Physical Sciences Section

Pak. j. sci. ind. res. vol. 33, no.4, April 1990

CHEMICAL CONSTITUENTS OF *NERIUM OLEANDER*

SALIMUZZAMAN SIDDIQUI, BINA S. SIDDIQUI, SABIRA BEGUM AND FARRUKH HAFEEZ

H.E.J. Research Institute of Chemistry, University of Karachi, Karachi-32, Pakistan

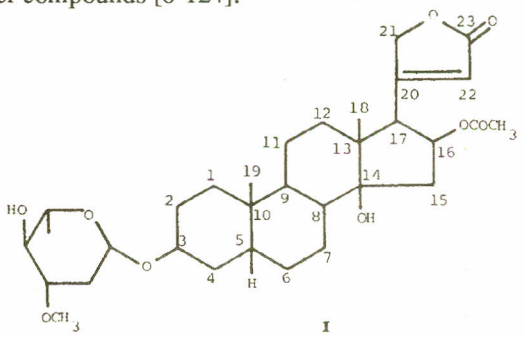
(Received April 3, 1990)

Studies on the chemical constituents of *Nerium oleander* are reviewed. The isolation, unique features of the structures, biosynthetic aspects, and biological significance of these constituents are discussed.

Key words: *Nerium oleander*, Biosynthetic aspects, Chemical constituents.

Introduction

Nerium oleander (Apocynaceae) (Syn. *N. odorum* Soland; *N. indicum* Mill) commonly known as "kaner", is a native of Indo- Pakistan sub-continent, widely distributed in the Mediterranean region and sub-tropical Asia. Various parts of the plant are highly reputed in the traditional systems of medicine, for the treatment of a variety of human ailments [1-5]. Leaves possess cardiotonic, diuretic, antibacterial properties and are used against snake bites. Roots have been used externally for the cure of different types of cancers, ulcers, leprosy, headache, eye diseases, ringworm and other skin complaints. Studies in the constituents of this plant were undertaken as far back as 1861, when Lukowski reported the isolation of the first cardio-tonic principle oleandrin [6] (I), from this plant. Subsequent investigations of different parts of the plant resulted in the isolation of about two hundred constituents including glycosides, steroids, terpenoids and other compounds [6-124].



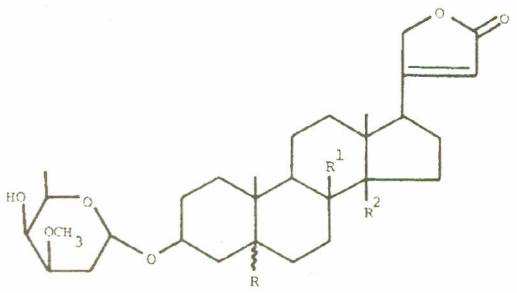
I

Extracts of various parts of the plant and their constituents have also been studied for their pharmacological activity by different groups of workers [6-9]. On the other hand, laboratory experiments carried out in 1957 showed insecticidal activity of the leaves against sugar cane mites and citrus leaf minor [125-126].

The object of this review is to briefly describe the chemical constituents isolated so far from this plant with a reference to their significant structural and pharmacological features. These are tabulated under the headings glycosides, terpenoids and steroids (Table 1) and miscellaneous compounds (Table 2).

Glycosides, steroids and terpenoids. Apart from oleandrin a series of cardiac and other steroidal and nonsteroidal glycosides have been reported by various groups of workers (Table 1). Several of these have been fully characterized through intensive chemical and spectral studies. One of the glycosides reported earlier with the name folinerin [12,13] is however now treated as the same glycoside as oleandrin*.

Pharmacologically and chemically oleandrin and adynerin [15] (II) belong to the group of digitalis genin, while foliandrin, a pure glycoside isolated [20] in 1944 from the Palestinian oleander bush *(N. oleander)* resembles in its action with that of the strophanthin glycoside. On the other hand nerium D was assumed to be a cardiac glycoside of digitalis-strophanthus type [27]. Odoroside B [24] (IV) gave diginose and an aglycone on hydrolysis, which was ultimately converted to Me-3 (β-)-acetoxy-14-hydroxy-14-isoetiocholanate, thus showing that odoroside B is allodigitoxigenin, which is identical with the uzarigenin of Tschesche, Bohle and Sah [25].

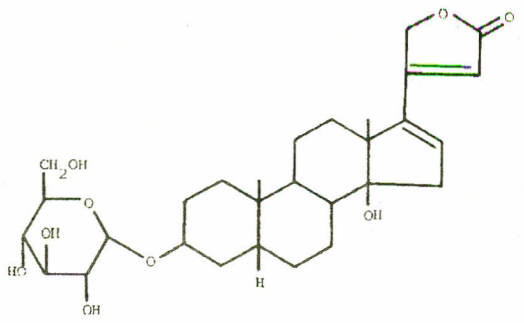


II. R=βH, R^1,R^2 = >O
III. R=βH, R^1=H, R^2=OH
IV. R = αH, R^1 = H, R^2 = OH
V. R= βH, R^1·R^2 = >O , Δ^{16}

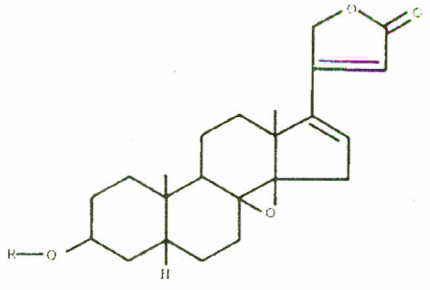
An active principle, neriodin, was extracted from the air dried leaves of *N. oleander* in 1949 by B. Nuki[26]. This glycoside was twice as active as digitoxin in digitalis-like action and has some similarity in action with oleandrin.

In 1972, T. Yamauchi and T. Ehara [50] reported that the less polar glycosides such as oleandrin are obtained from the leaves dried in oven at temperature above 80° or by incubation of the homogenates of the fresh leaves, whereas more polar

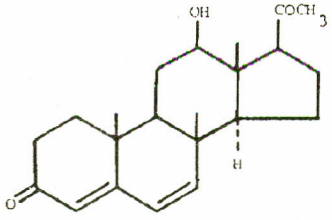
*Dictionary of Organic Compounds, Oxford University Press, 1978, p.2570



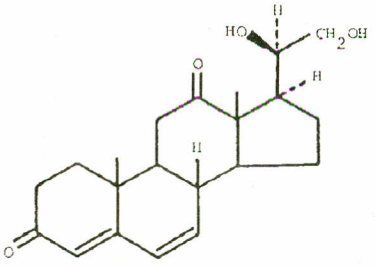
V



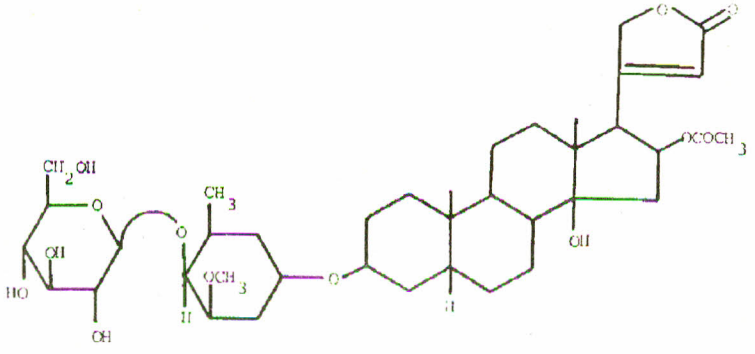
VI. R = β - D-diginosyl
VII. R =β - D-digitalosyl



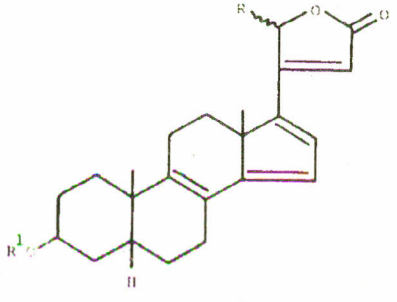
XIV



XV



VIII



IX. R = OH, R^1 = β=gentiobiosyl - (1 →4β) - D-digitalosyl
X. R = OH, R^1 =β=D=glucosyl - (1 →4β) - D-digitalosyl
XI. R =H, R^1 = β-gentiobiosyl -(1→4β) -D-digitalosyl
XII. R =H, R^1 =β-glucosyl -(1 →4β) -D-digitalosyl
XIII. R=H, R^1 β-gentiobiosyl -β-D-diginosyl

