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REVIEW ARTICLE

CARDENOLIDES—GLYCOSIDES AND GENINS*

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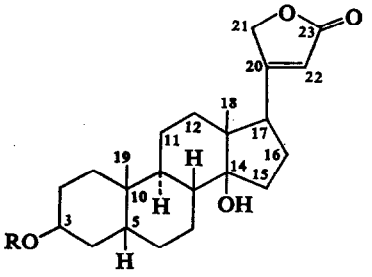
INTRODUCTION

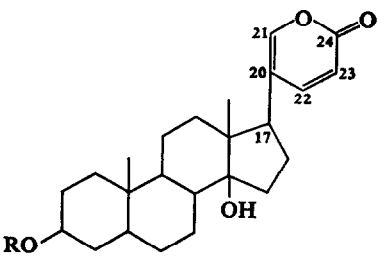
THE STEROIDAL cardenolides comprise one of the most interesting group of naturally occurring substances which are efficacious in the treatment of heart diseases. As components of arrow poisons, primitive people had used these substances for times immemorial.

The cardenolide-bearing plants have been found to occur in a dozen of plant families.[1, 2] The compounds are found in almost all parts of the plant, but the total amount or relative distribution in any given plant may vary with ecological factors, stage of development, time of harvest and mode of drying, etc.

Naturally occurring cardiotonic steroids are classified into two broad groups, cardenolides (I) and bufadienolides (II), depending on the nature of lactone ring at C-17 of the basic nucleus. The cardenolides constitute the predominant group in nature and are C_{23} steroids having an $\alpha:\beta$-unsaturated γ-lactone (butenolide) ring, whereas bufadienolides are C_{24} steroids having a doubly unsaturated six-membered lactone (α-pyrone or hexadienolide) ring. Chemical variations of these structural patterns are numerous and usually involve configuration at centres **3, 5, 17** and the presence or absence of oxygen functions and double bonds in the molecule.



(I) Cardenolide



(II) Bufadienolide

R = H or sugar moiety

* Communication No. 1387 from the Central Drug Research Institute, Lucknow, India.

[1] CH. TAMM, *Fortschr. Chem. Org. Naturstoffe* **13**, 137 (1956); ibid. **14**, 71 (1957); L. F. FIESER and M. FIESER, *Steroids*, p. 727, Reinhold, New York (1959); L. HILL, N. A. CHERNYKH *et al.*, *Rast. Resur.* **2**, 433 (1966); *Chem. Abst.* **66**, 22155 (1967); T. ALDAY-REDONNET, *Farmacognosia* **25**, 1 (1965); N. I. LIBIZOV and A. GUBANOV, *Farmatsiya* (*Moscow*) **16**, 29 (1967); T. REICHSTEIN, *Naturwissenschaften* **54**, 53 (1967).

[2] J. H. HOCH, *A Survey of Cardiac Glycosides and Genins*, University of South Carolina Press, South Carolina, U.S.A. (1961).

Cardenolides are used in clinical practice[3] and a formidable amount of data has accumulated regarding structure-activity relationship in this group.[4] Bufadienolides, on the other hand, are mainly of theoretical interest because of their very low therapeutic index and serious side-effects. The present review, therefore, is limited to the cardenolides and covers various developments during 1960–1967, with emphasis on chemical and biochemical aspects. Progress prior to 1960 has been covered by an excellent survey[2] published in 1961.

ISOLATION AND IDENTIFICATION

The poor stability of cardenolides towards acids and bases, their lability to hydrolytic enzymes and their presence often in very small amounts in plants had been a great hinderance to their detection and isolation. Recent refinements in chromatographic techniques[5, 6] have provided a more efficient tool for their separation and characterization and the advent of thin-layer chromatography[7] (TLC) opened up a new era in the detection, isolation and identification of these compounds.

The modern physical tools, e.g. i.r. and u.v. have been increasingly used in the last decades in structural determinations of cardenolides. The recent additions, NMR,[8] ORD[9] and mass spectroscopy,[10] have vastly increased the efficiency of organic chemists probing this field.

CHEMICAL CONSTITUENTS

Genins

A consolidated list of new cardiac genins isolated during the period 1960–1967 together with their structural assignments, is given in Table 1.

In the 5α-series, seventeen new substances have been isolated. The novel additions to this type are C-2 and C-15 hydroxylated genins like β-anhydrogomphogenin, afrogenin and alloglaucotoxigenin.

In the more predominant digitalis-strophanthus type (5β-series), the isolation of 3α-hydroxy genins (carpogenin, carpogenol, 3-episarmentogenin, 3-epicorotoxigenin and its

[3] J. W. WILSON, *Medicinal Chemistry* (edited by A. BURGER), p. 626, Interscience, New York (1960).

[4] K. K. CHEN, *J. Med. Pharm. Chem.* **3**, 111 (1961); Idem, *Arch. Intern. Pharmacodyn.* **140**, 8 (1962); B. T. BROWN, A. STAFFORD and S. E. WRIGHT, *Brit. J. Pharmacol.* **18**, 311 (1962); K. TOKITA, C. ISONO and Y. KIBAYASHI, *Nippon Yakurgaku Zasshi* **58**, 350 (1962); *Chem. Abst.* **60**, 6077 (1964); K. K. CHEN, *1st Intern. Pharmacol. Meeting, Stockholm*, Vol. 3, p. 27, Pergamon Press, Oxford (1963); CH. *Tamm*, ibid. p. 11 (1963); W. FOERSTER, *Arch. Intern. Pharmacodyn.* **148**, 334 (1964); F. G. HENDERSON and K. K. CHEN, *J. Med. Chem.* **8**, 577 (1965).

[5] R. NEHER, *Steroid Chromatography*, Elsevier Publishing Co., Amsterdam (1964).

[6] E. BAKER-SKRZYDLEWSKA and M. ZELECKA, *Pharmazie* **22**, 115 (1967); A. ELBANOWSKA and F. KACZMAREK, *Herba Pol.* **12**, 173 (1966); *Chem. Abst.* **67**, 84898 (1967); K. GRADE, W. FOERSTER and S. SCHULZECH, *Biochem. Pharmacol.* **16**, 1299 (1967); L. NOVER, G. BAUMGARTEN and M. LUCKNER, *J. Chromatog.* **32**, 93, 123, 141 (1968).

