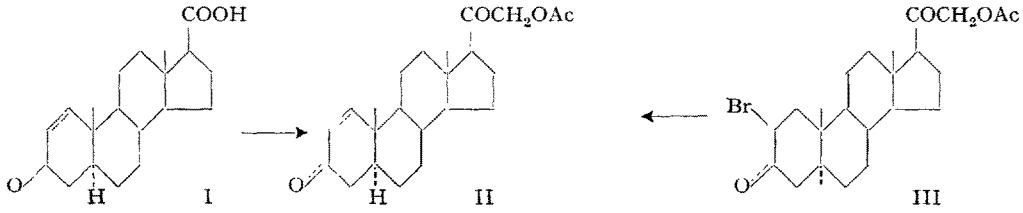
Δ^1-Desoxycorticosterone Acetate

The recent interest[1] in analogues of desoxycorticosterone acetate prompts us to record the synthesis and biological activity of Δ^1-*allo*pregnen-21-ol-3,20-dione 21-acetate (II), for which the trivial name "Δ^1-desoxycorticosterone acetate" is suggested.



Δ^1-3-Ketoetio*allo*cholenic acid (I), obtained by saponification of the corresponding methyl ester[2], was converted to the acid chloride by the oxalyl chloride method[3] and thence with diazomethane to the crystalline Δ^1-diazoprogesterone (m. p. 183–185° with gas evolution). Decomposition of the latter in boiling acetic acid solution gave a 50% overall yield (based on the acid I) of Δ^1-desoxycorticosterone acetate (II), m. p. 215–217°, $[\alpha]_D^{26} = +139°$ (chloroform), (Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74·16; H, 8·66; acetyl, 11·55. Found: C, 74·17; H, 8·64; acetyl, 11·10). The product exhibited an ultra-violet absorption maximum at 229 mμ, log ε 4·08, typical of Δ^1unsaturated 3-ketosteroids[2], and the $\Delta[M]_D$ value[4] of +69 was in excellent agreement with that observed[5] (+67) for ketones of this class. The diketone II could also be prepared by collidine dehydrobromination of 2-bromo-21-acetoxy-*allo*pregnane-3,20-dione (III) (m. p. 188–190° dec.), which was obtained by brominating 21-acetoxy*allo*pregnane-3,20-dione in glacial acetic acid with pyridine hydrobromide perbromide[6].

Δ^1-Desoxycorticosterone acetate (II) was tested in oil solution for life maintenance in adrenalectomized rats and proved to possess approximately one-fifth the activity of Δ^4-desoxycorticosterone acetate. It is interesting to note that the corresponding saturated derivative was found by WETTSTEIN and HUNZIKER[4] to be inactive when tested in twenty times the effective dose of Δ^4-desoxycorticosterone acetate. A comparison between the Δ^1-isomers and the natural hormones in the cortical, progestational and androgenic steroid series demonstrates that a shift of the double bond from the 4,5 to the 1,2 positions seems to have the least effect in the cortical hormone series as compared to the gestagens[7] (one-sixteenth the activity of progesterone) and androgens[1] (one-thirteenth the activity of testosterone).

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Zusammenfassung

Die Herstellung von Δ^1-Desoxy-corticosteronacetat wird beschrieben. Beim Übergang vom gewöhnlichen Desoxy-corticosteronacetat (Δ^4) zu dieser hinsichtlich der Lage der Doppelbindung isomeren Verbindung tritt ein Abfall der Wirkung im Überlebenstest an adrenalektomierten Ratten auf $^1/_5$ ein.

[1] See K. MIESCHER, Recent Progress in Hormone Research (Proceedings of the Laurentian Hormone Conference) *3*, 47 (1948) (or a review on the relation between structure and activity of the sex hormones.

[1] CH. MEYSTRE and A. WETTSTEIN, Helv. chim. acta *31*, 1890 (1948). – v. J. EUW and T. REICHSTEIN, ib. *31*, 2076 (1948).

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

[3] A.L. WILDS and C. H. SHUNK, J. Amer. Chem. Soc. *70*, 2427 (1948).

[4] For the calculation of this value, it is necessary to use the rotation of 21-acetoxy*allo*pregnane-3,20-dione. This known compound [see A. WETTSTEIN and F. HUNZIKER, Helv. chim. acta *23*, 764 (1940) who reported $[\alpha]_D = \pm 115° + 2°$ (chloroform)] was synthesized in this laboratory by the Wilds-Shunk procedure (ref. 3) from 3-ketoetio*allo*cholanic acid and was found to have $[\alpha]_D^{26} = \pm 120° + 1°$ (chloroform).

[5] C. DJERASSI, J. Org. Chem. *12*, 823 (1947).

[6] C. DJERASSI and C. R. SCHOLZ, J. Amer. Chem. Soc. *70*, 417 (1948).

[7] See K. MIESCHER, Recent Progress in Hormone Research (Proceedings of the Laurentian Hormone Conference) *3*, 47 (1948) for a review on the relation between structure and activity of the sex hormones.

The Injection of Embryonic Microsomes into early Amphibian Embryos[1]

Among the many hypotheses which have been advanced to explain the mode of action of the embryonic organizer is the idea, independently put forward by DALCQ[2] and by NEEDHAM[3], that there might be a similarity between the induction of a nervous system and the spreading of a virus infection. As has been noted by one of us (BRACHET[4]), if there is anything comparable to a virus in the embryo, we should expect to find it in the form of particles comparable in size and chemical composition to viruses. These criteria describe the so-called microsome fraction of CLAUDE[5], the composition of which has been studied by CLAUDE, BRACHET and JEENER[6], CHANTRENNE[7], and by many others, all of whom found that these granules are composed of ribonucleic acid associated with proteins (including enzymes) and lipids.

In order to test the possible morphogenetic activity of these particles, they were isolated from breis of frog gastrulæ or neurulæ in the following way. Embryos homogenized in ice-cold dilute phosphate buffer were centrifuged for ten minutes at 6,000 × *g* in order to get rid of the yolk, nuclei and pigment granules. The supernatant fluid was then centrifuged for twenty minutes at 18,000 × *g*, and the resultant pellets of granules were suspended in a small volume of dilute

[1] Aided by a grant from the American Philosophical Society.

[2] A. DALCQ, *L'œuf et son dynamisme organisateur* (Albin Michel, Paris 1941), p. 492, 526.

[3] J. NEEDHAM, *Biochemistry and Morphogenesis* (Cambridge, 1942), p. 268.

[4] J. BRACHET, *Embryologie chimique* (Desoer, Liège 1945).

[5] A. CLAUDE, Biol. Symp. *10*, 111 (1943).

[6] J. BRACHET and R. JEENER, Enzymologia, *11*, 196 (1944).

[7] H. CHANTRENNE, Biochim. et biophys. acta, *1*, 437 (1947): Enzymologia *11*, 213 (1944).