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SYNTHETIC NEW CARDENOLIDES

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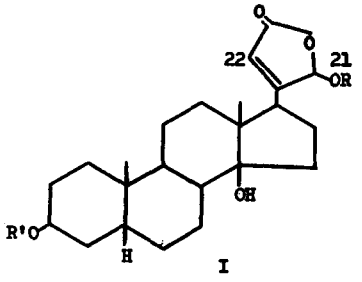
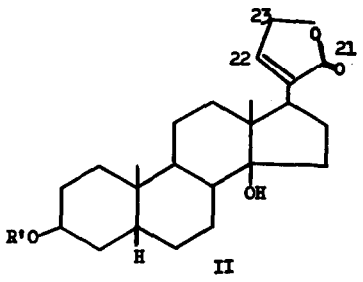
We wish to report the synthesis of novel cardenolides of structure I and II, by a general route that utilizes a furyl intermediate III [1] as



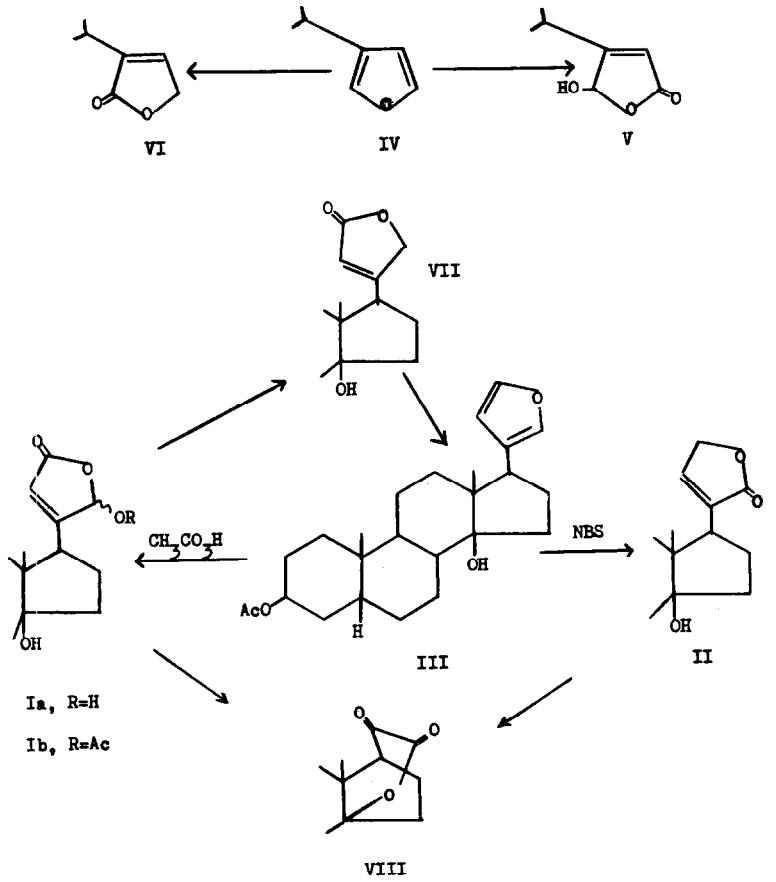
I



II

starting material.

Recent reports [1,2] of oxidations of furans to butenolides prompted us to report our syntheses in the cardenolide field. Our earlier work on a model substance, 3-isopropylfuran IV [3], led to its conversion, by the action of peracid (excess peracetic acid in $CHCl_3$ with NaOAc at 0°-5° for 2 hr.), to the butenolide V (m.p. 83-84°, $\varepsilon_{207m\mu}$ 13,600) in about 50% yield, whereas with N-bromosuccinimide (2 moles in dioxane-water at 0°-5° then up to 20° in about 15 min.), the isomeric butenolide VI (b.p. 49° at 0.13 mm.Hg) was


VI
IV
V
VII
OH
OR
CH_3CO_3H
AcO
H
OH
NBS
III
II
Ia, R=H
Ib, R=Ac
VIII

obtained in 60% yield [4].

Subsequently, a number of furylandrostanes and estranes were likewise converted to the corresponding steroidal butenolides [5] and, more specifically, compound III, obtained by hydride reduction of digitoxigenin acetate (VII) according to the method of Mimato and Nagasaki [1], was converted in about 50% yield to the "isomeric digitoxigenin" II (3β,14-dihydroxy-21-oxo-23-desoxo-5β-card-20(22)-enolide, 3-acetate), m.p. 172-173°, $[\alpha]_D^{23}$ -5.6°, when treated with 1.1 eq. of NBS in dioxane-water, at room temp. for 30 minutes [6].

When III was treated with excess peracetic acid at room temp. in chloroform in presence of sodium acetate for 30 min., the 21-hydroxyl derivative Ia of the "natural" cardenolide was obtained (16% yield) and characterized as the diacetate Ib, m.p. 190-191, $[\alpha]_D^{23}$ -25.9°.

Proof of structure of the novel compounds was obtained by consistent microanalytical and spectroscopical data (see Table for N.M.R. assignments) and by the following chemical conversions: the hydroxylactone Ia, upon refluxing with excess $NaBH_4$ in methanol containing 1.1 eq. of NaOH for 1 hr. followed by acidification with acetic acid at room temp., gave digitoxigenin acetate in good yield.

Potassium permanganate oxidation [7] of both Ib and II gave the known [7] ketolactone VIII thus confirming the β-stereochemistry of the side chains, also indicated by the 17α-proton signals at 3.8 p.p.m. [8].

N.M.R. data on chemical shift (p.p.m.)

Compound	Solvent	21-H	22-H	23-H
Digitoxigenin VII	$CDCl_3$	4.95 (2-H)	5.92	-
II	$CDCl_3$	-	7.37	4.83 (2-H)
Ia	DMSO	7.56 (OH)	5.90	-
		5.80 (H)		
Ib	DMSO	6.68 (H)	6.18	-

The biological activity of the novel compounds Ib and II will be reported elsewhere.

REFERENCES

1. H. Minato and T. Nagasaki, J. Chem. Soc., 377(1966).
2. F. Catala and J. Defaye, C.r. Acad. Sc. Paris, 258, 4094(1964).
3. N. Elming, Acta Chem. Scand. 6, 605(1952).
4. All new compounds had consistent microanalytical and spectroscopical data. Rotations were taken in chloroform, N.M.R. spectra at 60mC with TMS as reference standard.
5. Y. Lefebvre, et al., to be published.
6. When 2 moles of NBS were employed, a bromolactone was present in the product mixture and was converted to compound II by zinc in acetic acid. The structure of other minor components will be reported at a later date.
7. K. Meyer, Helv. Chim. Acta 33, 1238(1949).
8. K. Tori and K. Aono, Ann. Rept. Shionogi Res. Lab. 15, 130(1965).