[7] E. STAHL and V. KALTENBACK, *J. Chromatog.* **5**, 458 (1961); C. R. DUNCAN, ibid. **8**, 37 (1962); A. GAMP, P. STUDER, H. LINDE and K. MEYER, *Experientia* **18**, 292 (1962); R. W. JELLIFFE, *J. Chromatog.* **27**, 172 (1967); E. STAHL, *Thin-Layer Chromatography*, p. 272, Academic Press, New York (1965).

[8] R. F. ZUERCHER, *Helv. Chim. Acta* **46**, 2054 (1963); N. S. BHACCA and D. H. WILLIAMS, *Applications of NMR Spectroscopy in Organic Chemistry*, Holden-Day, San Francisco (1966).

[9] F. BURKHARDT, W. MEIER, A. FURST and T. REICHSTEIN, *Helv. Chim. Acta* **50**, 607 (1967).

[10] G. SPITELLER, *Z. Analyst Chem.* **197**, 1 (1963); H. BUDZIKIEWICZ, C. DJERASSI and D. H. WILLIAMS, *Structural Elucidation of Natural Products by Mass Spectrometry*, Vol. II, p. 106, Holden-Day, San Francisco (1964); M. V. ARDENNE, R. TUMMLER, Ek. WEISS and T. REICHSTEIN, *Helv. Chim. Acta* **47**, 1032 (1964); R. BRANDT, W. STOKLIN and T. REICHSTEIN, ibid. **49**, 1662 (1966); R. BRANDT, H. KAUFMANN and T. REICHSTEIN, ibid. **49**, 1844 (1966); St. HOFFMANN, Ek. WEISS and T. REICHSTEIN, ibid. **49**, 1855 (1966); U. P. GEIGER, Ek. WEISS and T. REICHSTEIN, ibid. **50**, 194 (1967); M. B. E. FAYEZ and S. A. R. NEGM, *Chem. Ind. (London)* 1361 (1968).

TABLE 1. CARDIAC GENINS ISOLATED 1960–1967

Name	Structure (see I)
Acoflorogenin	1?-OH; $\Delta^{4(5)}$
16-Acetoxystrophanthidin	5β-OH; 16β-OAc; 19-oxo
3-*O*-Acetylstrophandogenin	5β, 16β-OH; 3β-OAc; 19-oxo
Adenitoxologenin	16β, 19-OH
Adigenin	16β-O—CO—CH_2—$CH(CH_3)_2$
Adynerigenin	8, 14ββ-epoxy
Afrogenin	2α, ?, -OH; 5α-H
Anhydrocanarygenin	$\Delta^{3(4),5(6)}$
β-Anhydrogomphogenin	2α-OH; $\Delta^{14(15)}$; 5α-H
β-Anhydrouzarigenin	$\Delta^{14(15)}$; 5α-H
Alloglaucotoxigenin	15β-OH; 19-oxo; 5α-H
Antiarigenin	5β, 12β-OH; 19-oxo
Antiogenin	5β, 12β-OH
Bipendogenin	5β, 11α-OH
Calotropagenin	12ξ-OH; 19-oxo; 5α-H
Canarigenin	$\Delta^{4(5)}$
Canescegenin*	11β-OH; 19-oxo; 5α-H
Carpogenin	3α-OH; 19-oxo
Carpogenol	3α, 19-OH
17βH-Coroglaucigenin	19-OH; 5α-H; 17α-lactone ring
16-Dehydrostrophanthidin	5β-OH; $\Delta^{16(17)}$
16-Dehydrostrophanthidol	5β, 19-OH; $\Delta^{16(17)}$
5α-Desarogenin	11-oxo; 5α-H
Diffugenin	5β-OH; $\Delta^{14(15)}$; 19-oxo
Diginatigenin	12β, 16β-OH
Dihydrocalotropagenin	12ξ, 19-OH; 5α-H
3-Epicorotoxigenin	3α-OH; 19-oxo; 5α-H
3-Epi-17βH-corotoxigenin	3α-OH; 19-oxo; 5α-H; 17α-lactone ring
3-Episarmentogenin	3α, 11α-OH
11β, 12β-Epoxydigitoxigenin	11,12ββ-epoxy
Gratogenin	1β, 5β, 11α-OH
Hyrcanogenin	$\Delta^{4(5)}$; 19-oxo
Mallogenin	11β-OH; 5α-H
Menabegenin (= 17βH-digitoxigenin)	17α-lactone ring
Pachygenin	$\Delta^{5(6)}$; 19-oxo
Pachygenol	19-OH; $\Delta^{5(6)}$
Panogenin	11β, 19-OH; 5α-H
Sarmentosigenin A(= Nigrescigenin)	5β, 11α-OH; 19-oxo
Securigenin*	11β-OH; 19-oxo; 5α-H
Strophandogenin	5β, 16β-OH; 19-oxo
Strophanthiline A	11α-OH; $\Delta^{14(15)}$
17βH-Strophandogenin	5β, 16β-OH; 19-oxo; 17α-lactone ring
Strogogenin	1β, 5β, 11α-OH; 19 → 11 lactone
Syriogenin	12β-OH; 5α-H
Tanghinigenin	7,8ββ-epoxy
17βH-Uzarigenin	5α-H; 17α-lactone ring
Xysmalogenin	$\Delta^{5(6)}$

* Ref. 81 for ORD and structural assignment.

17βH isomer) have been reported for the first time. Two acetoxy genins and an interesting genin carrying a 16-*O*-isovaleryl group (adigenin) have been added to the rather rarer group of ester genins. The other new variants encountered are C7-8, C8-14 and C11-12 epoxides e.g. tanghinigenin, adynerigenin and epoxydigitoxigenin, the ring A or B unsaturated genins, e.g. xysmalogenin, pachygenin, pachygenol and canarigenin and $\Delta^{16(17)}$ genins such as 16-dehydrostrophanthidin and 16-dehydrostrophanthidol. Strogogenin is the first cardiac aglycone bearing an additional lactone ring.

