Zusammenfassung

Das anatomische Substrat der durch rhythmische Reizung der interlaminaren Nuclei des Thalamus hervorgerufenen «Rekrutierung» (recruiting responses) wird beschrieben. Weiterhin wird der Mechanismus der Ausbreitung der kortikalen Synchronisierung in beiden Hemisphären und die subkortikale Lokalisation der hierfür verantwortlichen Synapsen dargelegt. Zum Schluß werden die Beziehungen zwischen den Nuclei des intralaminären Thalamus und der Synchronisierung der bioelektrischen Erscheinungen in den kortikalen Neuronen besprochen.

Brèves communications - Kurze Mitteilungen Brevi comunicazioni - Brief Reports

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Steroids XV[1]. The Bromination of 3-Ketosteroids of the Normal Series

The behavior of 3-keto*allo*steroids (rings A/B *trans*) towards mono- or di-bromination (monobromination at C-2; dibromination at 2,2 followed by rearrangement to the 2,4-isomer) has been established unequivocally, principally by investigating the products obtained on collidine dehydrobromination[2]. The dehydrobromination products of such 2,4-dibromo-3-keto*allo*steroids, the 1,4-dien-3-ones (IV), represent the key intermediates for the partial synthesis[3] of estrogenic hormones on an industrial scale.

The bromination of 3-ketosteroids of the normal series (rings A/B cis) (I) has been interpreted[4] as proceeding through a 4-bromo derivative to a 4,4-dibromo compound (II) and hence the steroids of the *normal* series (coprostane, etiocholanes, pregnanes, etc.) were considered unsuitable as starting materials for the synthesis of the estrogens[5]. BUTENANDT[6] postulated that monobromination of *normal* steroids such as coprostanone (Ia) results exclusively in substitution at C-4, because pyridine dehydrobromination leads to Δ^4-3-ketosteroids. However, the poor yields in the latter reaction do not exclude the presence of some 2-bromo derivative, particularly since pyrolysis of 2-bromosteroidal pyridinium salts is known to yield Δ^4-3-ketones[1]. The recently described[2] dehydrobromination of mono-bromo *normal* ketones to the Δ^4-3-ketosteroids in nearly quantitative yield lends considerable support to BUTENANDT's formulation[3], but at the same time it has also been demonstrated[4] that some substitution occurs simultaneously at C-2 during the bromination. As is to be expected on mechanistic grounds, bromination should follow the same course as sulfonation and the work of WINDAUS[5] on the sulfonation of coprostanone at C-4 *and C-2* supports the belief, contrary to statements in the literature[6], that substitution at C-2 in steroids of the *normal* series (I) is possible. Since the 4,4-dibromo formulation (II)[7] rests primarily on evidence (reaction with *o*-phenylenediamine, potassium benzoate etc.) which is notoriously unreliable because of facile rearrangements, we have investigated the reaction of dibromo-3-keto*normal* steroids with collidine. The recent report of INHOFFEN[8] prompts us to communicate our results at this time.

Dibromocoprostanone[7] (90% yield in acetic acid; melting point 136–137°, $[\alpha]_D^{20} + 10°$) exhibits an infrared band[9] at 1756 cm^{-1} typical of 2,4-dibromo-3-ketoallosteroids[10] (gem-dibromo derivatives, such as 2,2-dibromo-3-ketones, possess one at 1739 cm^{-1}). Collidine dehydrobromination (1·6–1·8 moles collidine hydrobromide isolated), followed by chromatography and spectrophotometric analysis of the chromatogram

[1] Steroids XIV: O. MANCERA, G. ROSENKRANZ, and C. DJERASSI, J. Org. Chem. (in press).

[2] H. H. INHOFFEN, Angew. Chem. *59*, 207 (1947) and references cited therein. – C. DJERASSI and C. R. SCHOLZ, J. Amer. Chem. Soc. *69*, 2404 (1947); J. Org. Chem. *13*, 697 (1948).

[3] H. H. INHOFFEN, Angew. Chem. *59*, 207 (1947) and references cited therein. – A. L. WILDS and C. DJERASSI, J. Amer. Chem. Soc. *68*, 2125 (1946). – C. DJERASSI and C. R. SCHOLZ, *ibid.* *71*, 3962 (1949). – E. B. HERSHBERG, M. RUBIN, and E. SCHWENK, J. Org. Chem. *15*, 292 (1950).

