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TETRACYCLIC TRITERPENOIDS AND THEIR DERIVATIVES FROM *AZADIRACHTA INDICA*

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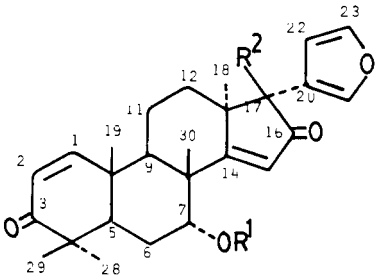
ABSTRACT.—Studies on the chemical constituents of *Azadirachta indica* (neem) are reviewed. The isolation, unique features of the structures, biosynthetic aspects, and biological activities of these constituents are discussed.

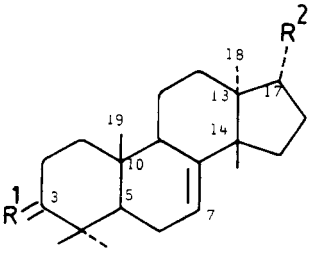
Azadirachta indica Juss. (syn. *Melia azadirachta* L., *Melia indica*, Margosa), known in the vernacular as "neem" and "nimba," belongs to the family Meliaceae and is widely distributed in Asia, Africa, and other tropical parts of the world (1–5). Almost every part of the tree has long been used in folkloric and traditional systems of medicine for the treatment of a variety of human ailments, particularly against diseases of bacterial and fungal origin (1–4). The chemical and therapeutic studies undertaken since about the beginning of this century were initially concerned with the fatty acid components and amorphous bitter substances of the oil (6). It was in 1942 that the first two crystalline constituents, nimbin [**1**] and nimbinin [**2**], were isolated from the oil along with an amorphous bitter principle, nimbidin, through solvent partitioning of the oil avoiding its prior saponification (7). Nimbidin is antiarthritic and anti-inflammatory (8) in its action and possesses significant antiulcer potential (9), whereas various other fractions have antipyretic and anti-inflammatory properties (10). The extracts and various factors derived from neem also possess diverse biological effects on insects such as repellency, phagodeterrence, reduced growth, abnormal development, and reduced oviposition (11,12).

After the isolation of nimbin and nimbinin (7), about 100 constituents have so far been isolated from different parts of the tree and their structures elucidated. These include proto-meliacins, meliacins (limonoids or tetranortriterpenoids, tetranortriterpenoid-γ-hydroxybutenolides, ring C seco-tetranortriterpenoids, and ring C seco-tetranortriterpenoid-γ-hydroxy butenolides), pentanortriterpenoids, a hexanortriterpenoid, and nontriterpenoidal constituents.

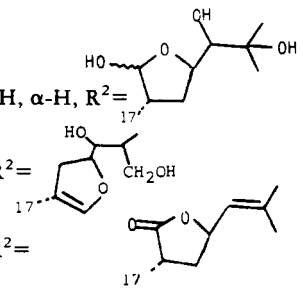
PROTO-MELIACINS.—Five C_{30} tetracyclic triterpenes (proto-meliacins or proto-limonoids) have so far been reported from various parts of neem, including three euphol/tirucallol derivatives, namely meliantriol [**3**] from neem oil and the fresh fruits of the closely related species *Melia azedarach* (13), nimbocinone [**4**] from undried leaves, and nimolinone [**5**] from the fresh fruits; and two apo-euphol/apo-tirucallol derivatives, namely azadirachtol [**6**] and azadirachnol [**7**], also from the fresh fruits. The structure of meliantriol [**3**] possessing the butyrospermol skeleton (14) was correlated with melianone (15), the structure and stereochemistry of which have been confirmed through chemical reactions (16). Thus, treatment of melianone with perchloric acid in dioxan solution afforded meliandiol that upon reduction with $NaBH_4$, gave meliantriol. It showed 100% antifeeding activity against desert locust (*Schistocerca gregaria* Forsk.). Nimbocinone [**4**] (17), the first 26-hydroxy triterpenoid from neem, is closely related to 20,21-anhydromelianone (18). The stereochemistry of the carbocyclic ring system was determined through dehydrogenation of its diacetyl derivative with mercuric acetate (19), while Horeau's method (20) and ^{1}H-nmr spectral data defined the stereochemistry of the side-chain carbons C-23 and C-24 as *S* and *R*, respectively (17). Nimolinone [**5**] (21) has previously been obtained through oxidation of flindissol (22), and the stereochemistry of various centers of nimolinone has been established thro ugh



2 R^1=Ac, R^2=H; 14,15-dihydro-14,15-epoxide
12 R^1=Ac, R^2=H
14 R^1=COPh, R^2=H
15 R^1=COPh, R^2=H; 14,15-dihydro-14,15-epoxide
18 R^1=R^2=H
29 R^1=Ac, R^2=OH
32 R^1=Ac, R^2=H; 1,2,14,15-tetrahydro-1α-methoxy-14,15-epoxide
33 R^1=Ac, R^2=H; 1,2,14,15-tetrahydro-1,2-,14,15-diepoxide