The C14-15 anhydrogenins have been so far obtained through dehydration, acid hydrolysis of glycosides or during the course of chromatography over activated adsorbents and, therefore, the C-14 hydroxyl has been assumed to be an integral part of the natural genins. During this period at least three such anhydrogenins (diffugenin, strophanthiline A, β-anhydrouzarigenin) have been claimed to be occurring naturally.

Five new 17βH genins (butenolide substituent in 17α position) have been characterized and it has been shown that the plants elaborating these genins contain certain enzymes which are responsible for this configurational inversion. The conversion[11] of several normal genins into 17βH isomers chemically by the action of sodium tosylate and sodium acetate has been accomplished. These isomers have lower R_f value than their normal congenors and they do not yield isogenins.

The transformation of sarmentogenin into cortisone was first reported by Lardon and Reichstein, but recently chemical conversion of digitoxigenin by a much simpler route to a compound bearing cortisone side-chain has been achieved.[12] A remarkable rearrangement of digitoxigenin to a *C*-nor-cardenolide having spiro C/D ring junction has been reported.[13] The general scope of this reaction and the ease with which it proceeds (via isogenin) indicate that such compounds may eventually be encountered in natural sources.

Sugars

Reichstein *et al.*[14] have reviewed the sugars obtained from the cardenolides which are comprised of normal sugars, 2-deoxy sugars and a special group of carbocyclic sugar derivatives. Apart from glucose, the normal sugars are unbranched aldohexoses mostly of 6-deoxy type and the new additions are 6-deoxy-D-glucose, 6-deoxy-D-allose, L-vallarose, D-javose, 2,3-*O*-dimethyl-D-fucose, 2-*O*-methyl-D-fucose, 2-*O*-acetyl-L-vallorose, 2-*O*-acetyl-L-thevetose and 2-*O*-acetyl-L-acofriose (Fig. 1). For the first time 2-*O*-methyl and 2-*O*-acetyl sugars have been isolated. D-Xylose, the first aldopentose, has been isolated from certain cardiac glycosides.

The 2-deoxy sugars[15] are abundantly distributed as 2,6-dideoxy hexoses, frequently as 3-*O*-methyl ethers. D-Canarose has been the only addition to this group.

D-Fucose and L-oleandrose are found to occur only in cardiac glycosides whereas L-fucose is widely[14, 16] distributed in various natural products and D-oleandrose is found only in steroidal glycosides like lanofolein, digifolin.[17] It is interesting to note that both D- and L-diginose occur in *Strophanthus* species; the D-form exclusively in the African and L-form in the Asian varieties.[14]

The novel carbocyclic sugar components from *Asclepiadaceae* glycosides are neither known in free form nor could be isolated without decomposition, but the recent work has shown that these are derived from 4,6-dideoxy hexosone. In *Asclepias fructicosa*, the glycosides have two ether bridges formed by the interaction of C-2 and C-3 hydroxyls of the genin with those at C-1 and C-2 of the sugar moiety, whereas in *Calotropis procera* calactin, calotropin and uscharidin arise by normal glycosidation at C-1 of the 4,6-dideoxy sugar.

[11] J. H. RUSSEL, O. SCHINDLER and T. REICHSTEIN, *Helv. Chim. Acta* **43**, 167 (1960).
[12] A. LARDON and T. REICHSTEIN, *Pharm. Acta Helv.* **27**, 287 (1952); N. DANIELI, Y. MAZUR and F. SONDHEIMER, *Tetrahedron* **23**, 715 (1967).
[13] G. R. PETTIT, J. C. KNIGHT and T. R. KASTURI, *Chem. Comm.* **334**, 688 (1967).
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[15] S. HANESSIAN, *Advan. Carbohydrate Chem.* **21**, 143 (1966).
[16] T. REICHSTEIN, *Angew. Chem. Intern. Ed.* **1**, 572 (1962).
[17] R. T. TSCHESCHE and G. BUSCHAUER, *Ann.* **603**, 59 (1957); C. W. SHOPPEE, R. LACK and A. V. ROBERTSON, *Proc. Chem. Soc.* **65**, (1962); idem *J. Chem. Soc.* 3610 (1962).

