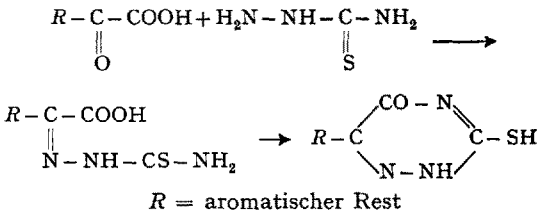
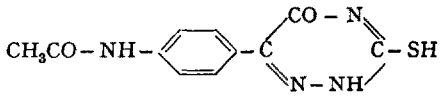
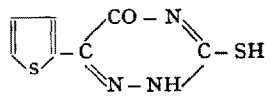


R = aromatischer Rest

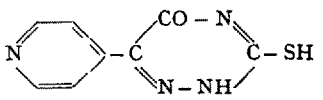
In unsern chemotherapeutischen Laboratorien hat J. HIRSCH[1] diese Triazinone auf ihre tuberkulostatische Wirksamkeit an Mäusen geprüft. Da dem 6-Phenyl-3-mercapto-1,2,4-triazin-5-on[2] eine schwache tuberkulostatische Wirksamkeit zukommt, wurde versucht, durch systematische Substitution im Phenylkern zu wirksameren Substanzen zu gelangen. Unter einer grösseren Zahl von Verbindungen zeigte nur das p-Acetylaminophenylderivat der Formel I eine sichere tuberkulostatische Wirkung *in vivo*, während Halogen-, Alkoxy-, Alkylthio-, Oxy-, Alkylsulfonyl-, Methylsulfonamido-, Alkylureido-, Alkylthioureido-, Nitro-, Amino-, Carboxygruppen als Substituenten im Benzolkern nicht oder völlig ungenügend wirksame Verbindungen lieferten.

I 

Werden an Stelle von Thiosemicarbazonen aromatischer Ketosäuren solche von heterocyclischen α-Ketosäuren zur Cyclisierung verwendet, so entstehen 6-heterocyclisch-substituierte 3-Mercaptotriazinone. Aus 2-Thienylglyoxylsäure-thiosemicarbazon erhielten wir die Verbindung II, die ungefähr die gleiche tuberkulostatische Wirksamkeit aufwies wie Verbindung I.

II 

Ersetzt man den Thienyl- durch den Pyridylrest, so werden Pyridyltriazinone erhalten. Während 2- und 3-Pyridyltriazinone *in vivo* völlig unwirksam waren, zeigte die 4-Pyridylverbindung III die beste tuberkulostatische Wirkung aller untersuchten Triazinone.

III 

In etwa 2facher Dosierung ist diese Substanz gleich wirksam wie Pyridin-3-aldehyd-thiosemicarbazon. Sie ist im Vergleich mit Isonicotinsäurehydrazid (INH) wesentlich weniger aktiv. Trotzdem kommt ihr ein besonderes Interesse zu, weil sie auch gegen INH-resistente Tuberkelbazillen wirksam ist. Ferner ist die Toxizität[3] niedriger als bei INH und den besten heterocyclischen Thiosemicarbazonen.

Während in der aromatischen Reihe die dem p-Acetylaminobenzaldehyd-thiosemicarbazon entsprechende Verbindung I ebenfalls eine gute Wirkung zeigt, ist die Übereinstimmung der Wirksamkeit zwischen den Mercapto-triazinonen und den Thiosemicarbazonen in der heterocyclischen Reihe nicht so gut. Thiophen-2-aldehyd-thiosemicarbazon[1] ist, im Gegensatz zur wirksamen Verbindung II, unwirksam. In der Pyridinreihe zeigen die Thiosemicarbazone sowohl des Pyridin-3- als auch des Pyridin-4-aldehyds eine gute Wirkung *in vivo*[1]. Bei den Mercapto-triazinonen hingegen ist nur die Pyridyl-4-Verbindung (Formel III) aktiv, wie dies auch bei den Pyridincarbonsäure-hydraziden der Fall ist.

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Wissenschaftliche Laboratorien der J. R. Geigy AG., Basel, den 29. Dezember 1953.

