and at 0.0165 M stannane rearrangement to **2** and **3** and reduction to **10** occurred (Chart 5).

Chart 5. *Irradiation of Compound* **1** *in the Presence of Tri-*n*-butyl-stannane*



The financial support of this research by the *Schweiz. Nationalfonds zur Förderung der wissenschaftlichen Forschung* and the *J. R. Geigy AG*, Basel, is greatfully acknowledged.

Experimental. – *General Remarks.* Silicagel *Merck* (0.05–0.2 mm) was used for *preparative column chromatography*, and *Merck* Plates F_{254} (silicagel) for *thin-layer chromatography* (tlc.). The tlc. spots were located by the use of uv. light and by spraying the dried plates with conc. H_2SO_4 and subsequent heating.

Melting points were measured in open capillaries and are not corrected. $[\alpha]_D$ values were determined in a 5 cm tube, concentrations (*c*) are added in parantheses.

Uv. spectra: λ_{max} are given in nm (ε values in parentheses). – *Ir. spectra:* ν_{max} in cm^{-1}. – *Nmr. Spectra* of **8** and **9** were recorded at 220 Mc, all other ones at 100 Mc. Chemical shifts are given in δ values, with $(CH_3)_4Si$ as the internal standard. Abbreviations: *s* (singlet), *t* (triplet), *b* (broad), *J* (coupling constant in cps). Proton integration of each signal is in agreement with the given assignments.

3-Oxo-4α-trideuteriomethyl-4β-methyl-17β-acetoxy-Δ⁵-androstene (**6**)[3]. 2 ml of CD_3J in *t*-butanol were added dropwise under N_2 to a solution of 2 g O-acetyl-4-methyltestosterone (**4**) [4] and 2.4 g $KOC(CH_3)_3$ in *t*-butanol. After stirring the mixture for 24 hr at room temperature, 200 ml H_2O were added and the precipitate was filtered and dried by azeotropic distillation with benzene. Direct acetylation of the crude product (1.94 g **5**) for 2 hr at 80° in pyridine + acetic anhydride was followed by the removal of the volatile material by repeated evaporation *in vacuo* with toluene. The crude product was then filtered in CH_2Cl_2 through neutral Al_2O_3 (activity III) and finally chromatographed in acetone-hexane 1:8 on 200 g silicagel to yield 1.23 g **6**, mp. 155–156° (1 × cryst. from acetone-hexane). $[\alpha]_D$ – 27° (1.01 in $CHCl_3$). Ir. (CCl_4): 1240, 1710, 1735, 2220. Nmr. ($CDCl_3$): 0.82/*s*, CH_3-18; 0.90 + 1.25/2*s*, 4β-CH_3 and CH_3-19; 2.05/*s*, 17-$OCOCH_3$; ca. 4.6/*bt*, CH-17; ca. 5.55/*b*, CH-6; (C_6D_6): 0.68 + 0.75 + 1.36/3*s*, 4β-CH_3, CH_3-18 and -19; 1.72/*s*, 17-$OCOCH_3$. Ms.: *m/e* 361 (M^+, $C_{23}H_{31}D_3O_3$). Cf. 3-Oxo-4,4-dimethyl-17β-acetoxy-Δ⁵-androstene: mp. 154–156°; $[\alpha]_D$ – 29° (C_2H_5OH) [10]; nmr. (C_6D_6), 1.13/*s*, 4α-CH_3[9]).

3,7-Dioxo-4α-trideuteriomethyl-4β-methyl-17β-acetoxy-Δ⁵-androstene (**7**)[3]. For the oxidation of **6** with *t*-butyl chromate in CCl_4 at 22°, the procedure described for the preparation of **1** [2] was followed. 1.57 g of **6** furnished 309 mg starting material **6** and 863 mg **7**, mp 155–158° (cryst. from acetone-hexane). $[\alpha]$ – 78° (1.05 in CH_2Cl_2). Ir. (CCl_4): 1240, 1620, 1675, 1720, 1740, 2220. Nmr. ($CDCl_3$): 0.83/*s*, CH_3-18; 1.13 + 1.35/2*s*, 4β-CH_3 and CH_3-19; 2.06/*s*, 17-$OCOCH_3$; ca. 4.7/*bt*, CH-17; 5.95/*s*, CH-6; (C_6D_6): Figure 1. Ms.: *m/e* 375 (M^+, $C_{23}H_{29}D_3O_4$). Cf. **1**: mp. 156–158° (an erroneous value for the mp. of **1** was given in [2]); $[\alpha]$ – 75° (CH_2Cl_2) [2][9]).

[9]) Compounds **5**–**9** showed identical tlc. retention times and proton magnetic resonance signals on comparison with the respective non-deuteriated analogues.