[4] A. BUTENANDT *et al.*, Ber. Dtsch. chem. Ges. *69*, 2779 (1936). – L. RUZICKA *et al.*, Helv. chim. acta *19*, 1147 (1936). – H. H. INHOFFEN, G. STOECK, and I. U. NEBEL, Ann. Chemie *563*, 135 (1949). On the basis of the present results INHOFFEN's diketone of melting point 116–117° is most likely coprostane-2,3-dione.

[5] H. H. INHOFFEN, Angew. Chem. *59*, 207 (1947) and references cited therein. – H. H. INHOFFEN and G. STOECK, Exper. *4*, 426 (1948).

[6] A. BUTENANDT and A. WOLFF, Ber. Dtsch. chem. Ges. *68*, 2091 (1935) and later papers.

[1] L. RUZICKA, PL. PLATTNER and R. AESCHBACHER, Helv. chim. acta, *21*, 866 (1938).

[2] V. R. MATTOX and E. C. KENDALL, J. Amer. Chem. Soc. *70*, 882 (1948). – C. DJERASSI *ibid.*, *71*, 1003 (1949).

[3] A. BUTENANDT and A. WOLFF, Ber. Dtsch. chem. Ges. *68*, 2091 (1935) and later papers.

[4] V. R. MATTOX and E. C. KENDALL, J. Biol. Chem. *185*, 593 (1950).

[5] A. WINDAUS *et al.*, Ann. Chemie *532*, 52 (1937); *ibid.* *536*, 116 (1938).

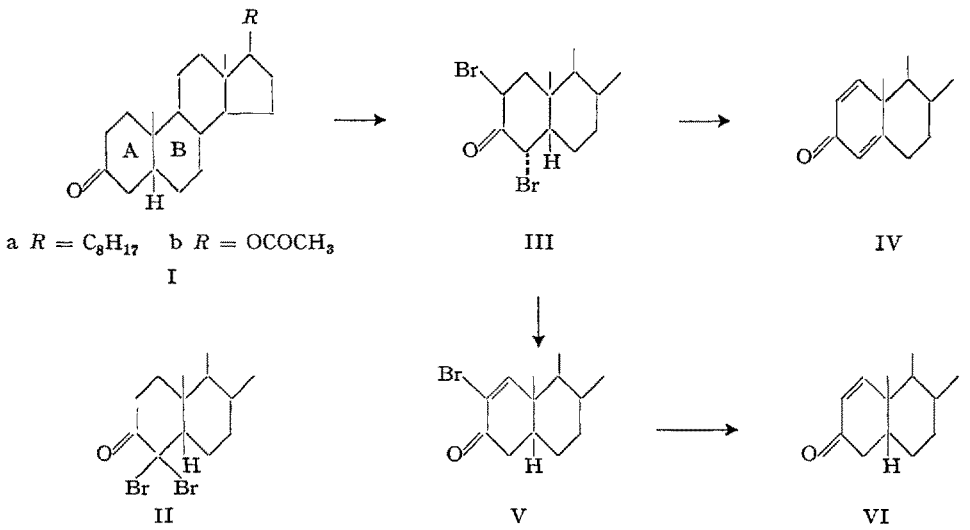
[6] H. H. INHOFFEN, Angew. Chem. *59*, 207 (1947) and references cited therein.

[7] A. BUTENANDT *et al.*, Ber. Dtsch. chem. Ges. *69*, 2779 (1936). – L. RUZICKA *et al.*, Helv. chim. acta *19*, 1147 (1936). – H. H. INHOFFEN, G. STOECK, and I. U. NEBEL, Ann. Chemie *563*, 135 (1949).

[8] H. H. INHOFFEN *et al.*, Chem. Z. *74*, 309 (1950).

[9] Kindly carried out by Dr. K. DOBRINER, Sloan-Kettering Institute for Cancer Research, New York City.

