e.g. according to:

$$(Fe^{3+} \cdot O_2^{2-} \cdot Fe^{3+}) + H^+ \rightarrow 2\,Fe^{3+} + HO_2^- \qquad (13)$$

followed again by the reaction sequence given above.

This somewhat more detailed interpretation of the primary process given above arises from the assumption that, in the case of an endothermic process, an unstable intermediate ionic complex may be stabilised by Coulombic interactions, a principle which appears to have wider applications in the mechanism of electron transfer processes in solution.

A full account will be published elsewhere. J. WEISS

University of Durham, King's College, Newcastle upon Tyne, 1, England, December 1, 1952.

Zusammenfassung

Der Primärprozess des bereits vor einiger Zeit gegebenen Mechanismus der Autoxydation von Ferroionen in verdünnten wässrigen Lösungen wurde erneut diskutiert, besonders im Hinblick auf die Rolle von elektrostatischen Wechselwirkungen bei der Bildung des primären Ionenkomplexes. Es zeigt sich, dass Coulombsche Wechselwirkungen, auch mit anderen in der Lösung vorhandenen Ionen, von Bedeutung für die Stabilisierung des primären Ionenkomplexes sein können, und es ist sehr wahrscheinlich, dass, ganz allgemein, solche Wechselwirkungen bei Elektronenübergangsprozessen in Lösungen in Betracht gezogen werden müssen.

Steroids XL
The Oxidation of Unsaturated Steroidal Alcohols with Manganese Dioxide[1]

Within the last few years the employment of manganese dioxide for the oxidation of polyene aliphatic primary and secondary alcohols to the corresponding aldehydes and ketones respectively has been finding increasing application[2]. Quite recently the scope of this type of reaction was considerably widened by the demonstration[3] that even simple singly unsaturated primary alcohols, such as allyl alcohol, could be oxidized smoothly to the α,β-unsaturated aldehydes. We have been studying for some time the action of manganese dioxide on a variety of unsaturated steroidal alcohols. This study has led to a number of interesting observations, and has resulted in a convenient new route to testosterone, and a simple synthesis of steroidal $\Delta^{4,6}$-dien-3-ones.

The first examples to be studied were Δ^4-cholesten-3β-ol and Δ^4-22a-spirosten-3β-ol, containing the Δ^4-3-ol system (I*a*). In view of the insolubility of many steroids in light petroleum the solvent usually employed for oxidations with manganese dioxide[2], a variety of other solvents were investigated. It was found that oxidation proceeded rapidly by shaking (I*a*) at room temperature with freshly precipitated manganese dioxide in inert solvents such as benzene, chloroform, ethylene chloride, acetone, etc., conversion to the Δ^4-3-ones (I*b*) being complete in *circa* 2 hours; the latter could be isolated in excellent yield. Similarly oxidation of Δ^5-22a-spirostene-3β:7α-diol 3-acetate (II*a*)[1] led to the Δ^5-7-one (II*b*), $\Delta^{9,11}$-22a-5α-spirostene-3β:12-diol (III*a*)[2] gave the $\Delta^{9(11)}$-12-one (III*b*), and $\Delta^{5:17(20)}$-pregnadiene-3β:21-diol[3] furnished the corresponding 21-aldehyde. All these products were isolated in satisfactory yield.

Δ^4-Cholestene-3β:6β-diol (IV*a*)[4] in benzene solution with manganese dioxide at room temperature was only oxidized at C-3, and Δ^4-cholesten-3-one-6β-ol (IV*b*) was produced in 75% yield. This procedure represents a simple new synthesis of such 6-hydroxylated Δ^4-3-ketones, and has already been applied in other series [*inter al.*: 6β-hydroxy-progesterone (m.p. 181–183°, $[\alpha]^{20}_D$ + 105° (all rotations in $CHCl_3$), λ^{EtOH}_{max} 236 mμ, logε 4·22, found: C, 75·97; H, 9·32), 6β-hydroxy-Δ^4-androstene-3,17-dione[5] (m.p. 192–194°, $[\alpha]^{20}_D$ + 114°, λ^{EtOH}_{max} 236 mμ, logε 4·25, found: C, 75·56; H, 8·81)]. When this reaction was carried out at reflux temperature, the corresponding diketones (IV*c*) were formed.

