Hingegen besteht eine Korrelation zwischen der acetylierenden Wirkung[5] und dem im Blut enthaltenen Coenzym A. Aus einer Gruppe von 28 Untersuchungen erhält man einen Korrelationskoeffizienten von $r = +0{,}6244$ ($P \sim 0{,}001$). Diese Untersuchungen lassen uns zum Schluss kommen, dass das im Blut vorhandene Coenzym A zum grössten Teil in den Leucozyten und vielleicht auch in den Thrombozyten enthalten ist; hingegen ist der Gehalt im Plasma und in den Erythrozyten niedrig.

Diese Befunde stehen vielleicht in Beziehung zu kürzlich veröffentlichten Untersuchungen, wonach die Synthese der Lipoide – ein Vorgang, in welchem das Coenzym A eine erste Rolle spielt – im zirkulierenden Blut vorwiegend in den Leucozyten und in geringerem Grade in den Thrombozyten stattfindet, während sie in den reifen Erythrozyten und im Plasma fast ganz fehlt[6,7].

Riassunto. Il Coenzima A nel sangue di soggetti leucemici, in particolare con leucemia mieloide, appare nettamente aumentato in confronto al sangue normale.

Il Coenzima A è contenuto in prevalenza nei leucociti e probabilmente anche nelle piastrine, mentre è scarso nel plasma e nei globuli rossi.

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C16-Methyl Derivatives of Progesterone and 17α-Acetoxyprogesterone: Preparation and Biological Activities

In view of the recent publication[1] describing the preparation of certain C16-methyl steroids, we wish to report here the progestational activities associated with several derivatives of 16α-methylprogesterone prepared in these Laboratories.

In Table I are given the comparative biological activities of 16α-methylprogesterone[2] (I) and its 2α-methyl (II)-, 6α-methyl (III)[3]- and 6α-fluoro (IV)-derivatives. Also included are the physical properties of the newly prepared compounds II and IV. 2α,16α-Dimethylprogesterone (II) was obtained by alkylation[4] of the C2-glyoxylic ester of 16α-methyl-progesterone (I). 6α-Fluoro-16α-methylprogesterone was prepared by employing either the epoxide-hydrofluoric acid[5] or the N-bromoacetamide-hydrofluoric acid[6] techniques for the introduction of the C6-fluorine atom, each utilizing 16α-methylpregnenolone[2] as starting material.

Summarized in Table II are the biological activities and physical properties of the 16α-methyl derivatives of 17α-hydroxyprogesterone. 16α-Methyl-17α-hydroxyprogester-

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Tab. I. Subcutaneous progestational activity – Clauberg assay[a]

Compound	M.P. °C	$[\alpha]_D$ ($CHCl_3$)	λ_{max}^{MeOH} mµ (ε)	Approx. activity (Progesterone = 1)
16α-Methylprogesterone (I)	135–138.5	+ 160°	240 (16900)	1
2α,16α-Dimethylprogesterone (II)[b]	151–152	+ 169°	240 (14800)	inactive[c]
6α,16α-Dimethylprogesterone (III)	113–116.5	+ 145°	242 (16100)	1
6α-Fluoro-16α-methylprogesterone (IV)	144–146	+ 18°	236 (14900)	1

[a] Assays were performed by the Endocrine Laboratories, Madison (Wisconsin, U.S.A.) and the MacPhail modification of the Clauberg assay was used. [b] All new compounds recorded therein have been satisfactorily characterized by elemental analysis. [c] i.e. at a 1 mg total dose level.

Tab. II. Oral progestational activity – Clauberg assay[a]

Compound	M.P. °C	$[\alpha]_D$ ($CHCl_3$)	λ_{max}^{MeOH} mµ (ε)	Approx. activity (17α-Acetoxyprogesterone = 1)
16α-Methyl-17α-hydroxyprogesterone (V)[b]	180–183.5	+ 86°	242 (17200)	inactive[c]
16α-Methyl-17α-acetoxyprogesterone (VI)	233–236	+ 80°	242 (15200)	1
16α-Methyl-6-dehydro-17α-acetoxy-progesterone (VII)	212–214	+ 15°	283 (26100)	15
16α-Methyl-1-dehydro-17α-acetoxy-progesterone (VIII)	227–228	+ 30°	244 (15000)	8
16α-Methyl-1,6-bisdehydro-17α-acetoxy-progesterone (IX)	213–214	– 18°	221 (13900) 257 (12100) 299 (14000)	66

