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Newer Cardiac Glycosides and Aglycones[1]

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A total of 50 steroidal substances, mostly of plant origin, have been tested pharmacologically, and assayed in cats for their cardiac activity, using cessation of the heart as the end point. Forty-five of them are glycosides of the cardenolide type, or free aglycones. They are derivatives of digitoxigenin, uzarigenin, periplogenin, sarmentogenin, gitoxigenin, strophanthidin, and strophanthidol with various substituents. Monosides are generally more potent than biosides, or their corresponding aglycones. The most active glycoside of the entire series is panoside which has a value of 13.14 mean LD's/mg. 3-Epimerization, 17α-orientation, or formation of a double bond from the 5β- or 16β-hydroxy group usually results in a weak to an inactive product. Drevogenin A (XI) is a pregnane derivative; it has no digitalis-like effect. Calactin of the milkweed family is stored in the body of American monarch butterfly or African grasshopper. This is the first example of a potent glycoside of the cardenolide structure that occurs in the animal tissues. The toad synthesizes bufadienolides, but not their glycosides. In this collection of compounds, arenobufagin (XVI) and ψ-bufarenogin (XV) are derived from the toad poison. The results of two new glycosides (XIII and XIV) of red squill are reported; their aglycones have the bufadienolide structure.

While the 324th paper[2] appeared from the Institute of Organic Chemistry, University of Basel, we have accumulated pharmacological data on 50 additional cardiac glycosides and aglycones. As shown in Table I, 49 of them were obtained from natural sources, and one was partially synthesized. The results afford some structure–activity relationships of variations in the steroid nucleus or side chain. It becomes evident that animals other than the toad are capable of storing glycosides of the cardenolide type from their plant foods. Such examples are pointed out in the discussion. Most of the 50 substances studied are biosynthesized by plants.

Methods

As in previous investigations[3,4] the first objective was to demonstrate the presence or absence of digitalis-like action of each new substance, and to assess its potency in etherized cats if positive evidence was obtained. The cat is the most sensitive laboratory animal, less subject to environmental changes. When sufficient (8–10) animals are used the geometrical mean lethal dose (LD) can be determined and the standard error computed as the limit of reliance. Similar compounds are best compared simultaneously in the same colony of cats in order to minimize any bias. The electrocardiographic changes from start to finish are so characteristic that they are not duplicated by any known drug.

The supply of each rare and valuable material from our collaborators seldom exceeded 30–50 mg. If the mean LD is 0.1 mg/kg, or smaller, a quantity of 5–10 mg is ample for the necessary information. The initial procedure consisted of making a stock solution of 0.1% by weighing 5 mg into a 5-ml volumetric flask, and dissolving the substance in EtOH followed by H_2O in equal volumes. A dilution of 50,000 was then made up, and injected into an etherized cat from a 50-ml buret at the rate of 1 ml/min with the electrocardiograph connected to the animal. The results of this first experiment guided further dilutions so that a 2-kg cat was killed within 30–60 min in order to arrive at the mean LD. The weight of cats varied from 1.6 to 2.9 kg. Female animals in advanced pregnancy were rejected. The mean LD so determined is an expression of potency, actually the full cardiotoxicity. It can serve as a safe hint for initial clinical trials. A dose of 3 to 5 mean LD, injected iv, lowers the ventricular rate of auricular fibrillation. Examples can be found in the first human tests of cinobufagin[5] and thevetin.[6]

It must be realized that the cat method, even though by the identical procedure, only gives a figure for comparative purposes, but does not measure the rate of destruction–accumulation *vs.* rapid disappearance. Fortunately, none of the substances left the animal body as fast as it was injected. Additional investigations would establish the optimal clinical dose. Thus the digitalization and maintenance doses of digitoxin

(1) This work was supported in part by U. S. Public Health Service Grant HE-07714 and the Indiana Heart Association.