The observation that a saturated alcohol, such as the 17β-hydroxy grouping, is stable towards manganese dioxide at room temperature opened up the way for a new synthesis of testosterone. Δ^4-Androstene-3:17-dione was reduced with lithium aluminium hydride to what is presumably essentially a mixture of Δ^4-androstene-3β:17β-diol and the 3α:17β-diol[6], which in chloroform solution with manganese dioxide at room temperature was only oxidized at C-3 to yield pure testosterone in 90% overall yield[7]. Investigation into the reaction conditions of the oxidation stage revealed that the amounts of oxide and solvent could be reduced to such an extent without loss in yield, so as to make the large-scale commercial production of testosterone by this method the simplest and most economical yet devised.

The readily available Δ^5-3β-ols (type V) with manganese dioxide in refluxing benzene were found to yield the corresponding $\Delta^{4:6}$-dien-3-ones (VII) in conversions of *circa* 30%. In this way the following dienones (VII) were prepared (properties given only for new compounds): $\Delta^{4:6}$-22a-spirostadien-3-one[8], $\Delta^{4:6}$-cholestadien-3-one, $\Delta^{4:6}$-androstadiene-3:17-dione[8], $\Delta^{4:6}$-androstadien-17β-ol-3-one (6-dehydrotestosterone), $\Delta^{4:6}$-pregnadiene-3:20-dione (6-dehydroprogesterone)[8], $\Delta^{4:6}$-pregnadien-20β-ol-3-one (m.p. 197–199°, $[\alpha]^{20}_D$ + 15°, λ^{EtOH}_{max} 282 mμ, logε 4·54, found: C, 80·41; H, 9·87), $\Delta^{4:6:16}$-pregnatriene-3:20-dione (prepared from $\Delta^{5:16}$-pregnadiene-3β:20β-diol)

[1] Steroids XXXIX. J. ROMO, A. ZAFFARONI, J. HENDRICHS, G. ROSENKRANZ, C. DJERASSI, and F. SONDHEIMER, Chem. a. Ind. *1952*, 783.

[2] Cf. S. BALL, T. W. GOODWIN, and R. A. MORTON, Biochem. J. *42*, 516 (1948). – N. L. WENDLER, H. L. SLATES, N. R. TRENNER, and M. TISHLER, J. Amer. Chem. Soc. *73*, 719 (1951). – B. C. L. WEEDON and R. J. WOODS, J. Chem. Soc. 2687 (1951). – E. A. BRAUDE *et al.*, *ibid.* 1755 (1951); 1419, 1430 (1952). – K. R. FARRAR, J. C. HAMLET, H. B. HENBEST, and E. R. H. JONES, *ibid.* 2657 (1952); R. AHMAD, F. SONDHEIMER, B. C. L. WEEDON, and R. J. WOODS, *ibid.* 4089 (1952).

[3] J. ATTENBURROW, A. F. B. CAMERON, J. H. CHAPMAN, R. M. EVANS, B. A. HEMS, A. B. A. JANSEN, and T. WALKER, J. Chem. Soc. *1952*, 1094.

[1] H. J. RINGOLD, G. ROSENKRANZ, and C. DJERASSI, J. Amer. Chem. Soc. *74*, 3318 (1952).

[2] C. DJERASSI, H. MARTINEZ, and G. ROSENKRANZ, J. Org. Chem. *16*, 1278 (1951).

[3] *Inter al.*, H. HEUSSER, K. EICHENBERGER, and PL. A. PLATTNER, Helv. chim. Acta *33*, 1088 (1950).

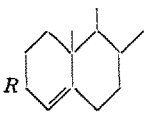
[4] *Inter al.*, V. A. PETROW, O. ROSENHEIM, and W. W. STARLING, J. Chem. Soc. *1938*, 677.

[5] The relationship between these compounds with the known corresponding 6-acetoxy-Δ^4-3-ones [M. EHRENSTEIN, J. Org. Chem. *6*, 626, 908 (1941)] will be discussed in a forthcoming detailed paper.

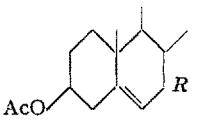
[6] Cf. W. G. DAUBEN, R. A. MICHELI, and J. F. EASTHAM, J. Amer. chem. Soc. *74*, 3852 (1952).