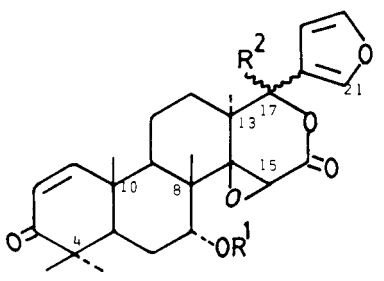


3 R^1=β-OH, α-H, R^2=

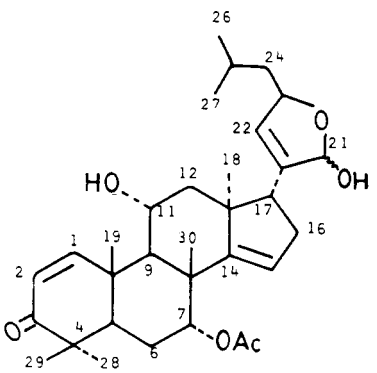


4 R^1=O, R^2=

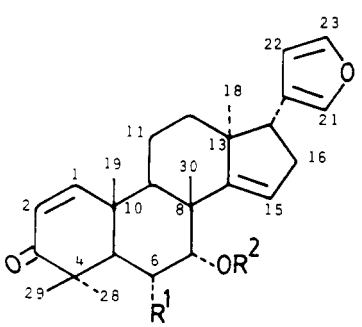
5 R^1=O, R^2=



13 R^1=Ac, R^2=β-H
16 R^1=COPh, R^2=β-H
30 R^1=Ac, R^2=α-OH; 14,15-deoxy



6
7 20,22-dihydro



11 R^1=H, R^2=Ac
17 R^1=H, R^2=COPh
19 R^1=OAc, R^2=H; 1,2-dihydro
21 R^1=OH, R^2=Ac; 1,2-dihydro
22 R^1=OH, R^2=H; 1,2-dihydro
23 R^1=OH, R^2=Ac

NOESY experiments (21). Azadirachtol [**6**] (23) and azadirachnol [**7**] (24) are the first apo-euphol/apo-tirucallol derivatives possessing an eight-carbon side chain with an oxygenated ring system isolated from neem. Moreover, these are the first examples of the isolation of 11-hydroxy triterpenoids from any of the various parts of the neem tree.

It has been suggested by in vitro experiments (25,26) that proto-meliacins or proto-limonoids (euphane or tirucallane derivatives) are the biosynthetic precursors of meliacins or limonoids (tetranortetracyclic triterpenoids), the expected precursor being the Δ^7-isomer (butyrospermol derivative) of euphane (Δ^8, H-20β; 20*R* or tirucallane (Δ^8, H-20α, 20*S*).[1] Thus, in the biosynthesis of meliacins a Δ^7-euphane (or Δ^7-tirucallane) derivative, i.e., butyrospermol, undergoes an euphol-apo-euphol (or tirucallol-apo-tirucallol) rearrangement induced by the opening of the 7α,8α-epoxide ring, with the migration of the C-14 β Me to C-8, formation of a C-7 hydroxyl group having the correct α-orientation, and a double bond at C-14,15 (Scheme 1). Meliantriol [**3**] and nimolinone [**5**] represent the tirucallane derivatives (Δ^7, H-20α) with a C-8 side chain, whereas in the case of nimbocinone [**4**] the configuration at C-20 has not been determined. In azadirachtol [**6**] and azadirachnol [**7**] (apo-euphol or apo-tirucallol[2] derivatives, because the C-20 stereochemistry is undefined), the rearrangement has occurred without degradation of the C-8 side chain. The isolation of these two triterpenoids indicates that the rearrangement precedes the oxidative degradation of the side chain in the biosynthesis of meliacins. This is also exemplified by the occurrence in nature of grandifoliolenone (28) and a few other tirucallane derivatives (26,29).

It has been further demonstrated by in vitro experiments that the formation of the furan ring of meliacin proceeds through a cyclic hemiacetal (25). Thus, periodate oxidation of turraeanthin A gave a labile cyclic hemiacetal that, upon treatment with toluene-*p*-sulfonic acid, afforded the furan. Ekong *et al.* (30,31) carried out feeding experiments with tritium-labeled euphol, tirucallol, butyrospermol, and Δ^7-tirucallol and noted that Δ^8-isomers were more efficiently utilized than Δ^7-isomers in the biosynthesis of nimbolide [**8**] (32) in the leaves of *A. indica*. This observation, which apparently contradicts the general expectation for the biosynthesis of the meliacin nucleus, was explained by the suggestion that as nimbolide is a ring C-seco compound, its biosynthesis might involve a $\Delta^{7,9(11)}$-diene, which is easily formed from an 8α,9α-epoxide. The Δ^7-function of the $\Delta^{7,9(11)}$-diene system would give the 7α-hydroxy-apo skeleton, while the $\Delta^{9(11)}$-function would activate the C-12 position towards eventual oxidation leading to ring C fission (Scheme 2). Thus, the naturally occurring tetranortriterpenoid nimbidinin [**9**] (33), with a carbonyl function at C-12, may be an intermediate in the biosynthesis of ring C-seco compounds. This possibility is also supported by its co-occurrence with nimbidic acid (33) and salannin [**10**] (34) in neem.