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Table I

Source and Activity of Glycosides and Aglycones

Source	Compound	Reference	LD ± SE, mg/kg, cats
Pergularia extensa, stem and seed, or *Calotropis procera*, latex	Calactin	*b*	0.118 ± 0.006
	Calotropageoin	*c*	1.572 ± 0.151
Asclepias glaucophylla, root	Asrleposide	*d*	0.746 ± 0.114
Gongronema gazense, wood	Periplogenin-Dgx-Cym[a]	*e, f*	0.308 ± 0.021
	3-Episarmentogenin		2.960 ± 0.214
	Sarmentogenin-Cym-Cym		0.399 ± 0.029
	Sarmentogenin-Dgx-Cym-Cym		0.311 ± 0.019
	Sarmentogenin-Dgx-Cym		0.180 ± 0.011
Pachycarpus schinzianus, root and seed	Pachygenin	*g, h*	2.552
	Pachygeool		Survived 6.171
	Carpogeool		4.171
	Pachomoboside		0.665 ± 0.058
Xysmalobium undulatum, root	Uzarigeoin	*i, j, k, l*	1.379 ± 0.085
	3-Epiuzarigenin		7.605
	17α-Uzarigenin		3.159 Survived
Coronilla glauca, seed	*allo*-Glaucotoxigenin	17	One died with 3.57, one survived 4.62
Parquetina nigrescens, wood	Nigrescigenin	*m, n*	0.229 ± 0.007
	16-Dehydrostrophanthidin	25	2.067 ± 0.284
Dregea volubilis, seed	Drevogeoin A	*o*	Survived 14.4 and 20
Strophanthus gratus, seed	Strogoside	*p*	4.850
Strophanthus kombé, seed	Erysimoside	*q, r*	0.174 ± 0.007
	Erysimosol		0.149 ± 0.009
	17α-Helveticoside		Survived 1.745
Beaumontia grandiflora, seed	Beaumontoside	*s*	0.173 ± 0.011
	Wallichoside		0.200 ± 0.010
	Beauwalloside		0.200 ± 0.013
Nerium oleander, seed	Adigoside	*t*	Survived 4.91 and 11.3
Acokanthera oppositifolia, seed	Acobioside A	*u, v*	0.153 ± 0.004
	Opposide		0.104 ± 0.005
Acokanthera oblongifolia, seed	Acospectoside A	11	1.806
Vallaris solanacea, seed	Vallaroside	*w, x*	0.171 ± 0.007
	Mono-*O*-acetylvallaroside		0.314 ± 0.023
	Vallarosolanoside		0.329 ± 0.003
	Solanoside		0.175 ± 0.009
	Mono-*O*-acetylsolanoside		0.317 ± 0.012
	Mono-*O*-acetylacoschimperoside P		0.302 ± 0.023
	16-Desacetyl-16-anhydroacoschimperoside P		Survived 2.88 and 3.56
Streblus asper, root bark	Ghcostrebloside	*y*	0.208 ± 0.015
Mallotus philippinensis, seed	Corotoxigenin-Rha[a]	*z*	0.105 ± 0.007
Mallotus paniculatus, seed	Malloside	*a,a*	0.165 ± 0.012
	Panoside		0.076 ± 0.003
Mansonia altissima, seed	Strophothevoside	*b,b*	0.103 ± 0.004
	al-Dihydromansonin		0.140 ± 0.010
	al-Dihydrostrophothevoside		0.103 ± 0.006
Erysimum perofskianum, seed	Eryperoside	*c,c*	0.175 ± 0.012
	Erycorchoside		0.301 ± 0.028

TABLE I (*Continued*)

Source	Compound	Reference	LD ± SE, mg/kg, cats
Urginea maritima, bulb	Scillarenin-Gls[a]	*d,d*	0.111 ± 0.006
	Scillirubroside		0.163 ± 0.012
Chan Su, toad poison cake	ψ-Bufarenogin	*e,e*	Survived 2.65 and 4.92
Partial Synthesis	16-*O*-Isovalerylgitoxin	12	2.27