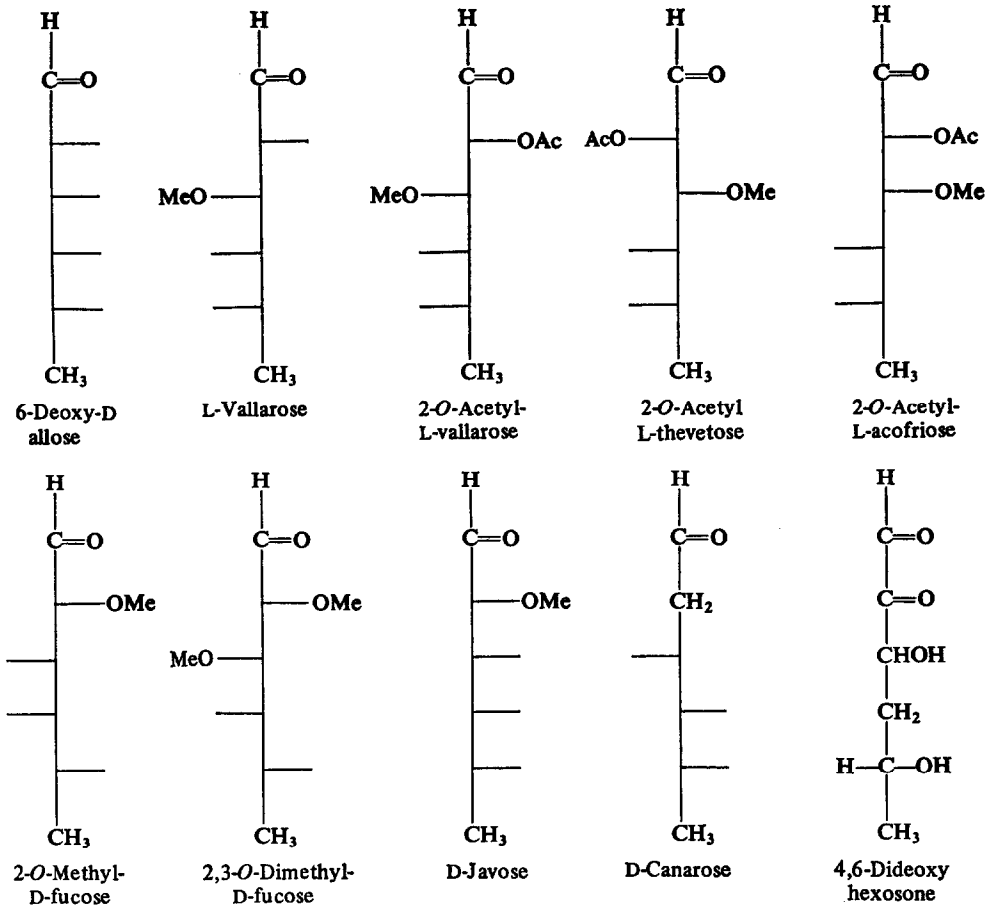

FIG. 1. NEW SUGARS FOUND IN CARDENOLIDES.

The linkage of sugars to aglycones in the cardiac glycosides follows the general pattern: aglycone-(rare sugar)$_m$-(glucose)$_n$. The nature of the glycosidic linkage is determined by hydrolysis with selective enzymes[18] or by application of Klyne rule.[19]

The ring size of the sugars in cardiac glycosides is not well-established and the conclusions have been mainly derived from the difference in the rate of hydrolysis[20] which is faster in the case of aldofuranosides than the aldopyranosides.

CLASSIFICATION OF AVAILABLE DATA

The available data on the occurrence of cardenolides is shown in Table 2. For the purpose of compactness, glycosides and genins whose structures were elaborated earlier[2] and substances of unknown structure have been excluded. However, in order to make the tabulation complete, plants which have only yielded known cardenolides are given at the end of each family list.

[18] H. BAUMANN and W. PIGMAN, *The Carbohydrates* (edited by W. PIGMAN), p. 562, Academic Press, New York (1957); K. WALLENFELS and O. P. MALHOTRA, *The Enzymes* (edited by P. D. BOYER, H. LARDY and K. MYRABACK), Vol. 4, p. 409, Academic Press, New York (1960).

[19] W. KLYNE, *Biochem. J.* **47**, XLI (1950).

[20] F. SHAFIZADCH, *Advan. Carbohydrate Chem.* **13**, 9 (1958).

TABLE 2. OCCURRENCE OF CARDENOLIDES IN THE PLANT KINGDOM

APOCYNACEAE

Species	Glycoside	Genin†	Sugar*	Reference
Acocanthera longiflora	Acolongifloroside K	Ouabagenin	L-talme	21
A. oppositifolia = *A. venenata* G. Don.	Acovenoside B	1-*O*-Acetyl acovenosigenin	L-acv	22
	Oppovenoside	Acoflorogenin	3-OMe-L-talme	
	Oppofrioside	Acovenosigenin A	3-OMe-L-rhm	
	Opposide	Gratogenin	L-talme	
	Acotaloside	Acovenosigenin A	L-talme	
	Acolongifloroside	Acoflorogenin	3-OMe-L-rhm	
Beaumontia grandiflora	Beanwalloside	Oleandrigenin	L-cym	23
	Beaumontoside	Digitoxigenin	L-ole	
	Wallichoside	Digitoxigenin	L-cym	
Cerbera floribunda, *C. dilatata*	Cerbertin	11β,12β-Epoxy digitoxigenin	2-OAc-L-thv	24
	Desacetyl cerbertin	11β,12β-Epoxy digitoxigenin	L-thv	
Nerium oleander	Adigoside	Adigenin	D-dgn	25
	Adynerin	Adynerigenin	D-dgn	
Roupellina boivini (Baill.) *Pichon* (= *Strophanthus boivini*)	17βH-Boistroside	17βH-corotoxigenin	D-dgx	26
	Glycoside ϕ	Coroglaucigenin	D-sar	
	Glycoside ϕ'	17βH-Coroglaucigenine	D-sar	
	Madagascoside	Uzarigenin	D-sar	
	17βH-Madagascoside	17βH-Uzarigenin	D-sar	
	17βH-Paulioside	17βH-Corotoxigenin	D-sar	
	Sadleroside	3-Epicorotoxigenin	D-boi	
	17βH-Sadleroside	3-Epi-17βH-corotoxigenin	D-boi	
	Zettoside	Uzarigenin	D-boi	
	17βH-Zettoside	17βH-Uzarigenin	D-boi	
Strophanthus divaricatus	—	Strophanthiline A	—	27
Strophanthus gratus	Strogoside	Strogogenin	L-talme	28
S. kombe	Gluco cymarol	Strophanthidol	D-cym + D-glu	29
	Strophanthidol-digitoxosido-glucoside	Strophanthidol	D-dgx + D-glu	
	Strophanthidin-digitoxosido-glucoside	Strophanthidin	D-dgx + D-glu	
S. sarmentosus	Bipindaloside	Bipendogenin*	D-dgl	30
S. thollonii	—	Sarmentosigenin A = Nigrescigenin	—	31

[21] P. HANSCHILD-ROGAT, EK. WEISS and T. REICHSTEIN, *Helv. Chim. Acta* **45**, 1244 (1962).

[22] P. HANSCHILD-ROGAT, EK. WEISS and T. REICHSTEIN, *Helv. Chim. Acta* **45**, 2612 (1962); ibid. **50**, 2299, 2323 (1967).

[23] A. F. KRASSO, EK. WEISS and T. REICHSTEIN, *Helv. Chim. Acta* **46**, 1691 (1963); idem *Pharm. Acta Helv.* **39**, 168 (1964).