[10] R. N. JONES, P. HUMPHRIES, and K. DOBRINER, J. Amer. Chem. Soc. *72*, 956 (1950).



a $R = C_8H_{17}$ b $R = OCOCH_3$

I III IV

II V VI

fractions[1] yielded *ca.* 25% of 1,4-cholestadien-3-one (IVa)[2] and 8% of a *substance*, $C_{27}H_{43}OBr$ (found: C, 70·26; H, 9·31; Br, 17·24), with melting point 133·5–135·5°, $[\alpha]_D^{20}$ + 53° (chloroform), u.v. maximum at 256 mμ (log ε 3·87), infrared band[3] at 1697 cm^{-1}. The absorption spectra are fully consistent with the formulation V, Δ^1-2-bromocoprosten-3-one, a C-5 diastereoisomer of Δ^1-2-bromocholesten-3-one[4], which exhibits maxima at 256 mμ and 1697 cm^{-1} [5]. Debromination with zinc in ethanol afforded Δ^1-coprosten-3-one (VIa), $C_{27}H_{44}O$ (found: C, 84·00; H, 11·25), melting point 101°, u.v. maximum at 230 mμ (log ε 4·01), infrared band at 1685 cm^{-1}. The physical constants of this substance are again in concordance with the spectral results observed for the isomeric Δ^1-3-ketoallosteroids[6]. Similarly, dibromination of etiocholanolone acetate (Ib) in acetic acid led in nearly quantitative yield to dibromoetiocholan-17β-ol-3-one-17-acetate[7], $C_{21}H_{30}O_3Br_2$ (found: C, 51·32; H, 6·23; Br, 32·49) with melting point 204–205°, $[\alpha]_D^{20}$ + 8° (chloroform), infrared bands at 1739 cm^{-1} (acetate) and 1756 cm^{-1}, which on dehydrobromination with collidine (1·7 moles of collidine hydrobromide isolated) gave 9% of Δ^1-2-bromoetiocholen-17β-ol-3-one 17-acetate, (Vb) $C_{21}H_{29}O_3Br$ (found: C, 61·81; H, 7·31) with melting point 223–225°, $[\alpha]_D^{20}$ + 80° (chloroform), u.v. maximum at 256 mμ (log ε 4·05) and 34% of 1,4-androstadien-17β-ol-3-one 17-acetate (IVb), melting point 149–151°[8], identified after saponification by direct comparison with an authentic sample of 1,4-androstadien-17β-ol-3-one[9], melting point 167 to 169°, and by dienone-phenol rearrangement to the known aromatic phenols[1]. The formation of 1,4-dien-3-ones (IV) from 3-keto*normal*steroids (I) thus makes possible the direct synthesis of the female sex hormones from this important class of steroids, a reaction which has previously been carried out only indirectly[2] via the intermediate Δ^4-3-ketosteroids.

While it is not possible with absolute certainty to exclude the earlier 4,4-dibromo structure (II)[3], since hypothetical rearrangement products could be postulated to account for the formation of the dehydrobromination products, the present evidence coupled with the infrared results strongly suggests[4] that the dibromination products of the normal series are the 2,4-dibromo-3-ketones (III). The same conclusion has been put forward by GALLAGHER *et al.*[5], on the basis of infrared spectra and by INHOFFEN[6] on account of the isolation of 1,4-dien-3-ones (IV) by collidine dehydrobromination similar to the one described in this communication. The present isolation in poor yield of the previously unknown Δ^1-2-bromo-3-keto*normal* steroids (V) can be rationalized by either assuming the presence of a small amount of 2,2-dibromo-3-ketone in the original dibromo ketone or an *in situ* rearrangement to such a structure in the collidine reaction. As we have already demonstrated in the case of Δ^4-3-ketosteroids[2], contrary to earlier assumption[7], substitution can occur at C-2 in 3-keto-

[1] A.L.WILDS and C.DJERASSI, J. Amer. Chem. Soc. *68*, 1712 (1946).

[2] H.H.INHOFFEN, Angew. Chem. *59*, 207 (1947) and references cited therein. – A.L.WILDS and C.DJERASSI, J. Amer. Chem. Soc. *68*, 1712 (1946).

[3] Kindly carried out by Dr. K. DOBRINER, Sloan-Kettering Institute for Cancer Research, New York City.

[4] C.DJERASSI and C.R.SCHOLZ, J. Amer. Chem. Soc. *69*, 2404 (1947).