[a] Abbreviations of sugars: Dgx, digitoxose; Cym, cymarose; Rhs, rhamnose; Gls, glucose. [b] O. P. Mittal, Ch. Tamm, and T. Reichstein, *Helv. Chim. Acta*, **45**, 907 (1962). [c] C. H. Hassall and K. Reyle, *J. Chem. Soc.*, **85**, (1959). [d] J. M. do Nasciemnto, Jr., Ch. Tamm, H. Jäger, and T. Reichstein, *Helv. Chim. Acta*, **47**, 1775 (1964). [e] M. L. Lewbart, W. Wehrli, and T. Reichstein, *ibid.*, **46**, 540 (1963). [f] M. L. Lewbart, W. Wehrli, H. Kaufmann, and T. Reichstein, *ibid.*, **46**, 517 (1963). [g] W. Schmid, H. P. Uehlinger, Ch. Tamm, and T. Reichstein, *ibid.*, **42**, 72 (1959). [h] L. F. Fieser, T. Golab, H. Jäger, and T. Reichstein, *ibid.*, **43**, 102 (1960). [i] J. Polonia, A. Kuritzkes, H. Jäger, and T. Reichstein, *ibid.*, **42**, 1138 (1959). [j] A. Kuritzkes, J. V. Euw, and T. Reichstein, *ibid.*, **42**, 1502 (1959). [k] R. Tschesche, W. Freytag, and G. Snatzke, *Chem. Ber.*, **92**, 3053 (1959). [l] A. M. Kuritzkes, Ch. Tamm, H. Jäger, and T. Reichstein, *Helv. Chim. Acta*, **46**, 8 (1963). [m] E. Schenker, A. Hunger, and T. Reichstein, *ibid.*, **37**, 1004 (1954). [n] R. Berhold, W. Wehrli, and T. Reichstein, *ibid.*, **48**, 1634, 1659 (1965). [o] H. H. Sauer, Ek. Weiss, and T. Reichstein, *ibid.*, **48**, 857 (1965). [p] U. P. Geiger, Ek. Weiss, and T. Reichstein, *ibid.*, **50**, 194 (1967). [q] F. Kaiser, E. Haack, M. Gube, U. Dölberg, and H. Spingler, *Naturwissenschaften*, **46**, 670 (1959). [r] R. Zelnik, J. V. Euw, O. Schindler, and T. Reichstein, *Helv. Chim. Acta*, **43**, 593 (1960). [s] A. F. Krasso, Ek. Weiss, and T. Reichstein, *ibid.*, **46**, 1961 (1963). [t] St. Hoffmann, Ek. Weiss, and T. Reichstein, *ibid.*, **49**, 1855 (1966). [u] P. Hauschild-Rogat, J. V. Euw, O. Schindler, Ek. Weiss, and T. Reichstein, *ibid.*, **45**, 2116 (1962). [v] P. Hauschild-Rogat, Ek. Weiss, and T. Reichstein, *ibid.*, **50**, 2299, 2322 (1967). [w] H. Kaufmann, W. Wehrli, and T. Reichstein, *ibid.*, **48**, 65 (1965). [x] H. Kaufmann, *ibid.*, **48**, 83 (1965). [y] A. R. Manzetti and T. Reichstein, *ibid.*, **47**, 2303, 2320 (1964). [z] K. D. Roberts, Ek. Weiss and T. Reichstein, *ibid.*, **46**, 2886 (1963). [a,a] K. D. Roberts, Ek. Weiss, and T. Reichstein, *ibid.*, **49**, 416 (1966); *ibid.*, **50**, 1645 (1967). [b,b] H. Allgeier, Ek. Weiss, and T. Reichstein, *ibid.*, **50**, 431, 456 (1967). [c,c] Z. Kowalewski, H. Jäger, O. Schindler, and T. Reichstein, *ibid.*, **43**, 957 (1960). [d,d] A. V. Wartburg, *ibid.*, **47**, 1228 (1964); *ibid.*, **49**, 30 (1966). [e,e] K. Huber, H. Linde, and K. Meyer, *ibid.*, **50**, 1994 (1967).

