U/P concentrations and concentration ratios following vasopressin administration

Subject	Experiment	Urine Flow		Creatinine		U/P concentrations				U/P concentration ratios	
		c[a]	v[c]	c	v	Urea c	Urea v	Acetaminophen c	Acetaminophen v	v/c urea / v/c creatinine	v/c acetaminophen / v/c creatinine
M.B.	1	8.0	0.39	16.8	409.1	8.1	46.2	2.10	12.10	0.23	0.23
M.B.	2	10.2	0.70	13.0	212.5	7.7	62.5	0.58	6.85	0.45	0.72
J.F.	1	8.6	0.43	13.7	203.2	6.7	24.9	1.82	8.73	0.25	0.32
J.F.	2	9.7	0.61	12.1	143.2	7.0	18.8	0.82	4.12	0.25	0.42
P	1	9.0	1.25	13.0	104.2	9.0	46.3	1.45	8.0	0.65	0.69
P	2	11.9	2.56	12.6	83.7	7.6	38.2	1.23	5.20	0.75	0.64
F.N.	1	8.7	0.66	14.2	315.8	7.2	69.0	3.02	17.60	0.43	0.26
mean[b]										0.39	0.44
99% confidence limits										0.20–0.78	0.22–0.83

Abbreviations: [a] C, control period data derived from the mean of the period immediately before giving vasopressin and in the period 80–120 min afterwards when urine flow had returned to within 70% of control. [b] V, vasopressin period when urinary creatinine concentration was maximal. [c] Mean and confidence limits derived from the $\log_{10}$ distribution.

The results indicate that vasopressin increases the tubular reabsorption of acetaminophen in man and would lead to its sequestration at high concentration in the renal papilla[4]. It is possible that acetaminophen at a sufficiently high concentration may itself have a direct toxic effect on the papilla. Alternatively it may play a part in the nephrotoxicity of phenacetin by its ability to potentiate the action of vasopressin[5] and thereby the toxicity of other metabolites of this drug, such as *p*-phenitidine.

Résumé. Nous avons comparé les concentrations U/P d'acétaminophène et de créatinine avant et après l'administration de vasopressine à l'homme. Nous avons constaté que l'hormone augmente la réabsorption tubulaire d'acétaminophène, ce qui peut être important dans la production de la néphropathie du type analgésique.

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Structure-Activity Relationship of the Cardenolide, with Special Reference to the Substituents and Configurations at C-14 and C-15

In previous communications, we reported: 1. 14-Deoxy-14βH-uzarigenin was about one-third as active as uzarigenin, indicating that the presence of 14β-hydroxyl group is not indispensable for the positive inotropic activity of cardenolides, 2. the introduction of an oxygen function to C-15 of digitoxigenin profoundly affected the inotropic activity in the following order: digitoxigenin (I) > 15β-hydroxydigitoxigenin (II) > 15-oxodigitoxigenin (III) > 15α-hydroxydigitoxigenin (IV) the last being practically inactive[1]. Extending these observations, six derivatives of 14-deoxy-14βH-digitoxigenin (V) and 14-deoxy-14β-chloro-digitoxigenin with oxygen functions at C-15 were examined and compared.

The compounds used in this experiment were digitoxigenin (I), 3β, 15β-dihydroxy-5β, 14β-card-20 (22)-enolide (VI)[2], 3β-hydroxy-15-oxo-5β, 14β-card-20 (22)-enolide (VII)[3], 3β, 15α-dihydroxy-5β, 14β-card-20 (22)-enolide (VIII)[2], 3β, 15β-dihydroxy-14-chloro-5β, 14β-card-20 (22)-enolide (IX)[2], 3β-hydroxy-15-oxo-14-chloro-5β, 14β-card-20 (22)-enolide (X)[2] and 3β, 15α-dihydroxy-14-chloro-5β, 14β-card-20 (22)-enolide (XI)[2]. Stock solutions were prepared with each compound dissolved in 70% ethanol in concentration of 1 mg/ml.

The inotropic activities of these compounds were tested with the isolated frog's heart (Straub's preparation), by the same method used in the previous papers[1,4]. The Straub's cannula contained 2 ml of Ringer's solution, the composition of which was: NaCl 111 m*M*, KCl 2.7 m*M*, $CaCl_2$ 1.8 m*M*, $NaHCO_3$ 1.2 or 18 m*M* and glucose 2.7 m*M*. When the solution contained 1.2 m*M* $NaHCO_3$, it was aerated with air. When it contained 18 m*M* $NaHCO_3$, aeration was made with 95% O_2 + 5% CO_2. The contraction of the heart was recorded with an isotonic lever. The heart was first made hypodynamic by reducing the concentration of calcium to 0.6 m*M*, $^1/_3$ of the normal, and then the effect of one of the compounds was tested in the following way.