Summary

From thiosemicarbazones of aromatic and heterocyclic α-ketoacids, a number of aromatically and heterocyclically substituted mercapto-triazinones were prepared, some of which, especially 6-(γ-pyridyl)-3-mercapto-1,2,4-triazin-5-one, show definite antitubercular properties and low mammalian toxicity.

[1] Vgl. Exper. *8*, 184 (1952).

[1] Worüber von J. HIRSCH an anderer Stelle berichtet wird.
[2] J. BOUGAULT und L. DANIEL) C. r. Acad. Sci. *186*, 151 (1928).
[3] R. DOMENJOZ: Unveröffentlichte Versuchsergebnisse.

Low Angle Reflection in X-Ray Diffraction Patterns of Bone Tissue

In an earlier study[1] of the low angle scatter of X-rays from compact human bone, an attempt was made to deduce the dimensions of the apatite particles from the rate of decrease in intensity of scattered radiation with increase in scattering angle. The marked asymmetry of the particle scatter from longitudinal bone sections indicated a pronounced elongation of the apatite particles and a precise alignment of their long axes along the collagen fibres. It was possible to apply the theory of independant particle scatter[2] directly along the long axis of scatter, and, assuming an ellipsoidal shaped scattering particle, a value of about 75 Å was obtained for the particle diameter. In the direction of the short axis of scatter (corresponding to the long particle dimension), a collagen diffraction pattern appeared to be superimposed, and therefore the particle scatter along this axis could not be treated directly. However, an estimation of the particle length was made from a consideration of the variations in intensity of scatter along lines parallel to but at regular intervals away from this central axis, the value thus obtained being approximately 210 Å. The fact that the scatter could be treated in this way implied sufficient disorder in the system of particles to prevent the formation of regular reflecting planes for X-rays. On the other hand, the particles appeared to be of uniform size and well aligned.

In a recent examination of the diffraction of X-rays from specimens of fish bone, definite low angle diffraction peaks were observed which could readily be associated with the mineral salt component. The wide angle diffraction patterns showed reflections identical with those obtained from human and other bone (hen, frog, cow), thus indicating a similar apatite component in all systems. In the low angle pattern obtained from a

[1] A. ENGSTRÖM and J. B. FINEAN, Nature *171*, 564 (1953). – J. B. FINEAN and A. ENGSTRÖM, Biochim. Biophys. Acta *11*, 178 (1953).
[2] A. GUINIER, *X-ray Crystallographic Technology*, English translation (Hilger and Watts Ltd., London, 1952).

longitudinal section of the membrane bone of pike (Fig.1), the curve of decrease in intensity along the long axis of scatter showed a pronounced shoulder which suggested the superimposition of a definite diffraction peak on the low angle scatter corresponding to the particle diameters. When this was treated to the first approximation as a Bragg diffraction, a spacing of 65 Å to 70 Å was obtained. In the direction of the short axis of scatter, the low angle reflections usually attributed to collagen appeared to be of exceptionally high intensity. This has been observed to a less marked degree in previous patterns, and suspected to reflect a reinforcing of the collagen diffraction by associated apatite particles. In the case of the pike bone, the specimen was refluxed with ethylene diamine for 24 h to remove the collagen, and the complete extraction was confirmed by chemical analysis of the residual tissue. The diffraction pattern subsequently obtained from the extracted specimen is shown in Figure 2. The meridional low angle diffractions remain intense and well defined, and must be associated with the precise spacing of the apatite particles in the direction of the longitudinal axis of the bone. The main reflections gave Bragg spacings of 650 Å, 218 Å, and 130 Å, which coincide approximately with the first, third, and fifth order diffractions of collagen. As compared with the collagen diffraction, the 218 Å reflection of the apatite system appeared to have an unusually high intensity relative to the other reflections.

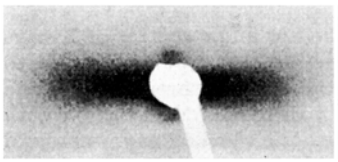

Fig. 1.

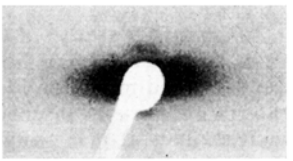

Fig. 2.