TABLE. 1. GLYCOSIDES, TERPENOIDS AND STEROIDS OF NERIUM OLEANDER

S.No.	Name	M.p °C	Molecular Formula	Optical Rotation	References
1.	16-O-Acetyldigitalinum verum	-	-	-	67
2.	16-O-Acetyleneogilostin	-	-	-	70
3.	Adigoside	138-142	-	$[\alpha]_D$-16.8°(M)	36
4.	Adynerin (II)	220-223	$C_{30}H_{44}O_7$	$[\alpha]_D^{18}$+7.5°(P) +21.6°(M)	14,16,18,67
5.	5α-Adynerin	222-224	$C_{30}H_{44}O_7$	$[\alpha]_D$-2.0°(M)	72
6.	α-Amyrin	186-188	$C_{30}H_{50}O$	$[\alpha]_D^{17}$ +83.5°(C)	45,52
7.	Δ^{16} -Anhydrodigitalinum verum	-	-	-	33,70
8.	Betulin	251-252	$C_{30}H_{50}O_2$	$[\alpha]_D^{15}$ +20.0°(P)	130
9.	Betulinic acid	275-278	$C_{30}H_{48}O_3$	$[\alpha]_D^{23}$ +7.9°(P)	130
10.	Campesterol	157-158	$C_{28}H_{48}O$	$[\alpha]_D^{23}$ -33.0°(C)	83
11.	Campherol-3-glucoside	178-179	$C_{21}H_{20}O_{11}$	-	75
12.	Campherol-3-rhamnoglucoside	-	$C_{27}H_{30}O_{15}$	-	32,75
13.	Conerin	-	-	-	97
14.	Cortenerin	168-187	-	inact.	19
15.	Cryptograndoside-A	115-120	$C_{32}H_{48}O_9$	$[\alpha]_D$ -31.2°(M)	36
16.	Δ^{16}-Dehydroadynerigenin β-D-diginoside (VI)	188-190	$C_{30}H_{42}O_7$	$[\alpha]_D^{20}$ +71.4°(M)	65
17.	$^{16}\Delta$-Dehydroadynerigenin β-D-digitaloside (VII)	234-235	$C_{30}H_{42}O_8$	$[\alpha]_D^{20}$ +81.7°(M)	65
18.	$^{16}\Delta$-Dehydroadynerigenin-β D-glucosyl-β-D-digitaloside	221-225	$C_{46}H_{68}O_{19}$	$[\alpha]_D$ +20°	67
19.	Digistroside	205-208	-	$[\alpha]_D$ -16.6°(M)	36
20.	Digitalinum verum	-	-	-	34
21.	Digitalinum verum hexaacetate	223-230	-	$[\alpha]_D^{19}$ -14.6°(C)	33,34,67
22.	Digitalinum verum odorobioside G	-	-	-	35
23.	Digitalinum verum odorobioside-K	-	-	-	35
24.	Digitoxigenin	253-255	$C_{23}H_{34}O_4$	$[\alpha]_D^{17}$ +19.1°(M)	36
25.	Digitoxigenin-α-L-oleandroside	205-208	-	$[\alpha]_D$ -27.7°(M)	20
26.	Foliandrin	-	-	-	20
27.	Folinerin	-	-	-	12,13
28.	Gentiobiosyl-adynerin	-	-	-	67
29.	Gentiobiosyl Δ^{16} -dehydroadynerin	221-225	$C_{46}H_{68}O_{19}$	[α]D +20.0°	67
30.	Gentiobiosyl odoroside-A	-	-	-	67
31.	Gentiobiosyl oleandrin	169-173	$C_{44}H_{68}O_{19}$	$[\alpha]_D$ -47.8°	67
32.	Gluconerigoside (VIII)	–	$C_{38}H_{58}O_{13}$	$[\alpha]_D$ -47.8°	66
33.	β-D-Glucopyranosyl Δ 5-pregnenolone	231-235	$C_{39}H_{62}O_{17}$	$[\alpha]_D$ -20.5°(P)	63

(Contd.)

(Table 1. Continued)

34.	Bis-β-D-glucopyranosyl-(1→2, 1→6)β-D-glucopyranosyl Δ^5-pregnenolone	231-235°	$C_{39}H_{62}O_{17}$	$[\alpha]_D^{20}$ -20.5°(P)	63
35.	β-D-Glucopyranosyl-(1→2) β-D-glucopyranosyl Δ^5-pregnenolone	255-259	$C_{33}H_{52}O_{12}$	$[\alpha]_D$ -11.9°(P)	63
36.	β-D-Glucopyranosyl-(1-6)β-D-Glucopyranosyl- Δ^5-pregnenolone	252-256	$C_{33}H_{52}O_{12}$	$[\alpha]_D$ -7.2°(P)	63
37.	Glucosylnerigoside	178-181	$C_{38}H_{58}O_{14}$	$[\alpha]_D$ +34.0°(P)	67
38.	Gracilloside	–	–	–	70
39.	12-β-Hydroxy-pregna 4,6-diene-3,20-dino	–	$C_{21}H_{28}O_3$	–	69
40.	12-βHydroxy-pregna-4-ene-3,20-dione	–	$C_{21}H_{30}O_3$	–	69
41.	12-β-Hydroxy-16α-methoxy-pregna-4,6-diene-3,20-dione	168-171	$C_{22}H_{30}O_4$	$[\alpha]_D$ +7.7°(P)	69
42.	Isoneriucoumaric acid (XXXI)	208-209	$C_{39}H_{54}O_6$	$[\alpha]_D^{24}$ +50.5°(C)	131
43.	Kaneric acid (XXXIV)	122	$C_{30}H_{48}O_4$	$[\alpha]_D^{24}$ +16.66°(C)	134
44.	Kanerocin (XXXII)	259-260	$C_{30}H_{46}O_3$	–	132
45.	Kanerodione (XXV)	178-180	$C_{30}H_{46}O_3$	$[\alpha]_D^{24}$ +36.36°(C)	128
46.	Kanerin (XXVI)	280-281	$C_{29}H_{44}O_4$	$[\alpha]_D$ 14.28°(C)	129
47.	Kanerol	185-86	$C_{30}H_{50}O_5$	$[\alpha]_D^{30}$ +80.1°(C)	82
48.	Kaneroside(XXIII)	110-111	$C_{30}H_{42}O_8$	$[\alpha]_D^{24}$ +26.66°(C)	127
49.	Nerein	–	–	–	39
50.	Neriantin (V)	206-208	$C_{29}H_{42}O_9$	–	16,101
51.	Neriaside (XVI)	–	–	$[\alpha]_D$ -17.6°(P)	71
52.	Neridienone-A (XIV)	–	–	–	69,93
53.	Neridienone-β (XV)	–	–	–	69
54.	Nerigoside	155-163	$C_{36}H_{56}O_{11}$	$[\alpha]_D$ -17.0°(M	36,73
55.	Neriin	–	–	–	9,10
56.	Nerin	–	–	–	23
57.	Neriodin	238-239	–	–	26
58.	Neriodorein	106-107	$C_{23}H_{34}O_{11}$	–	2,11
59.	Neriodorin	204-205	$C_{32}H_{46}O_8$	$[\alpha]_D^{17}$ +35.5°	2,11
60.	Neriolit	–	–	–	97
61.	Nerioside	–	–	–	22
62.	Neritaloside	135-140	$C_{40}H_{64}O_{14}$	$[\alpha]_D$ -11.4°(M)	36
63.	Neriucoumaric acid (XXX)	120-121	$C_{39}H_{54}O_6$	$[\alpha]_D^{24}$ +16.66°(C)	131
64.	Nerium-D	235-238	–	$[\alpha]_D^{15}$ -19.2°(DO)	27
65.	Nerium-E (16-Deacetyl-anhydro-oleandrin)	225-227	$C_{30}H_{44}O_7$	–	27,37,73
66.	Nerium-F (16-Anhydro-digitoxigenin acetate)	245-247	$C_{23}H_{32}O_4$	$[\alpha]_D^{21}$ +93.1°	27,30
67.	12,13-Dihydroursolic acid(XXVII)	230-232	$C_{30}H_{50}O_3$	$[\alpha]_D$ 6.0(C)	,129
68.	Neriumoside(XXIV)	140-142	$C_{30}H_{44}O_8$	$[\alpha]_D^{24}$ +23.20°(C)	127
69.	Neriumoside A-1 (IX)	–	–	–	68

(Contd.)