[7] This preferential oxidation has recently been carried out in these laboratories by means of Raney nickel in acetone, albeit in poorer yield (J. ROMO, G. ROSENKRANZ, and C. DJERASSI, to be published).

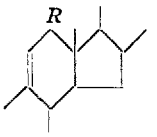
[8] Identified by comparison with an authentic specimen.



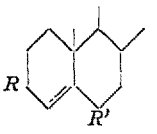
(I*a*): $R = -OH$
(I*b*): $R = =O$



(II*a*): $R = \cdots OH$
(II*b*): $R = =O$

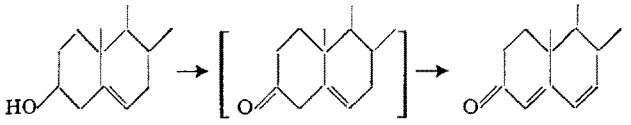


(III*a*): $R = \sim OH$
(III*b*): $R = =O$



(IV*a*): $R = R' = -OH$
(IV*b*): $R = =O$; $R' = -OH$
(IV*c*): $R = R' = =O$

(m.p. 253–256°, $[\alpha]^{20}_D$ + 144°, λ^{EtOH}_{max} 240 and 284 mμ, log ε 4·21 and 4·53 respectively, found: C, 81·58; H, 8·69), $\Delta^{4:6}$-pregnadien-17α-ol-3,20-dione[1] (m.p. 240–242°, $[\alpha]^{20}_D$ + 21°, λ^{EtOH}_{max} 284 mμ, log ε 4·53, found: C, 77·13; H, 8·77), $\Delta^{4:6}$-pregnadien-21-ol-3,20-dione acetate, and $\Delta^{4:6}$-pregnadiene-17α,21-diol-3,20-dione 21-acetate (6-dehydro Substance S acetate[1]) (m.p. 218–220°, $[\alpha]^{20}_D$ + 104°, λ^{EtOH}_{max} 284 mμ, log ε 4·48, found: C, 71·64; H, 8·15). This method for converting V to VII is similar to that of WETTSTEIN[2]. In common with the latter method it appears to proceed via the Δ^5-3-one (VI), for when such a compound (Δ^5-pregnene-3:20-dione) was treated with manganese dioxide at room temperature, the corresponding $\Delta^{4:6}$-dien-3-one (VII) was produced smoothly. The present method, although it appears to give yields similar to those obtained by the WETTSTEIN procedure, has the advantage that no D-homo rearrangement occurs with 17α-hydroxy-20-ketones, and that saturated hydroxyl groups elsewhere in the molecule do not have to be protected.



(V) (VI) (VII)

Further applications of the above described types of oxidation are being studied in these laboratories.

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Zusammenfassung

Die Oxydation gewisser Allylalkohole in der Reihe der Steroide mit MnO_2 liefert bei Zimmertemperatur die entsprechenden α,β-ungesättigten Ketone bzw. Aldehyde. Δ^4-3β, 6β-Diole werden bei Zimmertemperatur nur an C-3 angegriffen, womit eine bequeme Methode zur Darstellung der interessanten Δ^4-6β-hydroxy-3-Ketone gegeben ist.

Gesättigte Alkohole reagieren in der Kälte nicht. Daraus ergibt sich eine neue Synthese des Testosterons in 90prozentiger Ausbeute, ausgehend von Δ^4-Androsten-3, 17-dion: Reduktion dieser Verbindung mit $LiAlH_4$ und MnO_2-Oxydation des entstandenen Diolgemisches. MnO_2-Oxydation von Δ^5-3β-hydroxy Steroiden, vorzugsweise unter Erwärmung, liefert $\Delta^{4:6}$-Dien-3-Ketone.

[1] That no D-homo rearrangement had occurred was indicated by the fact that 17α-hydroxy-20-ones were unaffected when subjected to the conditions employed for the preparation of this substance.

[2] A. WETTSTEIN, Helv. chim. Acta *23*, 388 (1940).