The fundamental repeating unit in the apatite structure thus appears to coincide with that of collagen, precise reflecting planes occurring only at intervals of 650 Å, but the outstanding intensity of the third order reflection suggests that this spacing of 218 Å may be related to the apatite particle length of about 210 Å deduced previously from continous particle scatter. One can readily imagine a system of particles with lengths varying slightly about an average of 210 Å, which are aligned along the collagen fibres in such a way as to produce precise crystallographic reflecting planes only where they coincide with the collagen period. Such a picture would appear to be capable of explaining the observed diffraction effects. After extraction of collagen, the scattering curve corresponding to the short axis of the particles no longer shows the shoulder which in intact bone seemed to suggest a superimposed Bragg reflection. Instead, there is a regular decrease in intensity of scatter with increase in scattering angle which can be treated as independant particle scatter, and from which a particle diameter of about 65 Å has been calculated. This value agrees well with the Bragg spacing found in the pattern of intact bone, and both the continuous low angle scatter from the somewhat disordered systems of particles usually encountered and the well-defined reflections associated with the organisation in the membrane bone of pike, can be interpreted in terms of systems of particles whose basic dimensions are 65 Å and 215 Å. It is assumed that the removal of the collagen from the pike bone introduces sufficient disorder into the system to remove the diffuse reflection at 65 Å.

The basic structural components in all types of bone appear to be collagen and apatite. The collagen has the same essential characteristics in all systems, and it would appear that the apatite particles are of approximately uniform size, the length in particular being remarkably constant in all types of bone studied. The probable length of the apatite particle corresponds almost exactly to one third of the fundamental repeating unit in the structure of collagen, and X-ray diffraction and electron microscope studies have indicated that this may be an important repeating distance in the structure of collagen itself. There can be little doubt of the close relationship between the form of crystallization of the apatite component during the development of bone and the detailed structure along the collagen fibre, and it can be suggested that the structure is basically the same in all bone tissues, the observed differences in diffraction effects being associated with slight differences in degree of order among structural components and in their relative proportions.

J. B. FINEAN and A. ENGSTRÖM

Department of Physical Cell Research, Karolinska Institutet, Stockholm, August 12, 1953.

Zusammenfassung

Es konnten Kleinwinkel-Röntgenbeugungen an Diffraktionsbildern von dekollagenisiertem Fischknochen beobachtet werden. Diese Beugungen können vollständig zu der Partikelgrösse in der kontinuierlichen Kleinwinkelbeugung weniger geordneter Systeme in Beziehung gesetzt werden. Die Ergebnisse betonen die nahe Verwandtschaft zwischen der Grösse der Apatit-Partikel und der periodischen Struktur des Kollagens.

Cytological Demonstration of Female Heterogamety in Isopods

The nature of the sex-determining system in bisexual species of Isopods has repeatedly been discussed by several authors. VANDEL[1] assumed the presence of female heterogamety and postulated directed segregation of the sex chromosomes in female meiosis caused by cytoplasmic influence to account for the occurrence of unisexual (thelygenic and arrhenogenic) broods in many species of terrestrial Isopods. DE LATTIN[2], however, interprets his own and VANDEL's results as due to a system of multiple sex-determining factors distributed over several chromosomes and partly acting through female predetermination. Neither in male[3], nor in female meiosis of many species of Isopods, studied by VANDEL[4] and others, have sex chromosomes ever conclusively been shown to occur. On the whole, the sex-determining system of Isopods seems to be highly unstable, as it is indicated by the frequent occurrence of intersexuality, parthenogenesis, hermaphroditism, and unisexuality.

The first observations of sex chromosomes in Isopods have recently been made in 4 closely related marine

[1] A. VANDEL, Bull. biol. France Belg. *72*, 147 (1938); *75*, 316 (1941).

[2] G. DE LATTIN, Z. Vererbungslehre *84*, 1 (1951); *84*, 536 (1952).

[3] The statement of J. DWORAK (Fol. Morph. *5*, 209, 1935) about the finding of an XO mechanism in males of *Asellus aquaticus* is probably erroneous; cf. the paper of A. VANDEL, footnote 4.

[4] A. VANDEL, Bull. biol. France Belg. *81*, 154 (1947); review of earlier papers in this work.