[5] H.H.INHOFFEN, Angew. Chem. *59*, 207 (1947) and references cited therein. – C.DJERASSI and C.R.SCHOLZ, J. Amer. Chem. Soc. *69*, 2404 (1947); J. Org. Chem. *13*, 697 (1948). – R.N.JONES, P. HUMPHRIES, and K.DOBRINER, J. Amer. Chem. Soc. *72*, 956 (1950).

[6] See Note 10, page 93, right column.

[7] B.A.KOECHLIN, T.H.KRITCHEVSKY, and T.F.GALLAGHER, J. Biol. Chem. *184*, 393 (1950) recently isolated this compound in an impure state as a byproduct in the monobromination of Ib.

[8] H.H.INHOFFEN, G.ZUEHLSDORFF, and HUANG MINLON, Ber. Dtsch. chem. Ges. *73*, 451 (1940).

[9] A.L.WILDS and C.DJERASSI, J. Amer. Chem. Soc. *68*, 2125 (1946).

[1] H.H.INHOFFEN, Angew. Chem. *59*, 207 (1947) and references cited therein. – A.L.WILDS and C.DJERASSI, J. Amer. Chem. Soc. *68*, 2125 (1946). – Cf. C.DJERASSI, G. ROSENKRANZ, J. ROMO, J. PATAKI, and ST. KAUFMANN, *ibid.* *72*, 4540 (1950).

[2] G.ROSENKRANZ, C.DJERASSI, ST.KAUFMANN, J.PATAKI, and J.ROMO, Nature *165*, 814 (1950). – C.DJERASSI, G. ROSENKRANZ, J. ROMO, ST. KAUFMANN, and J. PATAKI, J. Amer. Chem. Soc., *72*, 4534 (1950).

[3] A.BUTENANDT *et al.*, Ber. Dtsch. chem. Ges. *69*, 2779 (1936). – L.RUZICKA *et al.*, Helv. chim. acta *19*, 1147 (1936). – H.H.INHOFFEN, G.STOECK, and I.U.NEBEL, Ann. Chemie *563*, 135 (1949).

[4] It should be remembered that the infrared values obtained earlier (R. N. JONES et al., loc. cit.) refer to the *allo* series and that the present deductions based on these values represent circumstantial but not conclusive evidence.

[5] B. A. KOECHLIN, T. H. KRITCHEVSKY, and T. F. GALLAGHER. J. Biol. Chem. *184*, 393 (1950).

[6] H. H. INHOFFEN *et al.*, Chem. Z. *74*, 309 (1950).

[7] H.H.INHOFFEN, Angew. Chem. *59*, 207 (1947) and references cited therein.

steroids regardless of the steric configuration of the A/B ring juncture.

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Research Laboratories, Syntex, S.A., Laguna Mayran 413, Mexico City, D.F., August 9, 1950.

Zusammenfassung

Die Bromwasserstoffabspaltung aus den bisher als 4,4-Dibrom-Verbindungen aufgefaßten *normalen* Dibrom-3-ketosteroiden führt zur Bildung von 1,4-Dien-3-onen (IV), welche bisher nur aus 2,4-Dibrom-3-keto*allo*steroiden erhalten worden waren. Daneben entstehen kleine Mengen von Δ^1-2-Brom-3-keto*normal*steroiden (V). Die Ergebnisse der vorliegenden Arbeit, die überdies durch UV- und Infrarotspektren gestützt sind, machen es äußerst wahrscheinlich, daß die Dibromierung der *normalen* 3-Ketosteroide in 2,4-Stellung erfolgt. Die in dieser Arbeit beschriebene Herstellung von 1,4-Dien-3-onen (IV) der Steroid-Reihe erweist sich somit als eine zweite Methode[1] zur partiellen Synthese östrogener Hormone, ausgehend von Steroiden der *normalen* Serie.

[1] G. ROSENKRANZ, C. DJERASSI, ST. KAUFMANN, J. PATAKI, and J. ROMO, Nature *165*, 814 (1950). – C. DJERASSI, G. ROSENKRANZ, J. ROMO, ST. KAUFMANN und J. PATAKI, J. Amer. Chem. Soc., *72*, 4534 (1950).

The Action of *t*-Butyl Hypochlorite on 1-Methyl-4-isopropyl-3-cyclohexene [*p*-Menthene-(3)]

For the reaction of α-pinene with *t*-butyl hypochlorite, RITTER and GINSBURG[1] have proposed a mechanism which involves addition of the reagent to the double bond and subsequent elimination of *t*-butanol. This mechanism suggested a number of interesting synthetic possibilities in the terpene series.