TABLE II

STRUCTURE–ACTIVITY RELATIONSHIP

Compound	Skeleton formula	Variant[a]	LD ± SE per mg
Beaumontoside	I	R = α-L-Ols	5.77 ± 0.38
Wallichoside	I	R = α-L-Cys	5.00 ± 0.24
Vallaroside	I	R = α-L-Vls	5.86 ± 0.23
Mono-*O*-acetylvallaroside	I	R = α-L-Vls (ac)	3.19 ± 0.23
Solanoside	I	R = α-L-Acfs	5.70 ± 0.29
Mono-*O*-acetylsolanoside	I	R = α-L-Acfs (ac)	3.16 ± 0.12
Uzarigenin	I	R = H; 5α-H	0.73 ± 0.04
3-Epiuzarigenin	I	R = α-OH; 5α-H	0.13
allo-Uzarigenin	I	R = H; 5α-H; 17α-	Inactive
Ascleposide	I	R = β-D-Alms	1.34 ± 0.20
Acobioside A	II	R = α-L-Acvs-β-D-Gls; R′ = H	6.51 ± 0.17
Acospectoside A	II	R = α-L-Acvs-β-D-Gls; R′ = Ac	0.55
Periplogenin cymarosido-digitoxoside	III	R = β-D-Dxs-α-L-Cys; 5β-OH	3.25 ± 0.23
3-Episarmentogenin	IV	R = 3α-OH; 11α-OH	0.34 ± 0.24
Sarmentogenin biscymaroside	IV	R = (α-L-Cys)$_2$; 11α-OH	2.50 ± 0.18
Sarmentogenin biscymarosido-digitoxoside	IV	R = β-D-Dxs (-α-L-Cys)$_2$; 11α-OH	3.21 ± 0.20
Sarmentogenin cymarosido-digitoxoside	IV	R = β-D-Dxs-α-L-Cys; 11α-OH	5.54 ± 0.35
Opposide	IV	R = α-L-Tls (des); 1β-OH, 5β-OH; 11α-OH	9.57 ± 0.42
Malloside	IV	R = α-L-Rhs; 5α-H; 11β-OH	6.05 ± 0.42
Vallarosolanoside	V	R = α-L-Vls; R′ = Ac	3.04 ± 0.003
Mono-*O*-acetylacosch-imperoside P	V	R = α-L-Acfs (ac); R′ = Ac	3.31 ± 0.40
Beauwalloside	V	R = α-L-Cys; R′ = Ac	4.99 ± 0.32
Adigoside	V	R = β-D-Dns; R′ = isovaleryl	Trivial action
16-*O*-Isovalerylgitoxin	V	R = (β-D-Dxs)$_3$; R′ = isovaleryl	2.28
16-Desacetyl-16-anhydro-acoschimperoside P	V	R = α-L-Acfs; R′ = Δ^{16}-	Inactive
Corotoxigenin rhamnoside	VI	R = β-D-Rhs	9.51 ± 0.62
Calotropagenin	VI	R = H; 2α-OH	0.64 ± 0.06
Calactin	VI	R = Uncertain sugar conjugated with 2α-OH and 3β-OH	8.47 ± 0.36

Table II (*Continued*)

Compound	Skeleton formula	Variant[a]	LD ± SD per mg
allo-Glaucotoxigeoin	VI	R = H; 15β-OH	0.28
Erycorchoside	VII	R = β-D-Bys-α-D-Gls	3.33 ± 0.31
Eryperoside	VII	R = β-D-Dxs-α-D-Gls	5.70 ± 0.39
Erysimoside	VII	R = β-D-Dxs-β-D-Gls	6.27 ± 0.27
Glucostrebloside	VII	R = β-D-Fcs (Me)$_2$-β-D-Glc	4.80 ± 0.34
allo-Helvetinoside	VII	R = β-D-Dxs; 17α-	Inactive
Strophothevoside	VII	R = β-D-Gls (Me, des)	9.66 ± 0.35
Nigrescigenin	VII	R = H; 11α-OH	4.36 ± 0.13
16-Dehydrostrophanthidin	VII	R = H; Δ^{16}-	0.48 ± 0.07
Pachygenin	VII	R = H; Δ^5-	0.39
Pachomoroside	VII	R = β-D-Gls; Δ^5-	1.50 ± 0.13
Erysimosol	VIII	R = β-D-Dxs-β-D-Gls	6.73 ± 0.40
al-Dihydromansonin	VIII	R = β-D-Gls (Me_2, des)	7.12 ± 0.49
al-Dihydrostrophothevoside	VIII	R = β-D-Gls (Me, des)	9.53 ± 0.60
Pachygenol	VIII	R = H; Δ^5-	Inactive
Carpogenin	IX	R = 3α-OH	0.24
Panoside	X	R = α-L-Rhs; 5α-H; 11β-OH	13.14 ± 0.57
Drevogenin A	XI	R = 3β-OH; Δ^5-; 11α-isovaleryl-O-; 12β-OH	Inactive
Strogoside	XII	R = α-L-Tls (des); 1β-OH; 5β-OH; 11, 19-lactone	0.21
Scillarenin glucoside	XIII	R = β-D-Gls	8.99 ± 0.48
Scillirubroside	XIV	R = β-D-Gls	6.13 ± 0.46
ψ-Bufarenogin	XV		Inactive
Arenobufagin	XVI		12.9 ± 1