[24] T. CABLE, R. G. COOMBE and T. R. WATSON, *Australian J. Chem.* **18**, 1079 (1965).

[25] P. S. JANIAK, EK. WEISS, J. VON EUW and T. REICHSTEIN, *Helv. Chim. Acta* **46**, 374 (1963); idem *Ann. Chim. (Rome)* **53**, 30 (1963); ST. HOFFMANN, EK. WEISS and T. REICHSTEIN, *Helv. Chim. Acta* **49**, 1855 (1966).

[26] J. H. RUSSEL, O. SCHINDLER and T. REICHSTEIN, *Helv. Chim. Acta* **44**, 1293, 1315 (1961).

[27] WEI-YUAN HUNG and YUH-CHENG CHEN, *Hua Hsueh Hsueh Pao* **24**, 151 (1958); *Chem. Abst.* **53**, 7233 (1959).

[28] U. P. GEIGER, EK. WEISS and T. REICHSTEIN, *Helv. Chim. Acta* **50**, 179 (1967).

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[30] B. FECHTIG, O. SCHINDLER and T. REICHSTEIN, *Helv. Chim. Acta* **42**, 1148 (1959); ibid. **43**, 727, 1570 (1960).

[31] EK. WEISS, O. SCHINDLER and T. REICHSTEIN, *Helv. Chim. Acta* **41**, 736 (1958); R. BRANDT, H. KAUFMANN and T. REICHSTEIN, ibid. **49**, 1844 (1966).

TABLE 2.—*continued*

APOCYNACEAE—*continued*

Species	Glycoside	Genin	Sugar	Reference
S. vanderijstii	Callengoside	New genin (3,?,14,16-OH)	L-dlg	32
	Diglucodigitoxigenin	Digitoxigenin	2D-glu	
	Diglucoemicymarin	Periplogenin	D-dgl + 2D-glu	
	Diglucoperiplogenin	Periplogenin	2D-glu	
	Diglucosyl sarmentocymarin	Sarmentogenin	D-sar + 2D-glu	
	Glycoside O	Periplogenin	D-dgn + 2D-glu	
	Glycoside Q_1	Sarmentogenin	D-dgn + 2D-glu	
	Kisantoside	New genin (16-OH or OAc)	D-dgl + D-glu	
	Sargenoside	Sarmentogenin	D-dgl + D-glu	
Tanghinia venenifera	Tanghinin	Tanghinigenin	Ac-L-thv	33
	Tanghinoside	Tanghinigenin	Ac-L-thv + 2D-glu	
Thevetia neriifolia	Ruvoside	Cannogenol	L-thv	34
	Thevetin A	Cannogenin	L-thv + 2D-glu	
Vallaris solanacea	16-Deacetyl-16-anhydroacoschimperoside P	16-Anhydrogitoxigenin	L-acf	35
	Acetyl acoschimperoside P	14,16-Dianhydrogitoxigenin	2-OAc-L-acf	
	Solanoside	Digitoxigenin	L-acf	
	Acetylsolanoside	Digitoxigenin	2-OAc-L-acf	
	Vallaroside	Digitoxigenin	L-val	
	Acetyl vallaroside	Digitoxigenin	2-OAc-L-val	
	Vallarosolanoside	Oleandrigenin	L-val	
Acocanthera spelabitis,[36] *Carissa carandas*,[37] *C. spinarum*,[38] *Melodinus monogynus*.[39]				

ASCLEPIADACEAE

Species	Glycoside	Genin	Sugar	Reference
Asclepias glaucophylla	Ascleposide	Uzarigenin	D-allme	40
A. fructicosa	Afroside	Afrogenin	4,6-dideoxy hexosone	41
	Gomphoside	Gomphogenin (isolated as anhydrogenin)	4,6-dideoxy hexosone	

[32] K. BRENNEISEN, J. VON EUW, CH. TAMM and T. REICHSTEIN, *Helv. Chim. Acta* **47**, 799, 814 (1964).

[33] E. FLURY and T. REICHSTEIN, *Ann. Chim. (Rome)*, **53**, 23 (1963); E. FLURY, EK. WEISS and T. REICHSTEIN, *Helv. Chim. Acta* **48**, 1113 (1965).

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[38] Unpublished work of the authors.

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TABLE 2—*continued*

ASCLEPIADACEAE—*continued*

Species	Glycoside	Genin	Sugar	Reference
A. lilacina *A. swynnertonii*	Ascleposide Frugoside	Uzarigenin Coroglaucigenin	D-allme D-allme	42
A. syriaca	Desglucouzarin	Uzarigenin	D-glu	43
	Syriobioside	Syriogenin*	L-rhm + D-glu	
	Syrioside	Syriogenin*	L-rhm + 2D-glu	
A. tuberosa	Glucofrugoside	Coroglaucigenin	D-allme + D-glu	44
Calotropis procera	Calactin	Calotropagenin*	4,6-dideoxy-hexosone	45
	Calotropin	Calotropagenin*	4,6-dideoxy-hexosone	
	Calotoxin	Calotropagenin*	6-deoxy-hexosone	
	Uscharidin	Calotropagenin*	6-deoxyhexos-dione	
	—	3-Episarmentogenin	—	46
Gongronema gazense	Glycoside C	Sarmentogenin	3D-cym	
	Glycoside E	Sarmentogenin	2D-cym	
	Glycoside G	Sarmentogenin	D-dgx + 2D-cym	
	Glycoside L	Periplogenin	D-dgx + D-cym	
	Glycoside M	Sarmentogenin	D-dgx + D-cym	
	Glycoside R	Sarmentogenin	2D-dgx + L-ole	
Glossostelma carsoni	Glycoside U	Acetylated genin	glu	47
	Glycoside F	Xysmalogenin	sar	
Menabea vernanata	—	Menabegenin	—	48
Pachycarpus distinctus	Bulloside	Digitoxigenin	thv + dgx	49
	Cannodixoside	Cannogenin	D-dgx	
	—	Pachygenin	—	50
	—	Pachygenol	—	
P. schinzianus	—	Carpogenin	—	51, 52
	—	Carpogenol	—	
	—	Xysmalogenin	—	
Parquetina nigrescens = *Periploca nigrescens*	—	Strophandogenin	—	53
	—	16-Dehydrostrophanthidol	—	
	Glycoside D	16-Dehydrostrophanthidin*	dgx	
	Glycoside K	16-Acetoxy strophanthidin*	L-rhm	