Table I

Compound	b.p.	n_D^{25}	d_{25}	$(\alpha)_D^{25}$
Menthenyl chloride A	90–94°/12 mm	1·4982[1]	1·033[2]	–0·74°
Menthenyl chloride B	102–105°/12 mm	1·4934[1]	0·955[2]	–0·69°
Menthenol A	105°/36 mm	1·4719	0·913	–4·52°
Menthenol B	95°/36 mm	1·4650	0·930	–1·06°
Menthenone A . . .	95–100°/23 mm	1·4864	0·935	
Menthenone B . . .	105–110°/23 mm	1·4798	0·941	

[1] n_D^{20}; [2] d_{20}

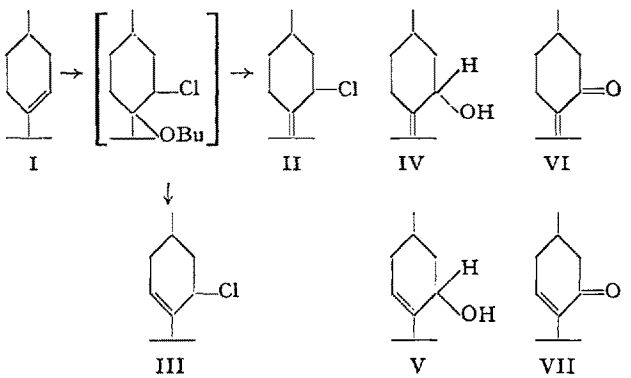
Table II

Dinitrophenylhydrazone	λmax calculated	λmax found	εmax found
Menthenone A (VI) . .	3860	3860	18,800
Menthenone B (VII) . .	3810	3820	30,800

[1] J. J. RITTER and D. GINSBURG, J. Amer. Chem. Soc., *72*, 2381 (1950).

From *p*-menthene-(3) (I), two isomeric chloromenthenes were obtained, which were separated by fractional distillation. Both of them were *secondary* chlorocompounds, as both corresponding alcohols (obtained by alkaline hydrolysis, and purified through the benzoates) could be oxidised to *ketones* by OPPENAUER's method. The physical constants of the substances isolated are summarized in Table I.

Both ketones were α,β-*unsaturated*, as the colour and the absorption spectrum of their 2,4-dinitrophenylhydrazones indicated. Using the data reported by BRAUDE and JONES[1], even more definite conclusions can be drawn, as to the *structure* of these unsaturated ketones, from the exact location of the ultraviolet absorption maxima and their extinction coefficients: both are dependent on the degree of substitution of the absorbing system C=C–C=N. From the data in Table II, it can be concluded that one of the dinitrophenylhydrazones belongs to the type $R_2C{=}CR{\cdot}CR{=}N$, the other to the type $R{\cdot}CH{=}CR{\cdot}CR{=}N$. The former could, therefore, be *pulegone* (VI), the latter *1-methyl-4-isopropyl-4-cyclohexen-3-one* (VII); their formation would be easily understood from the following reaction scheme:



As, however, no data are available regarding the spectral properties of the dinitrophenylhydrazones of these ketones, especially of the–somewhat unusual–type (VI), further evidence is being sought by conventional, chemical methods.

DAVID GINSBURG

Daniel Sieff Research Institute, Weizmann Institute of Science, Rehovoth, Israel, August 27, 1950.

Résumé

Les formules (II) et (III) sont proposées pour deux chlorures secondaires obtenus par l'action de l'hypochlorite de butyl tertiaire sur le *p*-menthène-(3) (I). La transformation de ces chlorures en deux cétones α,β-nonsaturées, par hydrolyse et déhydrogénation, confirme ces formules.

[1] E. A. BRAUDE and E. R. H. JONES, J. Chem. Soc., 498 (1945).

Etude de la molécule d'acide thymonucléique par des mesures de biréfringence d'écoulement dans des solvants de viscosité variable[1]

On admet généralement qu'une molécule en chaîne peut affecter suivant sa structure chimique et suivant la nature du solvant, des formes très variables, depuis le bâtonnet quasi-rigide jusqu'au peloton souple et recro-

[1] Une publication détaillée paraîtra dans un autre recueil.