Über die Struktur der nativen D-Polyglutaminsäure

Die Konstitutionsfrage der nativen D-Polyglutaminsäure, die in einheitlichem Zustand zuerst von IVÁNOVICS und BRUCKNER[1] isoliert wurde, ist noch umstritten. Bewiesen ist nur, dass die D-Polyglutaminsäure beider Herkunft, nämlich aus der Kapsel der Milzbrandbazillen und aus dem Nährboden der Bac.-subtilis-Gruppe angehörenden Sporenträger, ein vollständig aus Glutaminsäure-Resten aufgebautes Polypeptid darstellt[2], wie dies schon früher angenommen wurde[3]. Umstritten blieb noch die Frage, ob die Glutaminsäure in Form von α-Glutamyl- (IV) oder γ-Glutamyl-Resten in das Polypeptid eingebaut ist[4]. Besonders eingehend erörterten diese Frage HANBY und RYDON[5] und kamen zum Schluss, dass aus der Milzbrandbazillen-Kapsel gewonnene Präparate verhältnismässig kleineren Molgewichtes (zum Beispiel 6000) nur α-Gutamyl-Bindungen (IV) enthalten können, während in Präparaten höhern Molgewichtes stellenweise, jedoch in untergeordnetem Masse, auch γ-Glutamylketten (I) eingebaut sein können.

Wir haben vor kurzem gezeigt[6], dass der Curtiussche Abbau und eine darauffolgende saure Hydrolyse des Polyhydrazids der aus geeigneten Bac.-subtilis-Stämmen isolierten D-Polyglutaminsäure vom durchschnittlichen Molgewicht 6400 (die nach serologischen und analytischen Belegen mit der aus der Milzbrandbazillen-Kapsel isolierten D-Polyglutaminsäure ungefähr gleichen Molgewichtes gleich zu sein scheint[1]) in präparativ nachweisbarer Menge nur β-Formylpropionsäure (III), jedoch keine α·γ-Diaminobuttersäure (VI) liefert. Daraus wurde auf das Vorherrschen der γ-Glutamyl-Bindungen geschlossen, um so mehr, da der analoge Abbau des Polyhydrazids synthetisch gewonnener α-L-Polyglutamin-

[1] G. IVÁNOVICS und V. BRUCKNER, Naturwissenschaften *25*, 250 (1937); Z. Immunforsch. *90*, 304; *91*, 175 (1937).

[2] M. BOVARNICK, J. Biol. Chem. *145*, 415 (1942). – W. E. HANBY und H. N. RYDON, Biochem. J. *40*, 297 (1946). – G. PONGOR, Exper. *6*, 421 (1950).

[3] G. IVÁNOVICS und V. BRUCKNER, Naturwissenschaften *25*, 250 (1937); Z. Immunforsch. *90*, 304; *91*, 175 (1937). – V. BRUCKNER, G. IVÁNOVICS und M. KOVÁCS OSKOLÁS, Magyar. Chem. Folyóirat *45*, 131 (1939); vgl. Chem. Zentr. *1*, 3280 (1940) und Chem. Abstr. *34*, 3766 (1940). – V. BRUCKNER und M. KOVÁCS OSKOLÁS, Acta Univ. Szegediensis (Chem. et Phys.) *1*, 144 (1943); vgl. Chem. Abstr. *41*, 7423 (1947).

[4] M. BOVARNICK, J. Biol. Chem. *145*, 415 (1942). – W. E. HANBY und H. N. RYDON, Biochem. J. *40*, 297 (1946). – V. BRUCKNER, G. IVÁNOVICS und M. KOVÁCS OSKOLÁS, Magyar Chem. Folyóirat *45*, 131 (1939); vgl. Chem. Zentr. *1*, 3280 (1940) und Chem. Abstr. *34*, 3766 (1940). – V. BRUCKNER und M. KOVÁCS OSKOLÁS, Acta Univ. Szegediensis (Chem. et Phys.) *1*, 144 (1943); vgl. Chem. Abstr. *41*, 7423 (1947). – H. N. RYDON, Biochemical Society Symposia, Nr. 1, S. 42 (Cambridge 1948).

[5] W. E. HANBY und H. N. RYDON, Biochem. J. *40*, 297 (1946).

[6] J. KOVÁCS und V. BRUCKNER, Research *5*, 194 (1952); Chem. Soc. *1952*, 4255.