(Table 1. Continued)

70.	Neriumoside A-2 (X)	–	–	–	68
71.	Neriumoside B-1(XI)	–	–	–	68
72.	Neriumoside B-2 (XII)	–	–	–	68
73.	Neriumoside C-1 (XIII)	–	–	–	68
74.	Nicotifloroside	–	–	–	104
75.	Odorin	–	–	–	105,106
76.	Odorobioside-D	–	–		33
77.	Odorobioside-G Pantaacetate	219-231	–	$[\alpha]_D^{2o}$ -10.6°(C)	33
78.	Odorobioside-K	220-255	$C_{36}H_{56}O_{12}$	$[\alpha]_D$ -38.2°(DO)	34
79.	Odorobioside-K	256-263	–	$[\alpha]_D^{22}$ -28.4°(C)	33
80.	Odoroside A (III)	200-206	–	$[\alpha]_D$ -5.9°(C) -4.3°(M)	24,34,36,64
81.	Odoroside B (IV)	196-198	–	$[\alpha]_D$ -19.2°(C)	24,31,34
82.	Odoroside D	–	–	–	34
83.	Odoroside E	–	–	–	29
84.	Odoroside F (graciloside)	–	–	–	30
85.	Odoroside G	–	–	–	35
86.	Odoroside G octaacetate*	228-231	–	$[\alpha]_D^{25}$ -15.1°	28
87.	Odoroside H	231-238	–	$[\alpha]_D^{21}$ 7.8°(M)	29
88.	Odoroside K	242-265	$C_{42}H_{66}O_{17}$	$[\alpha]_D$ -37.6°(C)	29,31
89.	Odoroside K acetate*	–	–	–	29
90.	Odoroside K heptaacetate*	–	–	–	31
91.	Odoroside L-acetate*	178-183	–	$[\alpha]_D^{19}$ +74.0°(C)	29
92.	Odoroside-M-acetate*	219-224	–	$[\alpha]_D^{20}$ +31.9°(C)	29
93.	Odorotrioside-G octaacetate	228-233	–	$[\alpha]_D^{20}$-15.3°(C)	33
94.	Odorotrioside-K	–	–	–	34
95.	Odorotrioside-K-acetate	177-186	–	$[\alpha]_D^{20}$ -35.8°(C)	33
96.	Oleandrigenin	226-228	–	–	36,50
97.	Oleandrigenin-β-D-gentiobiosyl-(1-4)β-D-digitaloside	253-257	–	$[\alpha]_D$ -16.0°	70
98.	Oleandrigenin-β-D-glucoside	–	–	–	67
99.	Oleanderen (XXXIII)	215-217	$C_{30}H_{50}$	$[\alpha]_D^{24}$ +7.06°(D)	133
100.	Oleanderoic acid (XXXV)	293-295	$C_{21}H_{38}O_3$	$[\alpha]_D^{24}$ +83.33°(C)	133
101.	Oleanderol (XXIX)	206-208	$C_{30}H_{48}O_3$	$[\alpha]_D^{24}$ +6.15°(C)	130
102.	Oleanderolic acid(XXVIII)	262-264	$C_{37}H_{54}O_6$	$[\alpha]_D^{24}$ +50.0°(C)	128
103.	Oleandrin (I)	249-251	$C_{32}H_{48}O_9$	$[\alpha]_D$ -48.2°(M)	6,14
104.	Oleandroside	–	–	–	21
105.	Oleanolic aid	306-308	$C_{30}H_{48}O_3$	$[\alpha]_D^{12}$ +79.5°(C	53,81,130
106.	Oleaside A (XVII)	251-255	$C_{30}H_{44}O_7$	$[\alpha]_D$ +25.4°(M)	73,74
107.	Oleaside β (XVIII)	267-277	$C_{30}H_{44}O_8$	$[\alpha]_D$ -45.2°(M)	73,74
108.	Oleaside C (XIX)	198-205	$C_{36}H_{51}O_{12}$	$[\alpha]_D$+13.9°(M)	73,74
109.	Oleaside D (XX)	232-235	$C_{36}H_{51}O_{13}$	$[\alpha]_D$ +37.0°(M)	73,74
110.	Oleaside E (XXI)	182-184	$C_{42}H_{64}O_{17}$	$[\alpha]_D$+16.0°(M)	73,74
111.	Oleaside F (XXII)	–	–	–	73,74
112.	Phenyl glucoside	–	$C_{12}H_{16}O_6$	–	76
113.	Plumericin	–	–	–	124

(Contd.)

(Table 1. Continued)

114.	Quercetrin	182-185	$C_{21}H_{20}O_{11}$	–	51,77,78
115.	Quercetrin	–	–	–	51,77
116.	Rosagenin	–	–	–	6-8
117.	Rutin	214-215	$C_{27}H_{30}O_{16}$	$[\alpha]_D^{23}$+13.8°(Et)	51,79,80,120
118.	Rutoside	–	–	–	104
119.	Scopolin	170-171	$C_{16}H_{19}O_9$	$[\alpha]_D^{16}$+2.0°(C)	29
120.	Sitosterol	164-166	$C_{29}H_{48}O$	$[\alpha]_D^{28}$-1.7°(C)	85
121.	β-Sitosterol	136-137	$C_{29}H_{50}O$	$[\alpha]_D^{22}$-35.0°(C)	51,83,84
122.	Stigmasterol	170-171	$C_{29}H_{48}O$	$[\alpha]_D^{22}$_51.0°(C)	52,83
123.	1-Strosphanthin	180-181	$C_{29}H_{44}O_{12}$	–	6-8
124.	ψ-Strosphanthin	92-93	–	–	7,8
125.	Strospeside	253-255	$C_{30}H_{46}O_7$	$[\alpha]_D^{20}$+15.7°(C)	37,101
126.	Urechitoxin.	–	–	–	37
127.	Ursolic acid	292-293	$C_{30}H_{48}O_3$	$[\alpha]_D$+66.0°(E)	45,53,81,130
128.	Uvaol	222-224	$C_{30}H_{50}O_2$	$[\alpha]_D^{24}$+70°(C)	134
129.	Uzarigenin	246-249	$C_{23}H_{34}O_4$	–	25
130.	Uzarigenin-β-D-	239-240	$C_{30}H_{46}O_8$	[α]+4.2°	70
131.	Uzarigenin-β-D-glucosyl-(1-4)-B-D-digitaloside	315-325	$C_{36}H_{56}O_{13}$	$[\alpha]_D$-12.0°	70

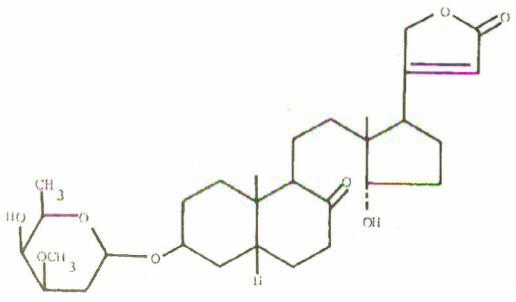
glycosides are obtained from the fresh and air-dried leaves. Thus they obtained oleandrin, adynerin (adynerigenin-β-D-diginoside), odoroside A (digitoxigenin-β-D-diginoside), 16-deacetylanhydro- oleandrin and oleandrigenin together with unknown cardenolides from the oven dried leaves. As a result of later studies (1975) T. Yamauchi *et al.* [67] noted that oleandrin, odoroside A, adynerin and Δ^{16}-dehydroadynerin, previously obtained from oven dried leaves, were also present in the fresh leaves as gentiobiosides.

T. Yamauchi *et al.* [63] in 1972 reported the isolation of mono-, di- and triglycoside of pregnenolone from the root and trunk bark of *N. oleander* and characterized them through their acetates and permethylated derivatives. They reported [72] the isolation and structure elucidation of a further steroid neridienone, a C-21 steroid, from the same source. They further noted that this is either substance 1 of T.Reichstein *et. al* [64] reported in 1949 or is closely related with it since both have UV absorption around 280 and 240 nm.

In 1974, T. Yamauchi [66] reported the isolation of a cardiokinetic and diuretic glyconerigoside from the leaves and elucidated its structure as oleandrigenin-β-D glycopyranosyl-β-D- diginopyranoside.

In 1976, T. Yamauchi and co-workers reported the isolation of three new uzarigenin and oleandrigenin glycosides from the root bark in addition to odorosides A,B,D,G,H,K, odoro-bioside K and a mixture of 16-O-acetyl and 16-anhydrodigitalinum verum (loc. cit.). The new constituents were characterized as β-D- digitaloside, β-D-glucoside-(1-4)-β-D-digitaloside of uzarigenin and oleandrigenin β-gentiobiosyl-(1-4)-β-D-digitaloside. Regarding the environmental variations they observed that the above compounds obtained from the stem bark of Japanese plant were not present in the stem bark of *N..oleander* grown in India. On the other hand, graciloside present in the Indian plant was not found in the plant of Japanese origin.

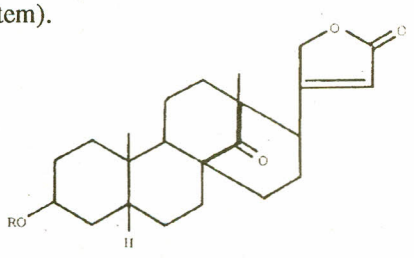
In 1978, a 8,14-seco-cardenolide, neriaside was isolated from the leaves dried at 80° by T. Yamauchi and F. Abe [71] and its structure elucidated as XVI. They further isolated [72] two new cardenolides digitoxigenin-α-L-oleandroside and 5 α-adynerin from the leaves. Their structures were elucidated with the aid of ^{13}C- NMR and conversion of oleandrin to digitoxigenin-α-L-oleandroside and synthesis of 5 α-adynerigenin respectively. Digitoxigenin-α- L-oleandroside is a rare glycoside in *oleander,* since L- oleandrose has been found only as the glycosides of oleandrogenin and its deacetyl or anhydro derivatives. Further, 5α-adynerin is the first 5α-cardenolide isolated from the leaves, although the root bark



XVI

contains a large amount of uzarigenin glycosides (loc.cit.).