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TABLE 2—*continued*

ASCLEPIADACEAE—*continued*

Species	Glycoside	Genin	Sugar	Reference
Pentopetia androsaemifolia	Digitoxigen-2-deoxy fucoside	Digitoxigenin	2-deoxy-fuc	54
Pergularia extensa	—	al-Dihydrocalotropagenin	—	55
Xysmalobium undulatum	—	Xysmalogenin	—	51
	—	17βH-Uzarigenin	—	56
Asclepias mellodora,[57] *A. curassavica*.[58]				

CRUCIFERAE

Species	Glycoside	Genin	Sugar	Reference
Erysimum canescens	Canescein	Canescegenin	glume	59
	Glucocanescein	Canescegenin	glume + D-glu	
E. cheiranthoides	Ericordin	Cannogenol	D-glume + D-glu	60
	Desglucoericordin	Cannogenol	D-glume	
E. gypsaceum	Gypsobioside	Strophandogenin	D-dgx + D-xy	61
	17α-Gypsobioside	17βH-Strophandogenin	D-dgx + D-xy	
	Gypsotrioside	Strophandogenin	D-dgx + D-xy + D-glu	
E. diffusum	—	Diffugenin	—	62
E. marschallianum	Allyonin	Cannogenol	D-glu	63
(? *Cheiranthus allionii*)	Violin	Cannogenol	2-deoxy-thu + D-glu	
E. perofskianum	Erycorchoside	Strophanthidin	D-boi + D-glu	64
	Eryperoside	Strophanthidin	D-dgx + D-glu	
	Erysimoside	Strophanthidin	D-dgx + D-glu	
	Kabuloside	Strophanthidin	2-deoxy-D-gu	
	Perofskoside	Strophanthidin	2-deoxy-D-glu	

Erysimum odoratum, E. hieraciifolium, E. pulchellum, E. repandum, E. cupsidatum,[65] *E. transsilvanieum*,[66] *E. crepidifolum*,[67] *E. pinifolum*,[68] *E. carniolium*,[69] *Hesperis matronalis*.[70]

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[65–70] (see over)

TABLE 2—*continued*

EUPHORBIACEAE

Species	Glycoside	Genin	Sugar	Reference
Mallotus paniculatus	—	5α-Desarogenin	—	71
	Malloside	Mallogenin*	L-rhm	
	Panoside	Panogenin	L-rhm	
	Glucopanoside	Panogenin	L-rhm + D-glu	

LILIACEAE

Species	Glycoside	Genin	Sugar	Reference
Convallaria keiskei	Lokundjoside	Bipendogenin	L-rhm	72
C. majalis	Lokundjoside	Bipendogenin	L-rhm	73
Ornithogalum umbellatum	Rhodexin A	Sarmentogenin	L-rhm	74
	Rhodexoside	Sarmentogenin	L-rhm + glu	

MORACEAE

Species	Glycoside	Genin	Sugar	Reference
Antiaris toxicaria	Antialloside	Antiarigenin*	D-allme	75
	Antiarojavoside	Antiarigenin*	D-jav	
	Antioside	Antiogenin	L-rhm	
	α-Antioside	Antiogenin	D-gume	
	Antiogoside	Antiogenin	D-allme	
	Malayoside	Cannogenin	L-rhm	
	al-Dihydromalayoside	Cannogenol	L-rhm	
	Strophanthojavoside	Strophanthidin	D-jav	
	Substance γ	Digoxigenin	L-rhm	
	Substance K	Antiarigenin	L-acf	
Castilla elastica	Strophanthidin-gulomethyloside	Strophanthidin	D-gume	76
	Helveticosol	Strophanthidol	D-dgx	

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TABLE 2—*continued*

MORACEAE—*continued*

Species	Glycoside	Genin	Sugar	Reference
Streblus asper	Asperoside	Digitoxigenin	2,3-di-OMe-glu	77
	Cannodimethoside	Cannogenol	2,3-di-OMe-glu	
	Glucogitodimethoside	Gitoxigenin	2,3-di-OMe-D-glu + D-glu	
	16-*O*-Acetyl-glucogitodimethoside	Oleandrigenin	2,3-di-OMe-D-glu + D-glu	
	Glucokamaloside	Periplogenin	2,3-di-OMe-D-fuc + D-glu	
	Glucostrebloside	Strophanthidin	2,3-di-OMe-D-fuc + D-glu	
	Kamaloside	Periplogenin	2,3-di-OMe-D-fuc	
	Sarmenthoside	Sarmentogenin	3-OMe-D-glu	
	Strebloside	Strophanthidin	2,3-di-OMe-D-fuc	
	Strophalloside	Strophanthidin	D-allme	
	Strophanolloside	Strophanthidol	D-allme	

PAPILIONATAE (N.O. LEGUMINOSAE)

Species	Glycoside	Genin	Sugar	Reference
Coronilla glauca	—	Alloglaucotoxigenin	—	78
C. scorpioides	Corotoxigenin glucoside	Corotoxigenin	D-glu	79
C. hyrcana	Hyrcanoside	Hyrcanogenin	Xy + glu	80
	Deglucohyrcanoside	Hyrcanogenin	Xy	
Securigera coronilla DC (= *S. securidacea*)	Securidaside	Securigenin	D-xy + glu	81

RANUNCULACEAE

Species	Glycoside	Genin	Sugar	Reference
Adonis vernalis	Adonitoxol	Adonitoxologenin	L-rhm	82
	—	3-*O*-Acetylstrophandogenin	—	83
	Vernadigin	Strophandogenin	dgn	

Adonis dentata,[84] *A. autumnalis*.[85]