[a] Sugars abbreviated after Nover, *et al.*[10] Ols = oleandrose; Cys = cymarose; Vls = vallarose; Vls (ac) = 2-acetylvallarose; Acfs = acofriose; Acfs (ac) = 2-acetylacofriose; Alms = allomethylose; Acvs = acovenose; Gls = glucose; Dxs = digitoxose; Tls (des) = 6-deoxytalose; Rhs = rhamnose; Dus = diginose; Bys = bivanose; Fcs (Me)$_2$ = 2,3-di-*O*-methylfucose; Gls (Me_2, des) = 2,3-di-*O*-methyl-6-deoxyglucose; Gls (Me,des) = 3-*O*-methyl-6-deoxyglucose.

are smaller than those of digoxin[7] although the former by iv measurement is theoretically less potent than the latter.

A few compounds in Table I were sparingly soluble in dil EtOH, requiring 58–68% by volume for the stock solution (uzarigenin, 3-epiuzarigenin, *allo*-uzarigenin, and pachygenin). An overwhelming majority of the products were soluble in 50% EtOH. The ultimate dilutions (with saline) for the most potent members of the group varied from 1:100,000 to 1:200,000; and those of lessor activity, from 1:10,000 to 1:25,000. Several others were so weak, or inactive, that their stock solutions were intermittently injected through a microburet. A total of 411 cats were employed in this work.

Frogs were used in a few instances for confirmatory purposes. They consumed much material and, with borderline active compounds, they often showed negative results in contrast with the cat.

Results and Discussion

The 50 substances are rearranged in Table II for convenient comparison of their structures. To save space, discussions were presented together with the results. The mean LD's of the active compounds were converted into their reciprocals as shown in the last column, namely, the number of LD's per milligram. This expresses a direct relationship of activity (or toxicity)—the larger the number, the more potent the product. In considering the data we found the recent reviews by the authorities of the field most helpful.[8–10]

The first 6 glycosides in Table II are those of digitoxigenin (I). They are all monosides and more active than the aglycone which has a value of 2.18 ± 0.07/mg.[3] Vallaroside, beaumontoside, solanoside, and wallichoside have the highest activity. The favorable influence of L-oleandrose, L-cymarose, L-vallarose, and L-acofriose, conjugated with the secondary OH group at C-3, is obvious. Monoacetylation in the sugar residue apparently diminishes the potency as indicated by mono-*O*-acetylvallaroside and mono-*O*-acetylsolanoside.