The stock solutions were diluted with either distilled water or with the low Ca Ringer to desired concentrations before experiment. Starting from a subthreshold dose, a small amount (0.02–0.14 ml) of a diluted solution was added to the cannula every fifteen minutes, so that a stepwise increase in the cumulative concentration of the test compound was achieved, until the heart went into systolic contracture. The way of increase in the cumulative

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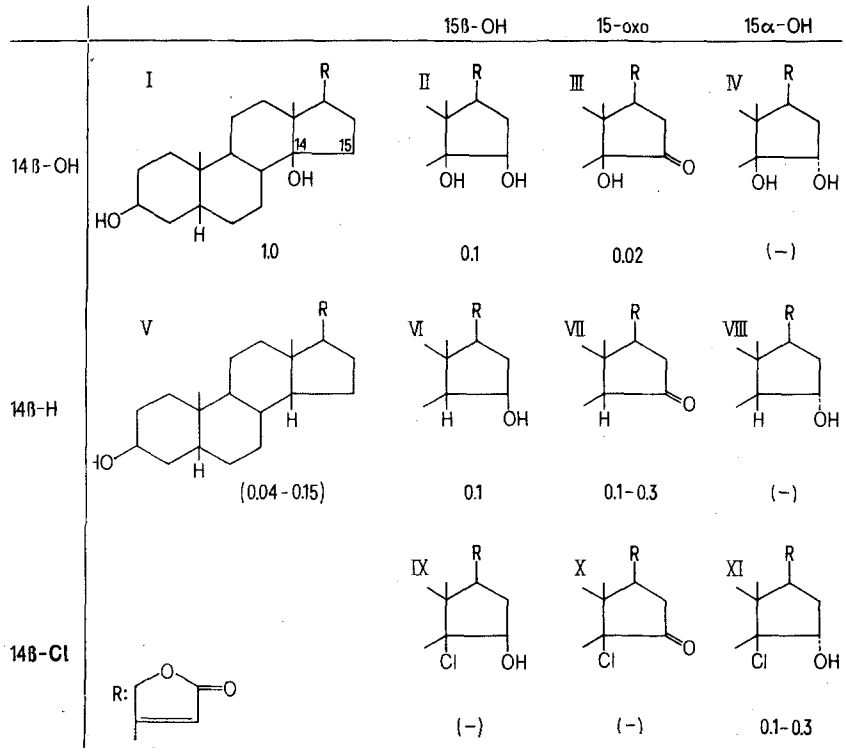

Structural formulae and relative potencies of digitoxigenin (I) and 10 derivatives (II–XI).

concentration was: 10^{-n}, 3×10^{-n}, $10^{-(n-1)}$, $3\times10^{-(n-1)}$, $10^{-(n-2)}$. The relative potencies were obtained on the basis of the concentration of each compound in which systolic contracture of the heart was brought about. As discussed elsewhere[4], this way of comparison provides reasonable values of relative potency. The experiments were carried out at room temperature of 20–26 °C.

The results are summarized in the Formulae. In the 14-deoxy-14βH-series (V–VIII), the relationship was similar, as a whole, to that in the 14β-hydroxy series (I–IV), 15α-hydroxy derivative being inactive again. In the 14β-Cl series (IX–XI), however, the results were quite unexpected. 15β-Hydroxy and 15-oxo derivatives were both inactive, while 15α-hydroxy derivative showed the relative potency of 0.1–0.3.

The relative potency of 14-deoxy-14βH-digitoxigenin was estimated as (0.04–0.15), about $^1/_{10}$ of digitoxigenin. (The figures are put in brackets, since the compound was not perfectly pure.) This confirms again the fact that 14β-hydroxyl group is not indispensable for the cardiotonic activity. The quantitative relationship is, however, not the same as our earlier observation that 14-deoxy-14βH-uzarigenin is about one third as active as uzarigenin. At present it is very difficult to draw any simple conclusion regarding the structure-activity relationship at C-14 and C-15[7].

Zusammenfassung. Es wurden die kardiotonischen Wirkungen sechs neuer Derivate von 14-Deoxy-14βH-digitoxigenin und 14-Deoxy-14β-chloro-digitoxigenin auf das isolierte Froschherz untersucht, sowie die Beziehungen zwischen deren chemischen Strukturen und Wirkungen diskutiert.

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Sodium [*o*-[(2,6-dichlorophenyl)-amino]-phenyl]-acetate (GP 45 840), A New Non-Steroidal Anti-Inflammatory Agent[1]

A series of substituted phenylaminophenylacetic acids was synthetized in an attempt to develop a non-steroidal anti-inflammatory compound with potent biological activity. This programme was based on the hypothesis that two structural features are essential to achieve such a pharmacodynamic effect: an acidic function giving a pH of about 6 and two aromatic nuclei whose substitution inhibits coplanarity[2]. Of the various compounds synthesized, GP 45 840, the sodium salt of the [*o*-[(2,6-Dichlorophenyl)-amino]-phenyl] acetic acid proved highly active in the animal test systems most relevant to the pharmacological characterization of such therapeutic agents.

As is shown in Figure 1, GP 45 840 displays a potent, dose-dependent, anti-inflammatory effect in the carrageenin paw-oedema test[3]. The compound already inhibits the formation of oedema when it is administered orally in a dose as low as 1 mg/kg. Since a reduction of more than 50% is rarely attained in this assay, the action elicited by