As a result of reinvestigation of the cardenolides of *N. oleander* they reported [73,74] further cardenolide, oleasides A-F. The structure of the common aglycone, oleagenin was established as 3β-hydroxy-15 (148)abeo-5β (8R)-14-oxo-card-20(22)-enolide. The sugars were identified as D-diginose (oleaside-A) (XVII), D- digitalose (oleaside-B) (XVIII), β-D-glucosyl-D-diginose (oleaside-C) (XIX), 4-O-β-glucosyl-D-digitalose (oleaside-D) (XX), β-gentiobiosyl-D-diginose (oleaside-E) (XXI) and 4-O-β- gentiobiosyl-D-digitalose (oleaside-F) (XXII). The oleasides are the first occuring cardenolides having bicyclo (3,3,1)nonan-9-one (C/D ring system).

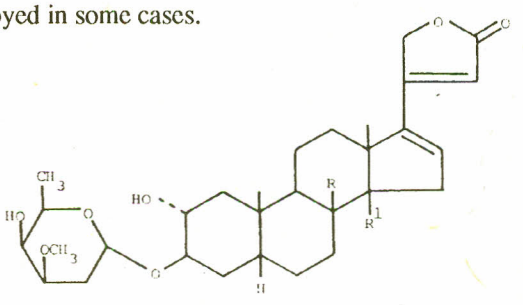


XVII.R = D-diginose
XVIII.R = D-digitalose
XIX.R = β-D-glucosyl-D-diginose
XX.R = 4-O-β-D-glucosyl-D-digitalose
XXI.R = β-gentiobiosyl-D-diginose
XXII.R = 4-O-β-gentiobiosyl-D-digitalose

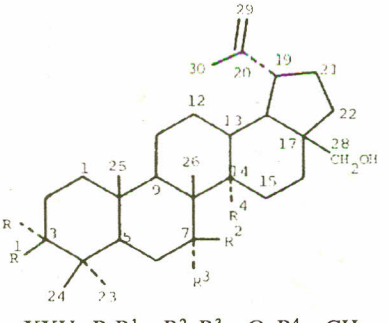
In more recent studies, T. Yamauchi and co-workers [58] investigated the quantitative variations in cardiac glycosides of the leaves from 20 horticultural and wild strains of *Nerium* and concluded that the plants studies fall in two groups based on their contents of adynerin and oleaside-A or gentiobioside adynerin and oleaside-E. A large variation in oleandrin content was noted in all samples.

Besides the cardiac and other steroidal glycosides noted above, some glycosides containing coumarins or flavonoidal aglycones as well as free steroidal constituents [51,52,69,83-85] have also been isolated from different parts of *N.oleander* as listed in Table 1.

It would be evident from the brief reference of literature noted above, that in most of the cases dried (air-or oven-dried) plant material was used in earlier investigations. Keeping in view the pharmacological significance attributed to the plant, and the fact that the use of fresh, undried plant materials avoids formation of the artefacts through oxidation and enzymatic degradation, Siddiqui *et al* [127-135] more recently undertook studies on fresh, undried and uncrushed leaves which resulted in the isolation and structure elucidation of several new constituents, including two cardiac glycosides namely kaneroside (XXIII) and neriumoside [127] (XXIV), ten pentacyclic triterpenoids kanerodione[128] (XXV) kanerin [129] (XXVI) 12,13-dihydroursolic acid [129] (XXVII), oleanderolic acid [128] (XXVIII), oleanderol [130] (XXIX), neriucoumaric acid [131] (XXX), isoneriucoumaric acid [131] (XXXI), kanerocin [132] (XXXII), oleanderen [133] (XXXIII) and kaneric acid [134] (XXXIV), one diterpene oleanderoic acid [133] (XXXV) (Table- 1) and two straight chain compounds nerifol [135] (XXXVI) and neriumol [135] (XXXVII) (Table-2) along with five known pentacyclic triterpenoids. Three of the known terpenoids namely betulin [130], betulinic acid [130] and uvaol [134] were isolated for the first time from this plant whereas ursolic and oleanolic acids [130], α- amyrin [45,52] and an uncharacterized compound kanero [182] with the molecular formula $C_{30}H_{50}O$ were reported earlier from this source. The structures of the new compounds were elucidated through intensive chemical and spectroscopic studies including high resolution mass, FABMS, 1D- and 2D-^{1}H-NMR (COSY-45, NOESY, 2D-J-resolved, heterocosy experiments) and ^{13}C-NMR (broad band and DEPT experiments). Homonuclear decoupling experiments and NOE difference measurements have also been employed in some cases.

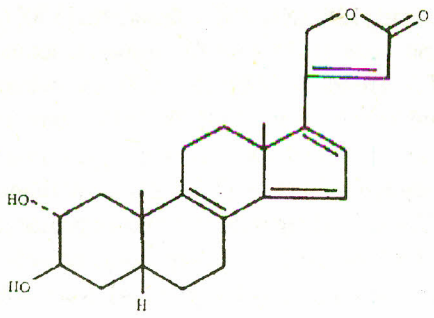


XXIII. R,R^1 = O,
XXIV. R = H, R^1 = OH



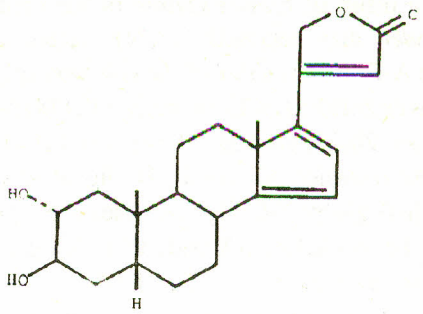
XXV. R,R^1 = R^2, R^3 = O, R^4 = CH_3,
XXIX. R = H, R^1 = OH, R^2 = R^3 = H, R^4 = CH_2 OH, Δ^{12-}

Neriumoside (XXIV) of Siddiqui *et al.* [127] is different from the series of neriumosides A-1, A-2, B-1, B-2 and C-1 of T. Yamauchi [68]. Hydrolysed products XXIIIa of XXIII and XXIVa, XXIVb and XXIVc of XXIV have all been fully characterized through intensive spectral studies and chemical transformations. The sugar was identified as diginose through co-paper chromatography with reference sugars and ^{1}H- and ^{13}C-NMR studies.

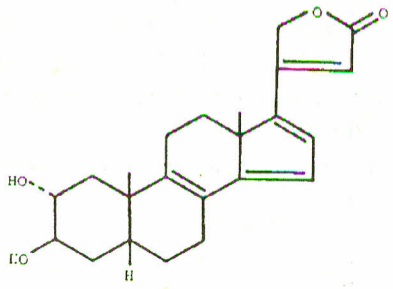


XXV. R,R^1 = R^2, R^3 = O, R^4 = CH_3

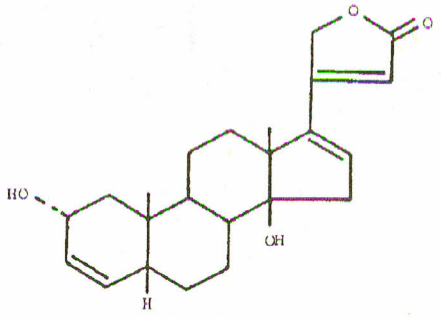
XXIX. R = H, R^1 = OH, R^2 = R^3 = H, R^4 = CH_2 OH, ∇^{12}-



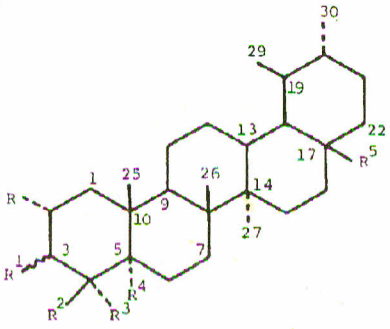
XXXIV-c



XXIV-b



Structure XXIV-C



XXVI. R=H, R^1 = βOH, R^2-R^3 = ++ CH_2, R^4 =OH, R^5 = COOH, ∇^{18}-

XXVII. R=H, R^1 = βOH, R^2 = R^3 = CH_3, R^4 = H, R^5 = COOH

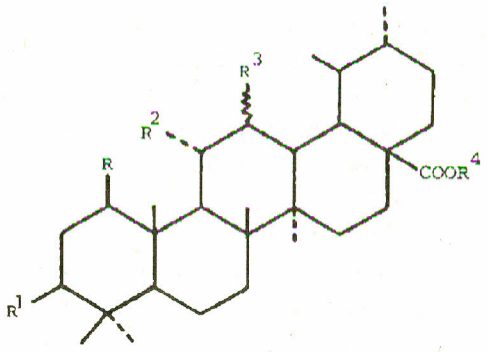
XXX. R = ρ=cis=coumaroyloxy, R^1 = βOH, R^2 = R^3 = CH_3, R^4 = H, R^5 = COOH, ∇^{12}-