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TABLE 2—*continued*

SCROPHULARIACEAE

Species	Glycoside	Genin	Sugar	Reference
Digitalis canariensis (= *Isoplexis canariensis*)	Canarigenin canaroside	Canarigenin	D-can	86
	Canarigenin digitoxoside	Canarigenin	D-dgx	
	Canariboivinoside side	Canarigenin	D-boi	
	Canarigen glucoside A	3,5-Dianhydroperiplogenin	D-glu	
	Xysmalogenin canaroside	Xysmalogenin	D-can	
	Glycoside A A_1	Uzarigenin	can + glu	87
	Glycoside A A_2	Canarigenin	can + glu	
	Glycoside A A_3	Xysmalogenin	can + glu	
	Glycoside B d_1	Uzarigenin	dgx + glu	
	Glycoside B d_2	Canarigenin	dgx + glu	
	Glycoside B d_3	Xysmalogenin	dgx + glu	
	Glycoside C	Canarigenin	D-fuc + D-glu	
D. isabelliana (= *Isoplexis isabelliana*)	Glycoside B	Uzarigenin	D-dgx + glu	88
	Digitoxigenin-6-deoxy guloside	Digitoxigenin	D-glume	
	Digitoxigenin-6-deoxy alloside	Digitoxigenin	allme	
	Digitoxigenin-6-deoxy-glucoside	Digitoxigenin	D-glume	
	Uzarigenin digitoxoside	Uzarigenin	dgx	
	Glycoside A A_1	Uzarigenin	D-can + glu	
	Glycoside A A_2	Xysmalogenin	D-can + glu	89
	Glycoside C C_1	Uzarigenin	D-dgx + D-glu	
	Glycoside C C_2	Xsysmalogenin	D-dgx + glu	
	Glycoside G	Digitoxigenin	3-OAcetyl-glume + glu	
	Glycoside K	Digitoxigenin	D-can + D-glu	
D. lanata	—	Diginatigenin	—	90
	Digitoxigenin glucomethyloside	Digitoxigenin	glume	91
	Digoxoside	Digoxigenin	4 dgl	
	neo-Digoxoside	Digoxigenin	4 dgl	
	Glucoevatromonoside	Digitoxigenin	D-dgx + D-glu	92
	Glucogitoroside	Gitoxigenin	D-dgx + D-glu	
	Glucolanadoxin	Gitaloxigenin	D-dgx + D-glu	
	Glucoverodoxin	16-Formylgitoxigenin	D-dgl + D-glu	

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TABLE 2—*continued*

SCROPHULARIACEAE—*continued*

Species	Glycoside	Genin	Sugar	Reference
D. lanata	*neo*-Odorobioside G	Digitoxigenin	D-dgl + D-glu	
	neo-Digitalinum verum	Gitoxigenin	D-dgl + D-glu	
	Digitoxigenin-*O*-glucosyl-6-deoxy glucoside	Digitoxigenin	D-glume + D-glu	
	O-Glucosyl-digitoxigenin *bis*-digitoxoside	Digitoxigenin	2-D-dgx + D-glu D-glu	
	neo-Glucoverodoxin	16-Formylgitoxigenin	D-dgl + D-glu	
	Digitoxigenin-*O*-glucosyl-*O*-acetyl-6-deoxy glucoside	Digitoxigenin	Ac-glume + D-glu	
	Digoxigenin digilandobioside	Digoxigenin	D-dgx + D-glu	
	Digoxigenin-glucosyl-*bis*-digitoxoside	Digoxigenin	2D-dgx + D-glu	
	Gluco-*neo*-digoxin	Digoxigenin	3D-dgx + D-glu	
D. purpurea	Acetylglucogitoroside	Gitoxigenin	Ac-dgx + D-glu	93
	Acetyl digitalinum verum	Gitoxigenin	Ac-dgl + D-glu	
	Purlanoside A	Digitoxigenin	Ac-dgx + 2dgx + glu	
	Purlanoside B	Gitoxigenin	Ac-dgx + 2dgx + glu	
	D. grandiflora.[94]			

STERCULIACEAE

Species	Glycoside	Genin	Sugar	Reference
Mansonia altissima	Mansonin	Strophanthidin	2,3-di-OMe-6 deoxy-D-glu	95
	Strophalloside	Strophanthidin	D-allme	
	Strophothevoside	Strophanthidin	3-OMe-D-glume	
	Glycoside P	Strophanthidin	glume	
	Glycoside Q	Nigrescigenin	allme + glume	
	Glycoside R	Nigrescigenin	glume	

* Ac—acetyl; acf—acofriose; acv—acovenose; all—allose; allme—allomethylose; boi—boivinose; can—canarose; cym—cymarose; dgx—digitoxose; dgl—digitalose; dgn—diginose; fuc—fucose; glu—glucose; gu—gulose; glume—glucomethylose; gume—gulomethylose; jav—javose; Me—methyl; ole—oleandrose; rhm—rhamnose; sar—sarmentose; tal—talose; talme—talomethylose; thu—thulose; thv—thevetose; val—vallrose; xy—xylose.

† The genins marked with an asterisk (*) were, in addition, isolated in the free state from the plant.

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SYNTHESIS

Despite the spectacular advances in the field of steroid synthesis in the last two decades, no attempts were made at the total synthesis of cardiac genins until 1962 when Sondheimer *et al.*[96] synthesized digitoxigenin from 3β-acetoxy-14β-hydroxy-5β-etianate. Soon after, the synthesis of periplogenin[97] was announced and recently syntheses of a variety of new cardenolides have been accomplished utilizing a furfural intermediate as the starting material.[98] Sondheimer has recently summarized the synthetic approaches towards cardiac genins.[99]

The synthesis of cardiac glycosides has been beset with difficulties because of the labile nature of C-14 hydroxyl of the genin which is easily removed by acids to give anhydrogenins and in the presence of methanolic alkali leads to the formation of isogenins. However, a large number of synthetic monosides have been prepared which have been recently reviewed[100] in a comprehensive manner.