[a] See Table I, footnote [a]. [b] See Table I, footnote [b]. [c] i.e. at a 1 mg total dose level.

one[7] (V) was prepared from 16α-methyl Reichstein's Substance S[8,9] by reduction[10] of the 21-tosylate of the latter. Compound V was also prepared in a seven-stage synthesis from 16α-methylpregnenolone acetate[2] *via* the intermediate 5α,6α-epoxy-17α-hydroxy-16α-methylpregnanolone benzoate [m.p. 228–230°, $[\alpha]_D = -49°$ ($CHCl_3$)]. Acetylation of the 17α-hydroxyl group provided the 17α-acetate (VI). Bromination[11] of the enol ether of the latter with subsequent dehydrobromination with calcium carbonate in dimethylformamide[11] gave 16α-methyl-6-dehydro-17α-acetoxyprogesterone (VII). Dehydrogenation of VI and VII with 2,3-dichloro-5,6-dicyanobenzoquinone[12] gave 16α-methyl-1-dehydro-17α-acetoxyprogesterone (VIII)[1] and 16α-methyl-1,6-*bis*dehydro-17α-acetoxyprogesterone (IX), respectively.

Whereas a large increase in antiinflammatory activity has been associated with the introduction of a C16-methyl group in the corticoid series[13], in no instance have we observed a pronounced increase in oral or subcutaneous progestational activity of the methylated progesterone over the corresponding desmethyl compound.

Zusammenfassung. Mehrere Derivate des 16α-Methylprogesteron wurden synthetisiert und biologisch geprüft. Die Einführung einer C16α-Methylgruppe ergab keine gesteigerte Progesteronaktivität in den getesteten Verbindungen.

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Structural Basis of Nucleolar Function

Due to the lack of a definite concept as to whether structure or function is basic to the study of biological organization of cells[1,2], an integrated approach is the accepted operational choice of biologists to-day. Accordingly, studies on structure and function are expected to proceed concurrently in a balanced sequence. Recently, some valuable contributions have been made on the (hetero)chromatin- nucleolus- protein synthesis relationships[3–7]. Curiously, however, the exquisite details of the fine structure of nucleolus are still lacking.

In the present study[8], some structural facets have been described by making a survey of extensive cytological changes that take place in the ophidian oocytes during their formation and development. The ophidian ovary was selected as being cytologically the least explored ovary. Moreover, the structural differentiation of the oocyte is perhaps the simplest. Yet, the biocytological processes cover a wide range of activities illustrative of cellular growth[9,10]. The study has revealed some architectural patterns peculiar to nucleolar function.

Nucleolar behaviour. A recounting of the chain of events during the formation and maturation of the oocytes would reveal some interesting features of nucleolar organization. The early oocytes may be distinguished by the possession of a prominent coiled spireme within the nucleus during the prophase stages. At these stages, there is no indication of the presence of nucleolus. Later, a single nucleolus makes its appearance enmeshed in a loose reticulum of achromatic strands in close association with the suspended chromatin material (Figure 1). Thus, in the early stages of its formation, the nucleolus appears homogeneous. It is negative to the Feulgen reaction and has, therefore, no indications of DNA constituents. In advanced oocytes, commensurate with the growth of the oocyte, the nucleolus grows to a considerable size and soon begins to bud off several smaller bodies. The budding process of the nucleolus is shown in Figures 2 and 3. This process of actual budding has rarely been described. The nucleolar derivatives are more or less of the same size. But exceptions to this may be found. The daughter nucleolar bodies come to lie near the nuclear membrane and are eventually extruded into the cytoplasm. In Figure 3, the much enlarged nucleolus is shown to be differentially stained. The central part is deeply stained while the outer part is lighter. This difference can be interpreted as due to variable concentrations of its constituent substances *or* to its duplex nature. Figures 2 and 3 also show in a clear manner the formation of daughter nucleolar bodies from the principal nucleolus, indicating that these daughter nucleolar bodies are not formed from any other source. The nucleolar organizers, which in earlier phases might be importantly concerned in the origination of nucleolus, do not seem visibly to participate in the formation of these nucleolar derivatives. There is no increase in the size of the nucleolar bodies after they reach the cytoplasm, neither do they multiply. They appear to be completely dissolved in the ooplasm without having directly transformed into any kind of yolk material. The extruded nucleolar bodies provide the cytological mechanism for the exchange of certain chemical substances from the nucleus to the cytoplasm (Figure 4). Presumably, these activating chemical

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