XXXa. R=p-2', 3'=diydrocoumaroyloxy, R^1 = βOH, R^2 = R^3 = CH_3, R^4 = H, R^5 = COOH

XXXI. R=ρ-trans-coumaroyloxy, R^1β-OH, R^2=R^3=CH_3, R^4 = H, R^5 = COOH, ∇^{12}

XXXII R=H, R^1 = α_2OH, R^2R^3=CH_3, R^4 = H, R^5 = COOH, ∇^{12}-

XXXIII. R=R^1=H, R^2R^3=CH_3, R^4 =H, R^5 =CH_3, ∇^{12}-

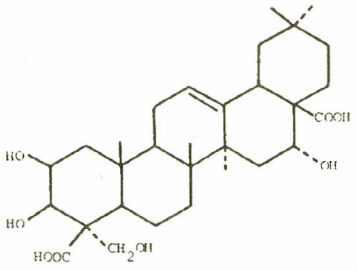


XXVIII. R=R^4=H,R^1=O=C^4H^4=p=OH, R^2 =OCH_3, R^3 =α-OH, ∇^{20}-

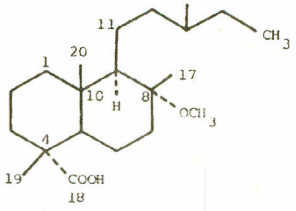
XXVIIIa. R=H, R^1O=$_c6_H4$ -p-OCH3 $_{,R}{}^2$=R^3 =OCH_3, R^4 =CH_3, —^{20}

XXIIIb. 20,21,dihydroxy-XXVIII-a

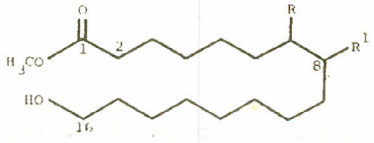
XXXIV. R=R^1 =OH, R^2=R^3 =H, R^4 =H, —^{12}-



Platycogenic acid A



XXXV



XXXVI. R = H, R^1 = OH,
XXXVII. R = OH, R^1 =H, ∇^8

The structure of XXV [128] was also determined through spectral studies and finally confirmed through its Wolf-Kishner reduction to the known 3-deoxybetulin.

Chemical proof of the double bond at C-4 (C-23) in XXVI, [129] located through spectral studies, was provided through Sarett oxidation to its 3 keto derivative. XXVI is the first naturally occurring 24-nor triterpenoid of the ursane series with a double bond at C-4 (C-23). It is interesting to note that only one 24- nor triterpenoid of this series namely methyl-3-oxo-24-norurs-12- en-28-oate has earlier been reported from a natural source [136] which was suggested to be an artifact derived from either the corresponding 23-hydroxy-3-oxo or 24-hydroxy-3-oxo compound [137] through formaldehyde elimination. The nor compounds may also be formed as artefacts through reverse Prins reaction during acidic hydrolysis of saponins [138]. As XXVI was isolated through solvent separation and preparative TLC under mild conditions without involving hydrolysis (acidic or basic) and was also detected in the fresh leaves extract, it was regarded as a naturally occurring compound. It was also noted that XXVI is the first constituent of ursane series with a hydroxyl function at C-5 as well as a first naturally occurring ursolic acid derivative with a double bond at C-18. Taking into consideration the triterpenoid platycogenic acid A [139] as a natural product from *Platycodon grandiflorum* they suggested a similar hypothetical intermediate of the ursane series (bearing both the carboxyl group and -CH_2OH function at C-4) for the formation of XXVI, decarboxylation of which followed by dehydration would result in XXVI.

Structure of XXVII [129] was proved by its synthesis from acetylmethyl ursolic acid through H_2O_2/AcOH oxidation followed by Wolf—Kishner reduction.

Structure and stereochemistry of various centres of XXVIII [128], were conclusively established through catalytic reduction of its trimethyl derivative (XXVIIIa) to dihydrotrimethyl derivative which was identified with the product XXVIIIb ultimately obtained through a series of reactions on acetylmethyl ursolic acid (Scheme 1).

Isolation of XXIX [130] is the first instance of a lupane triterpene from any of the various parts of *N. oleander* and makes an addition to the rare examples of reported A^{12}-27-hydroxy pentacyclic triterpenoids of lupane series.

The relationship of XXX and XXXI, the isomeric triterpenoids, was established through their catalytic reduction (H_2Pt) to a common reduction product [131] XXXa.

XXXII [132] obtained from the 1% methanolic extract of the fresh leaves is the first ursane derivative with the 18,20 diene system, and represents one of the rare triterpenoids with an a oriented hydroxyl group at C-3. XXXIII [133] (12 ursene), the parent hydrocarbon of ursane series of triterpenoid was considered a genuine naturally occurring product in the light of the fact that fresh plant material was used avoiding any drastic conditions.

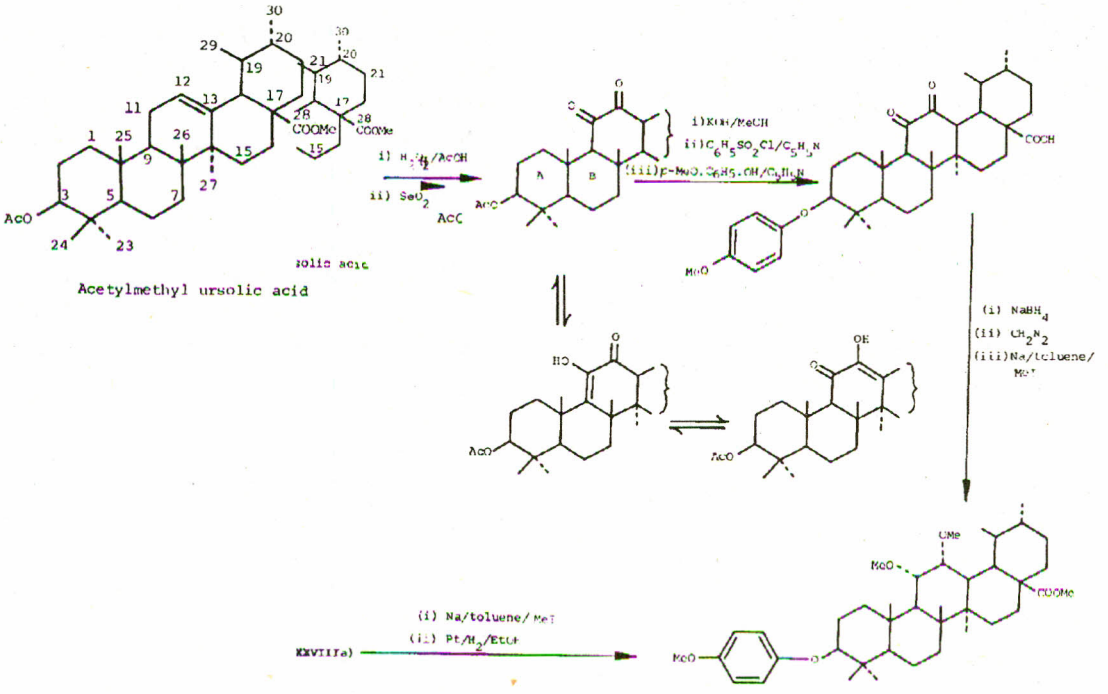
The structure of XXVIII [128], the first diterpenoid isolated from the plant was determined through spectroscopic and chemical studies.

Siddique. *et. al.* stressed that the isolation of several new terpenoids exemplifies the advantage of using fresh plant material.

Miscellaneous compounds.. Various fatty acids, sugars, hydrocarbons and other aliphatic and aromatic compounds have been reported by a number of authors, from different parts of the plant (Table 2).

More recently, straight chain hydroxy acid derivatives, nerifol (XXXVI) and neriumol (XXXVII) were isolated [135] (loc. cit.) from the fresh leaves and considered to be of potential pharmacological significance, since 15, 16-dihydroxyhexadecanoic acid forms a component of the antibiotic ustilagic acid [140]. Further, 11-hydroxy hexadecanoic acid and its glycoside are reported as anticancer and antimicrobial agents [141].

Pharmacology. N. oleander has been cautiously used in China and South East Asian countries as a heart tonic [142].



Scheme 1.