The synthetic lyxose, xylose and arabinose monosides of strophanthidin are less effective than the naturally occurring strophanthidin monosides. Nevertheless, synthetic α-L-mannoside of strophanthidin has the highest recorded potency[101] for any cardenolide so far. A partial synthesis[102] of erychroside from strophanthidin digitoxoside has been recently reported.

MICROBIOLOGICAL AND CHEMICAL TRANSFORMATIONS

The last decade has been significant for the developments in the field of microbiological transformations of the cardenolides.[103, 104] Tamm *et al.*[105] for the first time showed that *Fusarium lini* produced digoxigenin by 12β-hydroxylation of digitoxigenin and converted gitoxigenin into diginatigenin.[106]

After the success of these initial experiments a variety of micro-organisms have been employed to achieve dehydrogenations,[107] hydroxylations,[108] hydrolysis,[109] aromatiza-

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tions,[110] oxidations,[111] reductions,[112] etc. Fermentation procedures for the synthesis of genins have been developed[113] and in some cases new genins have been produced which have not been encountered so far in the plant kingdom.

METABOLISM AND INOTROPIC ACTION

The metabolism of cardenolides in animals is mainly effected by enzymes in the liver and no changes take place at the site of action, namely the heart. There does not seem to be any evident relationship, therefore, between metabolism and the mechanism of action of cardiotonic compounds.[114]

The major pathway of metabolism of cardenolides is via hydroxylation at various centres although the lactone ring appears to be unaffected. 12β-Hydroxylation of digitoxin, digitoxigenin digitoxoside, gitoxigenin-digitoxoside, xysmalogenin, etc., has been observed in many animals although not in guinea pigs.[115] It appears that hydroxylation converts the lipid-soluble compounds into polar derivatives which can be more easily excreted, generally as glucuronides.[116]

The 3β hydroxyl is another focus of enzymic action which gives rise to inactive 3α-hydroxylated products and can be regarded as a detoxification mechanism.[117] The sugars of the cardiac glycosides also undergo stepwise hydrolysis in the animal body but this is a slower process than the inversion of the C-3 hydroxyl. The attachment of a sugar moiety to 3β-hydroxyl thus acts as a protecting group against rapid epimerization and consequently glycosides have a longer duration of action.[117, 118]

It has now been established that the cardenolides exhibit an inotropic effect due to the presence of specific receptor enzymes in the cardiac muscle cell membrane and these have been identified as ATPases.[119, 120] These enzymes are involved in the active "transport" of Na and K ions which are gained or lost by the cell with each contraction of the heart.

The positive inotropic effect and toxic action of digitalis on the heart is diminished or eliminated by raising the K concentration in the medium. The basis of this antagonism may be a competition between digitalis and K for the same binding site on the outer surface of the cell.[121, 122] The role of Ca and Na ions is also becoming clear and, on the whole, a reasonable assumption has been made that the sodium influx during depolarization phase

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of the muscle contraction allows or facilitates an attack of digitalis on the transport-ATPase.[119, 123]

A comparison of 21 cardenolides[122] revealed that in most cases the ability of the drug to block the transport-ATPases parallels its inotropic action in the intact animal. Thus, affinity of the compounds for the receptor enzyme appears to be the decisive factor and not their distribution or metabolism in the body. The present information favours the view that the $\Delta\alpha\beta$ carbonyl function of butenolide ring is the key grouping which forms the link for the first one point attachment of the molecule through a hydrogen bond to the -OH of the phosphoric acid residue in the phosphorylated receptor enzyme.[124] This binding of the inhibitor to the enzyme prevents access of K to the phosphorylated enzyme and thus K-dependent phosphorolysis is inhibited—the overall result being the inhibition of ATPase system.

The lactone ring plays its crucial role only in the 17β orientation and, likewise, a C-3 hydroxyl in the β position possibly facilitates the close apposition of the molecule to the enzyme surface. The other polar groups appear to play only minor roles in contributing to the receptor-cardenolide association. From the experiments on ATPase inhibition[122, 125] by therapeutically and toxically active concentrations of digitalis (dose/effect relation), it has been postulated that the therapeutic and toxic actions are related to a moderate or strong inhibition of the transport-ATPase. The use of this system opens a new approach to the problem of structure-activity relationships and might be utilized as part of a screening programme.

Some cardenolides also exhibit cytotoxic and brain transport-ATPase inhibiting effect.[126–128] It has been suggested[127] that drug receptors in these systems may be structurally very similar to those present in the cardiac cell membrane.

BIOSYNTHESIS

The biosynthesis of digitoxigenin has been studied recently in *Digitalis purpurea* and it has been established that the steroid nucleus, as expected, originates from mevalonic acid (MVA) via squalene.[129] The butenolide ring of the molecule, however, originates from acetate as was shown by feeding the plant with acetate-1-^{14}C which yielded C-20 and C-23 labelled digitoxigenin.[130]

Tschesche *et al.* has found that C_{21}-steroids with a keto group at C-20 are specific precursors of cardenolides in plants. Feeding of Δ^5-pregnan-3β-glucoside-20-one-21-^{14}C to *D. lanata*[131] leads to the formation of radioactive butenolide derivatives such as digitoxigenin, xysmalogenin, gitoxigenin and digoxigenin. This has been confirmed by the studies of Reichstein[132] who fed mevalonic-3-^{14}C acid to *D. purpurea* and isolated C-20 labelled digitoxigenin. More recent studies using labelled pregnenolone and progesterone has

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confirmed these results for other cardenolides.[133] Thus the biosynthesis of cardenolides proceeds through a pregnan derivative which needs only 1 molecule of acetate to form the butenolide ring.

The biosynthesis of the deoxy sugar, digitoxose, has also been studied in *D. lanata* and *D. purpurea*[134] using D-glucose-6-^{14}C. In the resultant digitoxin, digitoxigenin was four times more active per mole than digitoxose which can best be explained on the assumption that the plant converts 1 mole of glucose into 3 moles of acetic acid. The digitoxose, thus obtained, was proved to be formed from glucose without rearrangement of the carbon chain.

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