Uzarigenin is isomeric with digitoxigenin, but has a 5α-H and thus an A/B-*trans* configuration. In cats, it is definitely active, although weak. Four samples were assayed, supplied by Professor T. Reichstein: three prepared from odoroside B with mean LD's of 1.52 ± 0.18 in 10 cats, 0.94 ± 0.07 in 5 cats, and 1.49 ± 0.16 in 8 cats; another isolated from *Xysmalobium undulatum* with a mean LD of 1.44 ± 0.14 mg/kg. Since the standard errors denoted narrow variance, all the figures for 31 cats were combined. The mean LD was computed to be 1.38 ± 0.08 mg/kg, and the reciprocal 0.73 ± 0.04 LD/mg (Table II). During the slow intravenous injection in cats, uzarigenin provoked convulsive movements of extremities, acceleration of

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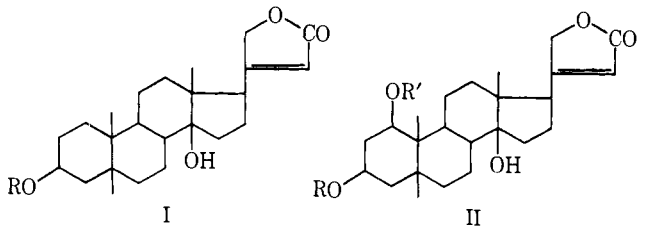

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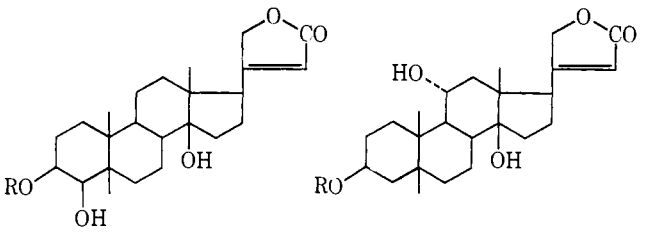
II



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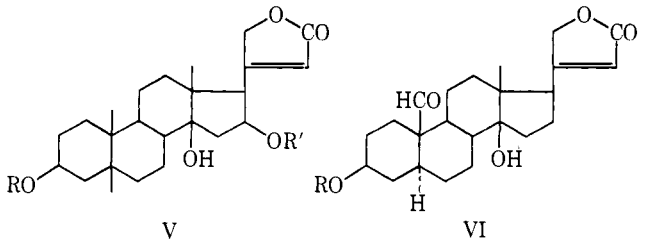

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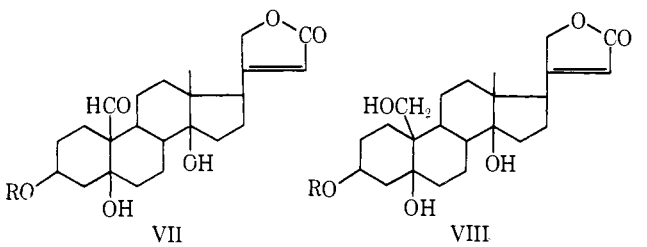

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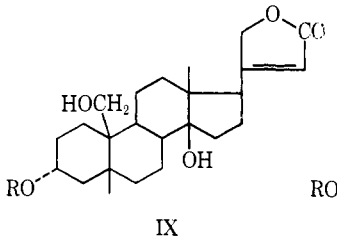
VIII



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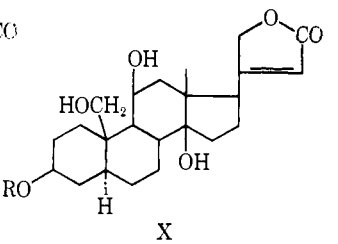

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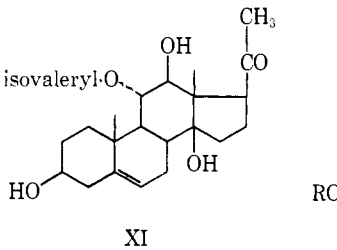

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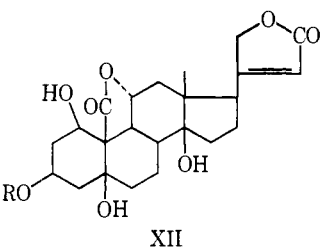

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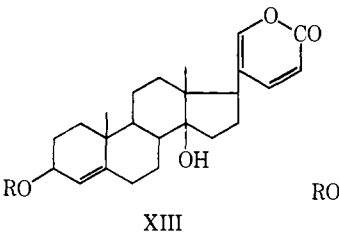