The studies carried out by various groups of workers on its glycosides and other constitutents [143-184] showed that they possess cardiotonic properties. The chief active principle, oleandrin, was found to stimulate the heart function and also noted for diuretic effect, while nerifolin is milder in these respects. More recent investigation on the bark of the plant has revealed the presence of several glycosides, such as odoroside, A,B,D,F,G;H,K, odorobioside K and odoroside L and M possessing digitalis like activity [29-31, 185-187].

Another cardiac glycoside neriin causes diuresis in dogs and is toxic, when administered in high doses. Nerigenin, obtained through acidic hydrolysis of nerin, is comparatively less toxic. The effect of odorin on the heart of rabbits and dogs is identical with that of digitalis group, whereas neriodin is twice as active as digitoxin in digitalis like action similar to that of oleandrin.

TABLE 2. MISCELLANEOUS COMPOUNDS OF *NERIUM OLEANDER*

S.No.	Name	Mp°C °C	Molecular Formula	Optical Rotation	References
1.	Aromatic acid	242-245	–	–	82
2.	Benzyl acetate	–	$C_9H_{10}O_2$	–	83
3.	Benzyl alcohol	–	C_7H_8O	–	83
4.	Bornesitol	–	$C_6H_{12}O_2$	–	86
5.	Butyric acid	-8.0	$C_4H_8O_2$	–	82
6.	Campherol	276-278	$C_{15}H_{10}O_6$	–	45
7.	Capric acid (Decanoic acid)	30.5	$C_{10}H_{20}O_2$	–	87,88
8.	Caproic acid (Hexanoic acid)	-2.0	$C_6H_{12}O_2$	–	87,88
9.	Caprylic acid (Octanoic acid)	16.5	$C_8H_{16}O_2$	–	87,88
10.	Choline	273-275	$C_5H_{15}O_2N$	–	52
11.	Chlorogenic acid	208-210	$C_{16}H_{18}O_9$	$[\alpha]_D^{16}$ -35.2°(W)	89
12.	Dambonitol	219-220	$C_8H_{16}O_6$	–	86,121,122
13.	2,4-Dihydroxy-acetophenone	148-149	$C_8H_8O_3$	–	90

(Contd.)

Table 2. continued

14.	Docosanoic acid	80-81	$C_{22}H_{44}O_2$	–	83
15.	Eicosanoic acid	77-78	$C_{20}H_{40}O_2$	–	83
16.	Formic acid	8.4-9.0	CH_2O_2	–	82
17.	Heptadecanoic acid	-7.5	$C_7H_{14}O_2$	–	83
18.	4-Hydroxy-aceto-phenone	109-110	$C_8H_8O_2$	–	90
19.	9-D-Hydroxy-cis-12-octadecenoic acid	–	$C_{18}H_{34}O_3$	–	84
20.	Karavi's Indicator	–	–	–	123
21.	Lauric acid (Dodecanoic acid)	44-45	$C_{12}H_{24}O_2$	–	83,87,88
22.	Linolenic acid (9,12,15-Octadeca-trienoic acid)	-11.3	$C_{18}H_{33}O_2$	–	91
23.	Linolic acid (9,12-Octadeca-dienoic acid)	-5.5-6.5	$C_{18}H_{32}O_2$	–	82,88
24.	Myristic acid (Tetradecanoic acid)	58-59	$C_{14}H_{28}O_2$	–	83
25.	Nerifol (XXXVI)	74.75	$C_{17}H_{34}O_4$	–	135
26.	Neriumol (XXXVII)	78-80°	$C_{17}H_{32}O_4$	$[\alpha]_D^{24}$ -458°(C)	135
27.	Nonadecanoic acid	68-69	$C_{19}H_{38}O_2$	–	83
28.	Oleic acid (9-Octadecenoic acid)	15.16	$C_{18}H_{34}O_2$	–	82,83,87,88
29.	Orange essential oil	–	–	$[\alpha]_D$ 4.0°(C)82	
30.	Palmitic acid (Hexadecanoic acid)	63-64	$C_{16}H_{32}O_2$	–	83,87,88
31.	Paraffin	70-71	$C_{30}H_{70}$	–	92
32.	n.Parrafin	–	–	–	83
33.	Pentadecanoic acid	53-54	$C_{15}H_{30}O_2$	–	83
34.	Phenolic Compound	140-141	–	–	82
35.	β-Phenyl ethyl	–	$C_{10}H_{12}O_2$	–	83
36.	β-Phenyl ethyl alcohol	–	$C_8H_{10}O$	–	83
37.	Quercetin	314-315	$C_{15}H_{10}O_7$	–	51
38.	Resene	245-246	–	–	92
39.	Scopoletin	204-205	$C_{10}H_8O_4$	–	74
40.	Stearic acid (Octadecanoic acid)	71.72	$C_{18}H_{36}O_2$	–	82,83,87,88
41.	Sucrose	184-185	$C_{12}H_{22}O_{11}$	$[\alpha]_D^{20}$ +66.3°(W)	52
42.	Tridecanoic acid	44-46	$C_{13}H_{26}O_2$	–	83

C = Chloroform , N = Water

The toxicity of various parts of the plant and their constituents has been studied by different groups of workers, [143,144] who noted that 15-20 g of oleander leaves are sufficient to cause death in horses, while in the case of cows the fatal dose is some what higher (12-25g).

Various groups of workers [23,157,177-184] further noted that nerin, oleandrin and other cardiotonic glycosides prove fatal, when given in higher doses.

References

1. E. Nasir, S.I. Ali, *Flora of West Pakistan* (Pakistan Agriculture Research Council, Islamabad, 1982),Vol. **148,** pp.19.
2. W. Dymock, C.J.H., Warden, D., Hooper, *Pharma-cographia* Indica, (The Institute of Health and Tibbi Research, Republished under the Auspices of Hamdard National Foundation of Pakistan, 1891),Vol. II, pp. 398.

