0430

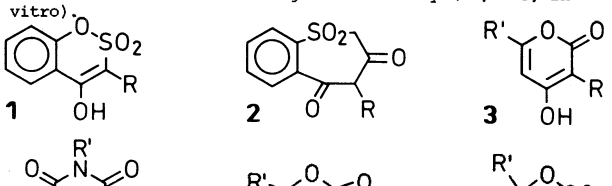
STUDIES ON PIVKA-VII. G. Mariani, G. Avvisati, D. Romoli, M.G. Mazzucconi and F. Mandelli.Department of Hematology, University of Rome, Italy.

The factor VII related antigen (Pivka-VII) in 25 random patients under long term treatment with oral anticoagulants was studied. All the patients had Thrombotest levels well within the therapeutic range (3 to 11%) and had been receiving the drugs for at least 4 months. Factor VII activity (VII:C) mean levels were 8.7 u/dl(sem 0.78) and factor VII antigen (VII:Ag) mean levels were 30.7 u/dl(sem 1.99), (ratio Pivka/Activity 4.04). Barium chloride adsorbed the same mean amount of factor VII:C and factor VII:Ag (8.7 u/dl and 8.0 u/dl respectively). After exposure to cold in 4/25 subjects the "cold activation" phenomenon became evident, characterised by an increase of factor VII:C levels and immodified VII:Ag levels. In the remaining 21 patients, mean VII:C as well as VII:Ag levels did not show modifications (8.5 u/dl and 30.7 u/dl respectively). Moreover, three normal volunteers received three different oral anticoagulants (Acenocoumarin, Coumarin and Ethyl-Biscomacetate). A sharp increase of factor VII:C levels was observed in all the three subjects (from 30 to 50%), a few hours after the beginning of the treatments, followed by consensual decrease of the two properties related to factor VII that reached the nadir after 48 hours. The vitamin K administration was followed by a rapid and consenual increase of the two parameters.

0431

QUALITITATIVE STRUCTURE ACTIVITY RELATIONSHIPS IN SERVERAL NEW TYPES OF ORAL ANTICOAGULANTS! K. Rehse, R. Bienfait, U. Emisch, W. Kapp, W. Schinkel and J. Tenczer, Institute of Pharmacy Free University of Berlin, Berlin FRG

Various 1,2-benzoxathiine-2,2-dioxides (**1**), 2,3,4,5-tetrahydrobenzothiepine-3,5-dione-1,1-dioxides (**2**), 4-hydroxy-2-pyrones (**3**) 2,4,6-(1H,3H,5H)-pyrimidinetriones(**4**), tetronic acids (**5**) and 1,2-oxathiolane-4-one-2,2-dioxides (**6**) have been synthezised to examine structure activity relationships in the field of oral anticoagulants. The compounds are substituted by 4-chlorocinnamoyl, 1-phenylpropyl or 1-(4-chlorophenyl)-3-oxo-butyl residues (R)in a suitable position.After single oral administration to rats (25-300 $mg \cdot kg^{-1}$) prothrombin levels (PT) of less than 25 percent are achieved within 10-48 hours with compounds of type **1-3** and **5**. Compound of type **4** and **6** were inactive. The results show that not only 4-hydroxycoumarines (**7**) and 1,3-indanediones (**8**) exhibit indirekt anticoagulant activity. The lactone moiety of **7** can be replaced by a sultone moiety. The benzene ring needs not to be fused to the heterocyclic part of the molecule (see **3**). The heterocyclic part may be a simple five membered lactone. The effects of **8** can be extended to seven membered and even heterocyclic ring systems. Furthermore some **2** showed platelet aggregation inhibiting activities (Born, $IC_{50} = 5 \cdot 10^{-4}M$). Some **5** showed direct anticoagulant activity (PT, PTT, in vitro).



0432

GENERATION OF COAGULATION FACTORS BY THE ISOLATED RAT LIVER PERFUSED WITH A SYNTHETIC BLOOD SUBSTITUTE. C.A. Owen, Jr. and E.J.W. Bowie, Departments of Biochemistry and Hematology Research, Mayo Clinic and Mayo Foundation, Rochester, MN U.S.A.

Measuring the release of small amounts of a clotting factor from an isolated perfused rat liver is difficult if the perfusate already contains some of the factor. Further, platelet-containing perfusates generate a coagulant activity that may invalidate clotting assays.

We have successfully employed a completely synthetic blood substitute for rat liver perfusions. The perfusate is "Fluosol-43" generously furnished by Alpha Therapeutic Corporation. The oxygen-carrying perfluorochemical is FC-43 (perfluorotributylamine) and the substitute for albumin is hydroxyethyl starch. Using the Brauer perfusion technique, we found that rat livers in 5 hours released an average of 2.3% of the normal plasma concentration of prothrombin, 8.4% factor V, 16.2% factor VII, 7.0% factor IX, 3.7% factor X, 28.3% factor XI and 12.3% factor XII. Antithrombin III and plasminogen were also generated.

Only minute amounts of factor VIII were released unless serum, cryoprecipitate or cryoprecipitate-free plasma was added; then the yield was 8.8% on average. The more "venom factor" (platelet aggregability with Bothrops alternata venom) added to the synthetic perfusate, the more factor VIII was released.