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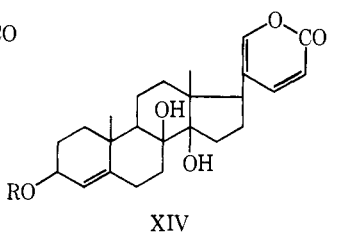

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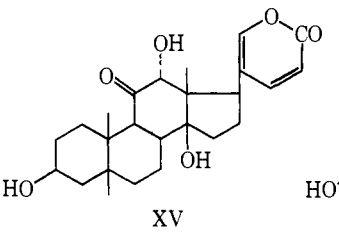

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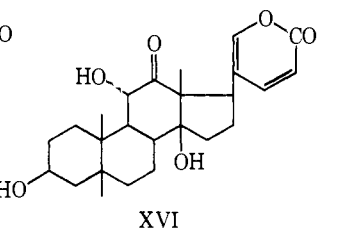

XVI

respiratory rate, and increase in salivary secretion. These effects did not occur with most active compounds. The results in frogs were negative in two series of experiments, the doses varying from 55 to 64 mg/kg.

Two other isomers of uzarigenin were also investigated: 3-epiuzarigenin and *allo-* or 17α-uzarigenin. The former killed a single cat with a dose of 7.60 mg/kg accompanied by primary bradycardia and terminal tachycardia. No systolic standstill was observed in frogs with doses of 40–43 mg/kg. 17α-Uzarigenin showed no activity in the amounts tested. One single cat survived a dose of 3.16 mg/kg, and a single frog, a dose of 60 mg/kg. Ascleposide, a monoside of uzarigenin, was proved moderately active. Like other glycosides of cardenolide, it is more potent than its aglycone.

Acobioside A is a bioside of *Acokanthera oppositifolia*. Its aglycone, acovenosigenin A,[8] has a free OH group at C-1 (II). Acospectoside A is a similar glucoacovenoside isolated from *A. oblongifolia*. In the last communication, Kapadia[11] suggested that it has an acetyl group at C-1. Both glycosides were studied in our laboratory. Acospectoside A had less than 0.1 the potency of acobioside A.

Of the 5 substances from *Gongronema ganzense* (Table I), periplogenin cymarosidodigitoxoside has a free 5β-OH (III) while the remaining four have an 11α-OH. Sarmentogenin cymarosidodigitoxoside is the most potent of the group showing the superiority of sarmentogenin (IV) over periplogenin. As expected from experience, the presence of a 3α-OH in the structure of 3-episarmentogenin weakens the activity even though the 11α-OH is preserved.

The aglycone, gratogenin, of opposide (IV) differs from ouabagenin in its lack of a carbinol group at C-10. Opposide has a slightly higher potency than that of ouabain (8.62 LD/mg). Malloside has an uncommon aglycone, mallogenin,[8] with 5α-*H* and 11β-OH. The rhamnoside of this aglycone has a substantial degree of cardiac activity (Table II).

The next 6 glycosides are derivatives of gitoxigenin (V). The three monosides of 16-acetyl esters have substantial activity. The rare occurrence of isovaleryl substitution in adigoside greatly reduced the activity. Two cats survived 4.91 and 11.29 mg/kg, respectively. The larger dose induced token response as evidenced by emesis; and electrocardiographically, nodal rhythm, ventricular premature beats, and bundle-branch-block. Baumgarten[12] succeeded in preparing 16-*O*-isovaleryl-gitoxin. A single cat succumbed to a dose of 2.28 mg/kg. The presence of a double bond between C-16 and C-17 in the case of 16-desacetyl-16-anhydroacoschimperoside P greatly diminishes the characteristic effect of digitalis, for two cats survived 3.56 and 2.88 mg/kg, respectively.

The rhamnoside of corotoxigenin (VI) which has a 5α-*H* and an aldehyde at the angular C-10, is unusually

(11) G. J. Kapadia, *J. Pharm. Sci.*, **58**, 1555 (1969).