3. R.N. Chopra, S.L. Nayar, I.C. Chopra, "Glossary of Indian Medicinal Plants", Council of Scientific and Industrial Research, New Delhi, 1956, p. 175.
4. B.L. Manjunath, *The Wealth of India*, (Council of Scientific and Industrial Research, New Delhi, 1966),Vol. VII, pp. 15.
5. K.M. Nadkarni, *The Indian Materia Medica*, Revised by A.K. Nadkarni, (Popular Prakashan Ltd., Bombay, 1976), Vol. I,Vol. I, pp. 847.
6. C. Wehmer, *Die Pflanzenstoffe*, (Verlag von Gustan Fischer, Jena, 1931), Vol. II, pp. 990.
7. A.J. Leulier, J. Pharm. Chim., **4,** 157 (1912).
8. A.Leulier, J. Chem. Soc., 922 (1912).
9. G. Tanret, Compt. rend., **194,** 914 (1932).
10. H. Simonnet, and G. Tanret, Compt. rend., **194,** 1099 (1932).
11. G.P. Pendse, S. Dutt, Bull. Acad. Sci., **3,** 209 (1934).
12. F. Flury, and W. Neumann, Klin. Nochschr., **14,** 562 (1935).
13. H.V. Hoesslin, Klin . Wochschv., **15,** 1677 (1936).
14. W. Neumann, Chem. Ber., **70,** 1547 (1937).
15. W. Neumann, and W. Lindner, Arch. Exptl. Path. Pharmakol, **185,** 630 (1937).
16. R. Tschesche, K. Bohle, and W. Neumann, Chem. Ber., **17B,** 1927 (1938).
17. R., Tschesche, G., Grimmer, Chem. Ber., **87,** 418 (1954).
18. T. Takemoto, and K. Kometani, J. Pharma. Soc. Japan, **74,** 1263 (1954).
19. N. Varlakov, Farmatsiya, **11,** 27 (1940).
20. L.F. Schindel, and K. Braun, British Heart. J., **6,** 149 (1944).
21. O.A. Rossi, and J.A. Izquierdo, Rev. Farm., **90,** 441 (1947).
22. G. Tanret, Bull. Soc. Chim. Biol., **14,** 708 (1932).
23. N. Pitchandi, J. Proc. Inst. Chemists, **20,** 27 (1948).
24. S. Rangswami, and T. Reichstein, Helv. Chim. Acta, **32,** 939 (1949).
25. R. Tschesche, K. Bohle, and P.T.P. Sah, Chem. Ber., **68B,** 2252 (1935).
26. B. Nuki, Folia. Pharmacol. Japan, **45,** 134 (1949).
27. M. Okada, J. Pharm. Soc. Japan, **73,** 86 (1953).
28. A. Rheiner, A. Hunger, and T. Reichstein, Helv. Chim. Acta, **35,** 687 (1952).
29. W. Rittel, A. Hunger, and T. Reichstein, Helv. Chim. Acta, **36,** 434 (1953).
30. W. Rittel, and T. Reichstein, Helv. Chim. Acta, **36,** 554 (1953).
31. W. Rittel, and T. Reichstein, Helv. Chim. Acta, **37,** 1361 (1954).
32. H. Wagner, and R. Luck, Naturwissenschaften, **42,** 607 (1955).
33. I. Turkovic, J. Pharm. Belg., **14,** 263 (1959).
34. I. Turkovic, J. Pharm. Belg., **14,** 376 (1959).
35. I. Turkovic, J. Pharm. Belg., **14,** 447 (1959).
36. K. Jager, O. Schlindler, and T. Reichstein, Helv. Chim. Acta, **42,** 977 (1959).
37. R. Tschesche, P.K. Chaudhuri, and G. Snatzke, Naturwissenschaften, **51,** 139 (1964).
38. Von B. Gorlich, Planta Medica, **9,** 442 (1961).
39. A. Leulier, J. Pharm. Chim., **5,** 108 (1912).
40. I. Isao, H. Sueo, and N. Sansei, Nagoya Shiriisu Daigaku Yakugakubu Kenkyu Nempo, **18,** 79 (1970).
41. G. Title, H. Wagner , Planta Medica, **43,** 252 (1981).
42. L.F. Libizova, P.M. Loshkarev, and T.V. Burdeleva, Otkrytiya, Izobret, Prom. Obraztsy. Touarnye, Znaki, **51,** 18 (1974).
43. P. Gastaldo, P. Profumo, Cajelli, E., Chialo, B., Fitoterapia, **6,** 247 (1979).
44. P.C. Maiti and A. Chatterjee, J. Ind. Acad. Forensic. Sci., **11,** 48 (1972).
45. T. Satyanarayana, P.P. Parashad, M.. Devi and P.V.K. Rao, Ind. J. Pharm., **37,** 126 (1975).
46. B. Chiarlo, E. Cajelli, P. Gastaldo, and P. Profumo, Chromatographia, **11,** 229 (1978].
47. M.H. Goetz, Arzneim. Forsch., **19,** 1146 (1969).
48. A. Voicu, I. Popa, and G. Bors, Farmacia, **19,** 11 (1971).
49. M. Daniel, S.D. Sabnis, Ind. J. Exp. Biol., **16,** 512 (1978).
50. T. Yamauchi and Y. Ehara, Yakugaku Zasshi, **92,** 155 (1972).
51. J.A. Domingues, M. Gallordoa, J. Arauz, and R. Riveva, Cinecca, **25,** 103 (1967).
52. M.S. Karawya, M.A. Alkiey, E.I. Moghazy and S.A. Saleem,U.A.R.J. Pharm. Sci., **11,** 221 (1970).
53. M. Ishidate, Z. Tamura, M. J. Okada, Pharm. Soc. Japan, **67,** 206 (1947).
54. I.B. Chiarlo, Boll. Chim. Farm., **103,** 423 (1964).
55. M.S. Krawya, S.I. Balbaa, S.E. Khayyal, Egypt. J. Pharm. Sci., **14,** 113 (1973).
56. H. T. Yousef, A.D. Zorina, L.G. Matyukhina, I.A. Saltykova, Khim. Prir. Soedin, **1,** 119 (1977).
57. D. Mantu, A.K. Sharma, Nucleus, **23,** 213 (1980).
58. T. Yamauchi, F. Abe, T. Toshishige, A.K. Chand, M. Sharma, M. Zeliha, Phytochemistry, **22,** 2211 (1983).
59. K.L. Yong, Y.L. Tho, J. Sains. Farm. Malays, **1,** 12 (1976).
60. R. Cortesi, Bull. Soc., Butan. Geneve, **32,** 102 (1939).
61. Z.A. Guseinova, M.A. Rigimov, Materily. Itog.

Nauchn. Konf. Farmatsevt. Fak. Azerb. Med. Inst. Poprobl., **73,** (1965).
62. M.S. Karawya, A.M. Elmoghazy, M.A. Elkiey, S.A. Saleem, U.A.R.J. Pharm. Sci., **11,** 193 (1970)
63. T.Yamauchi, M. Hara and K. Mihashi, Phytochemistry, **11,** 3345 (1972).
64. S. Rangaswami and T. Reichstein, Pharm. Acta, Helv., **24,** 159 (1949).
65. T. Yamauchi, Y. Mori and Y. Ogata, Phytochemistry, **12,** 2737 (1973).
66. T. Yamauchi, Kokai, **74,** 113 (1974); **45,** 698 (1972).
67. T. Yamauchi, N. Takata and T. Mimura, Phytochemistry, **14** , 1379 (1975).
68. T. Yamauchi, F. Abe and M. Takahashi, Tetrahedron Letters, 1115 (1976).
69. F. Abe and T. Yamauchi, Phytochemistry, **15,** 1745 (1976).
70. T. Yamauchi, M. Takahashi and F. Abe, Phytochemistry, **15,** 1275 (1976).
71. Y. Tamauchi and F. Abe, Tetrahedron Letters, 1825 (1978).
72. F. Abe and T. Yamauchi, Chem. Pharm. Bull., **26,** 3023 (1978).
73. F. Abe and T. Yamauchi, Tennenyuki-Kagubotsu-Toronkai. Keen, Yoshishu, 592 (1978).
74. F. Abe and T. Yamauchi, Chem. Pharm. Bull., **27,** 1604 (1979).
75. Y.M. Lin, T.S. Shih, Y.C. Lin, Y.M. Lin, K.K. Ho, Tai- wan K'o Hsueh, **29,** 47 (1975).
76. W. Straub, Arch. Exp. Path. Pharm., **82,** 327 (1918).
77. A. Heirmann, T. Kartnig and K. Lukasczyle, Sci. Pharm., **50,** 71 (1982).
78. L.H. Hammer, H. Wagner and R. Luck, Arch. Pharm., **289,** 613 (1956).
79. L. Horhammer, H. Wagner and Arch. Pharm., 290, 224 (1957).
80. I.T. Khalifa, J.F. Muhtadi and M.A. Hassan, Zentralbl. Pharm., **122,** 809 (1983).
81. W.C. Cheng, Pharm. Zentrahalle, **105,** 148 (1966).
82. S.T. Gadre, J. Ind. Inst. Sci., **I,** 181 (1916).
83. A. Yoshinori, H. Shuichi and M.Tamoon, J. Sci. Hiroshima Uni. Ser., **33,** 277 (1969).
84. R.G. Powell, R. Kleiman and C.R. Smith, Lipids, **4,** 450 (1969).
85. H. Matthes and P. Schutz, Chem. Zentr., **I,** 2753 (1927).
86. H. Kindyl and O. Hoffmann, Ostenhoff. Monatsch. Chem., **97,** 1778 (1966).
87. X.A. Dominguez and C. Villareal, Ciencia, **22,** 163 (1963).
88. X.A. Dominguez, C. Villareal, Ciencia, **21,** 125 (1961).
89. S. Duret and R. R. Paris, Bull. Soc. Bot., **124,** 503 (1977).
90. T. Yamauchi, M. Hara and Y. Ehara, Phytochemistry, **11,** 1852 (1972).
91. B. Chiralo and Riv. Ital. Sostanze. Grasse, **41,** 585 (1964).
92. H. Tauber, J. Zellner, Arch. Pharm., **264,** 689 (1929).
93. T. Yamauchi, F. Abe, Y. Ogata and T. Michiko, Chem. Pharm. Bull., **22,** 1680 (1974).
94. P.L. Pierre and F. Loius, Bull. Soc. Vaudoise. Sci. Nat., **67,** 205 (1960).
95. Von P. Janiak, E. Weiss, J.V. Euw and T. Reichstein, Helv. Chim. Acta, **46,** 374 (1963).
96. R. Tschesche and G. Snatzke, Chem. Ber., **88,** 511 (1955).
97. V.I. Sila, Aptechn. Delo, **14,** 72 (1965).
98. L. Schindel, Folia. Pharm., **2,** 215 (1953).
99. A.B. Lloypis, Galenica, Acta, **8,** 101 (1955).
100. W.C. Cheng, Pharm. Zentralhalle, **105,** 146 (1966).
101. L.F. Fieser, M. Feiser, Natural Products Related to *Phenantherene,* (1949), 3rd ed. pp.513, 514
102. W.C. Cheng, Greenish Pharm. J., **11,** 873 (1966).
103. C. Boonsong and S.E. Wright, Aust. J. Chem., **14,** 449 (1961).
104. S. Durret and R. Paris, Planta Med. Phytother., **6,** 210 (1972).
105. I. Niimoto, Mitt. Med. Ges. Okayama, **51,** 1549 (1939).
106. I. Niimoto, Chem. Zentr., **II,** 919 (1941).
107. A. Windraus and K. Westphal, Chem. Abstracts, **21,** 299 (1927).
108. A. Windraus and K. Westphal, Chem. Abstracts, **27,** 4032 (1933).
109. I. Popa, A. Voicu, S.I. Radian, Pharmazie, **26,** 764 (1971).
110. M. Ishidate and Z. Tamura, J. Pharm. Soc. Japan, **70,** 239 (1950).
111. R. Tschesche, Chem. Ber., **70,** 1554 (1937).
112. G. Hess, Chem. Ber., **70,** 2264 (1937).
113. T. Yamauchi, Ger. Offen., **2,** 248, 457 (1973). Japan Appl., 71, 77, 253, 18pp (1971), C.A. 78, 164077s.
114. J. Moir, Chem. Abstract, **18,** 1825 (1924).
115. L.F. Feiser, and W. Neumann, J. Biol. Chem., **114,** 705 (1936).
116. R. Tschesche, and W. Haupt, Chem. Ber., **70,** 43 (1937).
117. P.N. Chakravorty and E.S. Wallis, J. Am. Chem. Soc., **60,** 1379 (1938).
118. R.E. Marker, D.I. Turner, T.S. Oakwood and E.