Irradiation of **7** *in Dioxane at 2537* Å. The procedure described for **1** [2] was employed, using a low-pressure mercury lamp NK 6/20 (*Quarzlampen GmbH.*, Hanau; main emission at 2537 Å). Tlc. of the crude reaction mixture showed only the two spots corresponding to **7** and **8**+**9**, respectively. Column chromatography yielded 38% starting material (**7**; see nmr., Fig. 1) and 30% of the mixture **8a,b**+**9a,b**. Repeated crystallizations of the latter from acetone-hexane gave:

19% of the mixture of *C(4)-diastereoisomeric 3,7-dioxo-4-methyl-4-trideuteriomethyl-17β-acetoxy-3[4→5β]-abeo-4,6α-cyclo-androstanes* (**8a,b**), mp. 160–161°. Ir. (CCl_4): 1245, 1690, 1730. Nmr.: see Figure 2. Ms.: *m/e* 375 (M^+, $C_{23}H_{29}D_3O_4$). Cf. **2**: mp. 157–158° [2][4][9]), and

4% of the mixture of *C(4)-diastereoisomeric 3,7-dioxo-4-methyl-4-trideuteriomethyl-17β-acetoxy-3[4→5α]-abeo-4,6β-cyclo-androstanes* (**9a,b**), mp. 170–171°. Ir. (CCl_4): 1245, 1690, 1730, ca. 2350 (broad). Nmr.: see Figure 3. Ms.: *m/e* 375 (M^+, $C_{23}H_{29}D_3O_4$). Cf. **3**: mp. 158–159° [2][9]). The mp. of **3** and of **9a,b** remained constant on further crystallizations.

Irradiation of **7** *in Dioxane at >3400* Å *in the Presence of 1.0*M *Naphthalene.* 103 mg of **7** were irradiated in 9 ml of a 1.0 M dioxane solution of naphthalene in a pyrex tube, using a 125 W medium-pressure mercury lamp and an aqueous filter solution of 750 g NaBr + 8 g $Pb(NO_3)_2$/l in a turntable reactor. The solvent was then evaporated *in vacuo*. Tlc. of the crude product showed only the spots corresponding to naphthalene, **7**, and traces of unidentified material. Naphthalene was removed by chromatography on 10 g silicagel with benzene. Elution with benzene–ethyl acetate 6:1 and crystallization from acetone-hexane gave 60 mg starting material (**7**; identification by mp., mixed mp., tlc., ir., and nmr., see Fig. 1).

A parallel run with **1** without naphthalene (same solvent and concentration) resulted in the complete conversion to **2**+**3** after about two fifths of the irradiation time.

Irradiation of **1** *in Benzene + Tri*-n-*butyl-stannane at >3400* Å. – a) A solution of 1 g 3,7-dioxo-4,4-dimethyl-17β-acetoxy-Δ^5-androstene (**1**) [2] and 6.4 g (8.2 mole equiv.) (n-$C_4H_9)_3SnH$ in 150 ml benzene was irradiated for 1 hr (light source and filter used as described above). The solvent was then evaporated and excess stannane was removed by filtration in benzene through a column of 30 g silicagel. Elution with ethyl acetate furnished the crude product mixture[10]) which was chromatographed on 100 g silicagel with acetone-hexane 1:8. First a mixed fraction containing starting material (**1**) and **10** was obtained, followed by a 197 mg fraction of pure *3,7-dioxo-4,4-dimethyl-17β-acetoxy-5α-androstane* (**10**), mp. 181.5–182.5° (80 mg after three cryst. from CH_2Cl_2-hexane). $[\alpha]_D$ −55° (1.7 in CH_2Cl_2). Ir. (CCl_4): 1240, 1710, 1735. Nmr. ($CDCl_3$): 0.80/*s*, CH_3-18; 1.09 (6H) + 1.30 (3H)/2*s*, 4,4-$(CH_3)_2$ and CH_3-19; 2.03/*s*, 17-$OCOCH_3$; 4.70/*bt*, CH-17. Ms.: *m/e* 374 (M^+).

$C_{23}H_{34}O_4$ Calcd C 73.76 H 9.15% Found C 73.73 H 9.13%

Compound **10** was identical with a sample obtained by hydrogenation of **1** on Pt in CH_3COOH and subsequent reoxidation with CrO_3 (no depression of mixed mp., comparison of $[\alpha]_D$, tlc., ir. and nmr.). In this latter experiment, *3-oxo-4,4-dimethyl-17β-acetoxy-5α-androstane* (cf. [11]) was formed additionally, mp. 150–151°. $[\alpha]_D$ −19° (0.8 in CH_2Cl_2). Ir. (CCl_4): 1240, 1710, 1735. Nmr. ($CDCl_3$): 0.80/*s*, CH_3-18; 1.06 (9H)/*s*, 4,4-$(CH_3)_2$ and CH_3-19; 2.02/*s*, 17-$OCOCH_3$; ca. 4.6/*bt*, CH-17. Ms.: *m/e* 360 (M^+).