(12) G. Baumgarten, private communication, May 10, 1967.

active. Calotropagenin with an additional 2α-OH is weak, but its monoside, calactin, possesses outstanding cardiac activity. The cyclic conjugation of an unknown hexose offered a challenge to several research centers until clarification occurred lately.[13-15] Calactin is as potent as calotropin, the value of which was recorded previously.[16] The presence of a 15β-OH in *allo*-glaucotoxigenin results in low activity. The structure of this aglycone has been elucidated recently.[17]

There is another interesting feature regarding calactin. The monarch butterfly of North America stores cardiac glycosides. It is the larva of this insect that feeds on poisonous calactin-containing species of the milk-weed family (*Asclepiadaceae*), and carries the ingredients to adulthood. Experiments conducted in several laboratories[18-21] furnished evidence, both chemically and pharmacologically, to substantiate the presence of calactin. This is the first discovery to illustrate the presence of cardenolides in the animal body as glycosides.

A North African grasshopper, which consumes *Calotropis procera* as its food, develops a special pair of glands for storage of cardiac glycosides and other substances. Indeed, calactin and calotropin have been isolated in crystalline form from its glandular secretions.[20,22] The presence of the two cardenolides in the form of glycosides, ingested from plants, probably serves the purpose of self-protection.

For years, the toad has been known to elaborate digitalis-like substances in its parotoid secretion. Careful work by masters in chemistry shows that, without exception, the active products are bufadienolides, as reviewed recently.[23] This amphibian animal of different regions is capable of synthesizing highly potent aglycones, but does not utilize any molecule of sugar to produce glycosides. Occasionally, some bufadienolides are identical with aglycones of plant origin, such as bufotalidin *vs.* hellebrigenin.[24]

The next 10 products are analogs of strophanthidin (VII). The 4 biosides from erycorchoside to glucostrebloside all have strong cardiac action. Erysimoside is glucohelveticoside. Our material came from two sources. The first sample was supplied by Dr. F. Kaiser, and was found to have a mean LD of 0.17 ± 0.01 mg/kg in 10 cats; and the second by Professor T. Reichstein, the mean LD being 0.16 ± 0.01 also in 10 cats. *allo*-Helveticoside with a 17α configuration is devoid of action. The monoside, strophothevoside, is a highly potent glycoside, reminiscent of the enhancing effect of some deoxy sugars discussed by Zorbach and Bhat.[9] Nigrescigenin has been proven identical with sarmentosigenin A.[25] The 11α-OH group appears to increase the activity. A double bond between C-16 and C-17, or C-5 and C-6, decreases the cardiac action as shown by the next two cardenolides. The conjugation of a molecule of glucose, however, augments the potency more than 3 times as in the case of pachomonoside when compared with pachygenin.

The next 4 cardiac steroids are related to strophanthidol (VIII) which differs from strophanthidin in having a carbinol group at C-10 instead of CHO. Both substituents generally, and sometimes equally, make potent glycosides. When dehydration takes place to give rise to a Δ^5 derivative, unfavorable effects appear. Thus pachygenol practically loses its activity while pachygenin becomes very weak. Carpogenin (IX) with 3α-OH and 5β-H retains a slight action. Panoside, on the other hand, is the most potent of the whole series of compounds. Its aglycone, panogenin (X), has 5α-H and 11β-OH.[8] Drevogenin A was isolated some 20 years ago, but it proved to be a derivative of pregnane (XI), not a cardenolide.[26] Accordingly it has no cardiac action. Strogoside is an unusual glycoside in that it has a second lactone involving a 19-COOH and 11α-OH (XII). It has a low value (Table II).

The last 4 substances are derivatives of bufadienolides, two from the plant red squill, *Urginea maritima*, and the other two from the Chinese toad poison, *Chan Su*. Introduction of 8β-OH in scillarenin (XIII) glucoside, *i.e.*, scillirubroside (XIV) reduces activity. The very last two toad sterols are isomers (XV and XVI), but surprisingly arenobufagin is one of few potent bufadienolides while ψ-bufarenogin is entirely inactive in the doses studied. Professor Kuno Meyer sent the two samples at the same time so that direct comparisons were made with the same colony of cats. The difference of results is decisive, and reminiscent of the structure of sinoside which also has 11α-OH–12-keto configuration.[27]

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