Rohrmann, Ulshafer, P.R., J.Am.Chem.Soc., **64,** 720 (1942).
119. C. Mannich, G. Siewert, Chem. Ber., **75,** 737, 750 (1942).
120. T. Nakaoki, J. Pharm. Soc. Japan, **69,** 321 (1949).
121. V. Plouvier, Compt. rend., **251,** 131 (1960).
122. S. Nishibe, S. Hisada and I. Inagaki, Phytochemistry, **10,** 896 (1971).
123. P.K. Sanyal, H.K. I. Das, Proc. Inst. Chemists, **28,** 153 (1956).
124. D. Basu and A. Chatterjee, Ind. J. Chem., **11,** 297 (1973).
125. H.D. Bhasin, Rept. Operations Dept. Agr. Punjab, I (1925) and **II,** 69 (1926).
126. D.S. Rao, Econ. Botany, **II,** 274 (1957).
127. S. Siddiqui, F. Hafeez, S. Begum and B.S. Siddiqui, Phytochemistry, **26,** 237 (1987).
128. S. Siddiqui, S. Begum, F. Hafeez and B.S. Siddiqui, Phytochemistry, **28,** 1187 (1989).
129. S. Siddiqui, S. Begum, B.S. Siddiqui and F. Hafeez, J. Nat. Prod. (in press).
130. S. Siddiqui, F. Hafeez, S. Begum and B.S. Siddiqui, J. Nat. Prod., **51,** 229 (1988).
131. S. Siddiqui, B.S. Siddiqui, F. Hafeez and S. Begum, Planta Medica, 424 (1987).
132. S. Siddiqui, B.S. Siddiqui, S. Begum and F.Hafeez, Planta Medica, 292 (1989).
133. S. Siddiqui, B.S. Siddiqui, F. Hafeez and S. Begum, Planta Medica, 232 (1988).
134. S. Siddiqui, F. Hafeez, S. Begum and B.S. Siddiqui, J. Nat. Prod., **49,** 1086 (1986).
135. S. Siddiqui, S. Begum, F. Hafeez and B.S. Siddiqui, Planta Medica, **47** (1986).
136. F.B. Bowden, C.R. Cambie and C.J. Parnell, Aust. J. Chem., **28,** 91 (1975).
137. R.S. Johns, A.J. Lamberton, C.T. Morton, H. Suares and I.R.Willing, Aust. J. Chem., **36,** 2537 (1983).
138. R.S.A. Anjaneyulu, R.L.Row and A. Sree, Phytochemistry, **18,** 1199 (1979).
139. T. Kubota, H. Kitatani and H. Hinoh, J. Chem. Soc., Chem. Commun., 1313 (1969).
140. R.U. Lemieux and J. Canad. Chem., **31,** 396 (1953).
141. L.W. Brieber, A.A.D. Filho, R.M.O.C. Lima, A.D. Chiappeta, S.C.D. Nascimento, I.A. De Souza, J.F. De Mello and H.J. Venth, Phytochemistry, **25,** 1077 (1986).
142. L.M. Perry and J. *Metzger, Medicinal Plants of East and Southeast Asia*, (The MIT Press Cambridge, Massachusetts, and London, England, 1978), pp. 27.
143. F.W. Wilson, Ariz. Agr. Expt. Sta., Bull., **59** (1910).
144. E. Morandi, Allg. Med. Klin. Turin. Rass. ter., No. 21, through Biochem. Centre, **8,** 411 (1908).
145. M. Bockmuhl, G. Ehrhart, (to Winthrop Chemical Co.) U.S. **2,** 099, 158 (1938).
146. G. Farbenind, Brit., 478 (1938).
147. M.M. Likhachev, M.I. Palchevskaya, Sovet. Vrachebnyi. Zhur., **42,** 857 (1938).
148. M.M. Likhachev, M.I. Palchevskaya, Chem. Zentr., **II,** 1356 (1939).
149. K.H. Osterwald, Klin. Wochschr., **20,** 146 (1941).
150. Rudolf, Siefert. Suddeut. Apoth.-Ztg., **81,** 443 (1943).
151. Rudolf, Chem. Zentr., **I,** 383 (1942).
152. I. Z. Simon, Ges. Exptl. Med., **109,** 279 (1941).
153. I. Simon, Chem. Zentr., **II,** 310 (1942).
154. P. Stern and R. Balzer, Arch. Exptl. Path. Pharmakol, **199,** 421 (1942).
155. J.G. Queralto, Rev. Clinica. Espanola, **1,** 516 (1940).
156. J.G. Queralto, Rev. Sud-americana. endocrinol. immunol. quimioterap., **25,** 35 (1942).
157. R. Cortesi, Pharm. Acta. Helv., **18,** 229 (1943).
158. R. Springer, Pharm. Zentrahalle, **82,** 325, 337 (1941).
159. R. Springer, Chem. Zentr., **II,** 2109 (1941).
160. H. Gold, W. Modell, M. Cattell, J.G. Benton and E.W. Catlove, J. Pharmacol. Exptl. Therap., **91,** 15 (1947).
161. A. Boriani, Farm. Sci. Etec., **3,** 428 (1948).
162. K. Huang and C. Jang, Science and Technology China, **1,** 35 (1948).
163. F. Buffoni and A. Giotti, Bull. Soc. Ital. Biol. Sper., **25,** 108 (1949).
164. F. Buffoni and A. Giotti, Bull. Soc. Ital. Biol. Sper., **25,** 112 (1949).
165. R. Fabre, R. Cortesi, G. Rougier, J. Cortesi, J. Med. Bordeaux, **127,** 839 (1950).
166. R. Cortesi, Boll. Chim. Farm., **90,** 48 (1951).
167. R. Fabre, R. Cortesi, G. Rougier and J. Cortesi, Compt. Rend. Soc. Biol., **144,** 1496 (1950).
168. M. Ishidate, Japan, 179, 970 (1949).
169. T. Takahashi, Folia. Pharmacol. Japan, **44,** 83 (1948).
170. J.M.S. Marcos and J.M.S. Monsalve, Gac. Med. Espan., **27,** 570 (1953).
171. T. Matsukuma, Japan, **54,** 4948 (1955).
172. T. Matsukuma, Igaku Kenkyu, **28,** 4139 (1958).
173. T. Hsiao and T Yao Hsueh 'ung Pao., 390 (1959).
174. C.E. Eliakis, E.C. Eliakis and A.S. Coutselinis, Ann. Med. Legale. Criminol., Police. Sci. Toxicol., **41,** 367 (1961).
175. L.E. Burton, A.L. Picchioni and L. Chin, Arch. Intern. Pharmacodyn. Ther., **158,** 202 (1965).
176. F. Basilico, Corriere. Farm.., **21,** 417 (1966).

177. M. Szabuniewicz, J.D. McCrady and J.B. Camp, Arch. Int. Pharmacodyn. Ther., **189,** 12 (1971).

178. N. Singh, V.K. Kulshreshtha and R.P. Kohli, J. Res. Indian. Med., **5,** 32 (1970).

179. V.D. Dunk and P.T.A. Klaus, Prakt. Pharm., **8,** 340 (1979).

180. M.T.M. Costa, G.N. Marcos, S.N.J. Moises and M.J. Ellias, Cienc. Cult., 172 (1980).

181. F.D. Pinto, D. Palermo, M.A. Milillo and D. Iaffaldano, Clin. Vet., **104,** 15 (1981).

182. I.T., Li, C.C. Shao, Yao Hsueh Hsueh Pao., **10,** 215 (1963).

183. M.A. Mancini, Arch. Intern. Pharmacodyn., **139,** 42 (1952).

184. E.Y. Shass, Farmatsiya, **11,** 43 (1941).

185. K.K. Chen, F.G. Henderson and R.C. Anderson, J. Pharmacol. Exptl. Therap., **103,** 420 (1951).

186. W. Rittel and T. Reichstein, Helv. Chim. Acta, **36,** 787 (1953).

187. L. Fauconnet and P.L. Pouly, Pharm. Acta. Helv., **37,** 301 (1962).