$C_{23}H_{36}O_3$ Calcd C 76.62 H 10.07% Found C 76.66 H 10.06%

The same acetoxyketone was formed also upon hydrogenation and reoxidation as described above of 3-oxo-4,4-dimethyl-17β-acetoxy-Δ^5-androstene [10] (identified by mixed mp. and comparison of $[\alpha]_D$, tlc., ir., and nmr.).

b) In a similar run, a solution of 53 mg **1** and 35 mg (0.85 mole equiv.) (n-$C_4H_9)_3SnH$ in 8 ml benzene was irradiated for 2 hr. Tlc. analysis of the reaction mixture indicated the presence of **1**, **2**, **3**, and **10** (despite the similar tlc. retentions of **1** and **10**, these compounds and mixtures thereof can be differentiated by the spot colors in luminescence and after treatment with H_2SO_4).

Control runs in the dark were conducted parallel to the irradiation experiments a) and b). No reaction of **1** with stannane occured under these conditions.

---

[10]) Tlc. of the crude reaction mixture showed one spot corresponding to **1** and **10**, and it gave no indication for other reaction products except for traces of unidentified material which were isolated by preparative plate chromatography and contained Sn according to mass spectrometric analysis.

The elemental analyses were carried out by Mr. *W. Manser* of the Microanalytical Laboratory of ETH Zürich. Nmr. spectra were measured in our Instrumental Division (Prof. *W. Simon*), and mass spectra by PD Dr. *J. Seibl.*

REFERENCES

[1] Part 57: *M. Debono, R. M. Molloy, D. Bauer, T. Iizuka, K. Schaffner & O. Jeger,* J. Amer. chem. Soc. *92,* 420 (1970).
[2] *S. Domb, G. Bozzato, J. A. Saboz & K. Schaffner,* Helv. *52,* 2436 (1969).
[3] Cf. *R. B. Woodward & R. Hoffmann,* Angew. Chemie *81,* 797 (1969).
[4] *F. Sondheimer & Y. Mazur,* J. Amer. chem. Soc. *79,* 2906 (1957).
[5] *R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives & R. B. Kelly,* J. Amer. chem. Soc. *76,* 2852 (1954).
[6] *G. Just & K. S. C. Richardson,* Canad. J. Chemistry *42,* 464 (1964); cf. also *R. S. Matthews, P. K. Hyer & E. A. Folkers,* Chem. Commun. *1970,* 38.
[7] *G. Just & K. S. C. Richardson,* Canad. J. Chemistry *42,* 456 (1964).
[8] *E. Pfenninger, D. E. Poel, C. Berse, H. Wehrli, K. Schaffner & O. Jeger,* Helv. *51,* 772 (1968).
[9] *D. Belluš, D. R. Kearns & K. Schaffner,* Helv. *52,* 971 (1969), and references therein.
[10] *H. J. Ringold & G. Rosenkranz,* J. org. Chemistry *22,* 602 (1957).
[11] *M. Gorodetsky & Y. Mazur,* Tetrahedron Letters *1964,* 227.

78. Die Photoelektron-Spektren von $CH_3–CH\overset{t}{=}CH–CH_3$, $CH_3–N\overset{t}{=}CH–CH_3$, $CH_3–N\overset{t}{=}N–CH_3$, ein Beitrag zur Frage nach der Wechselwirkung zwischen den einsamen Elektronenpaaren der *trans*-konfigurierten Azogruppe [1]

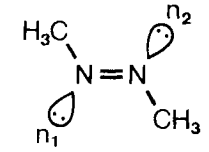
von **E. Haselbach** und **E. Heilbronner**

Physikalisch-Chemisches Institut der Universität Basel

(6. III. 70)

Summary. A correlation of the photoelectron spectra of *trans*-2-butene, *trans*-acetaldehyde-methylimin and *trans*-azomethane shows that the split $\Delta = \varepsilon(\mathbf{a}_g(n)) - \varepsilon(\mathbf{b}_u(n))$ between the lone pair orbitals $\mathbf{a}_g(n)$ and $\mathbf{b}_u(n)$ of *trans*-azomethane amounts to **3.3** ± **0.2** eV. Molecular orbital calculations by the MINDO/1 procedure indicate that $\mathbf{a}_g(n)$ lies above $\mathbf{b}_u(n)$. In agreement with the experimental results the π-orbital $\mathbf{a}_u(\pi)$ is predicted to fall into the interval between $\mathbf{a}_g(n)$ and $\mathbf{b}_u(n)$.

Im klassischen Modell der Azogruppe, wie sie in *trans*-konfigurierten aliphatischen oder aromatischen Azoverbindungen, z. B. im *trans*-Azomethan (I) vorliegt, besetzen die beiden einsamen Elektronenpaare die Atomorbitale $\mathbf{n}_1$ und $\mathbf{n}_2$. Dabei wird mei-

I 

stens angenommen, dass es sich bei $\mathbf{n}_1$ und $\mathbf{n}_2$ im wesentlichen um sp^2-Hybride handelt. Da die lokale Symmetrie der *trans*-Azogruppe aber C_{2h} ist, sind aus $\mathbf{n}_1$ und $\mathbf{n}_2$