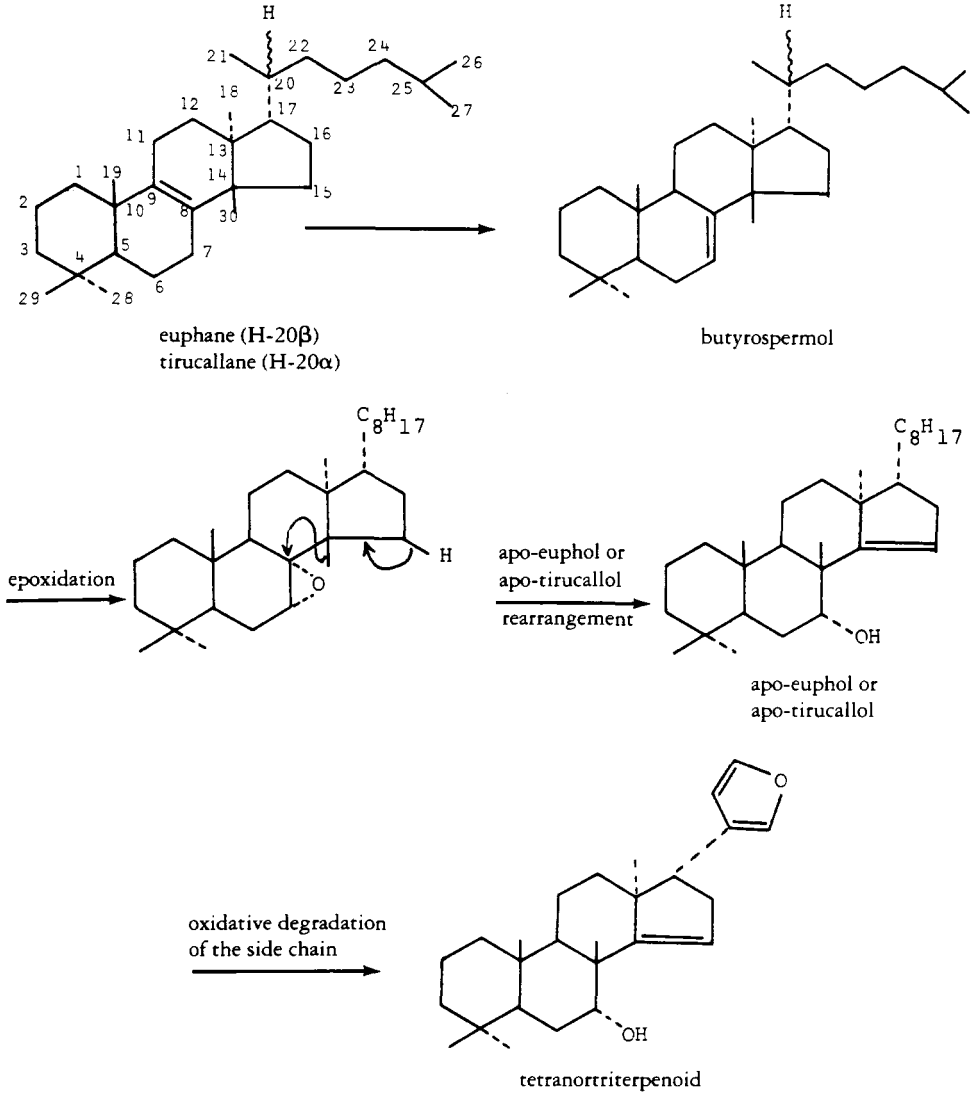
MELIACINS (LIMONOIDS)[3].—*Limonoids or tetranortriterpenoids*.—The postulated biosynthetic sequence of meliacins (degraded C_{26} triterpenoids) from a Δ^7-euphane (or Δ^7-tirucallane) derivative is supported by the fact that all the known meliacins possess an oxygen function at C-7. In order to account for an epoxylactone in ring D of limonin (35), an attractive sequence was proposed through the allylic oxidation of the corres-

[1]The crystal structure of euphol and tirucallol revealed that the hydrogen atom on C-20 was in back next to C-18 in both the compounds, and C-22 was found to be *cis*-oriented ("left-handed") to C-13 in euphol (20*R*) and *trans*-oriented to it ("right-handed") in tirucallol (20*S*) (27).

[2]Apo-euphol or apo-tirucallol derivatives possess a rearranged euphane (or tirucallane) skeleton in which C-14β Me has been migrated to C-8 with the creation of a double bond at C-14,15 (25,26).

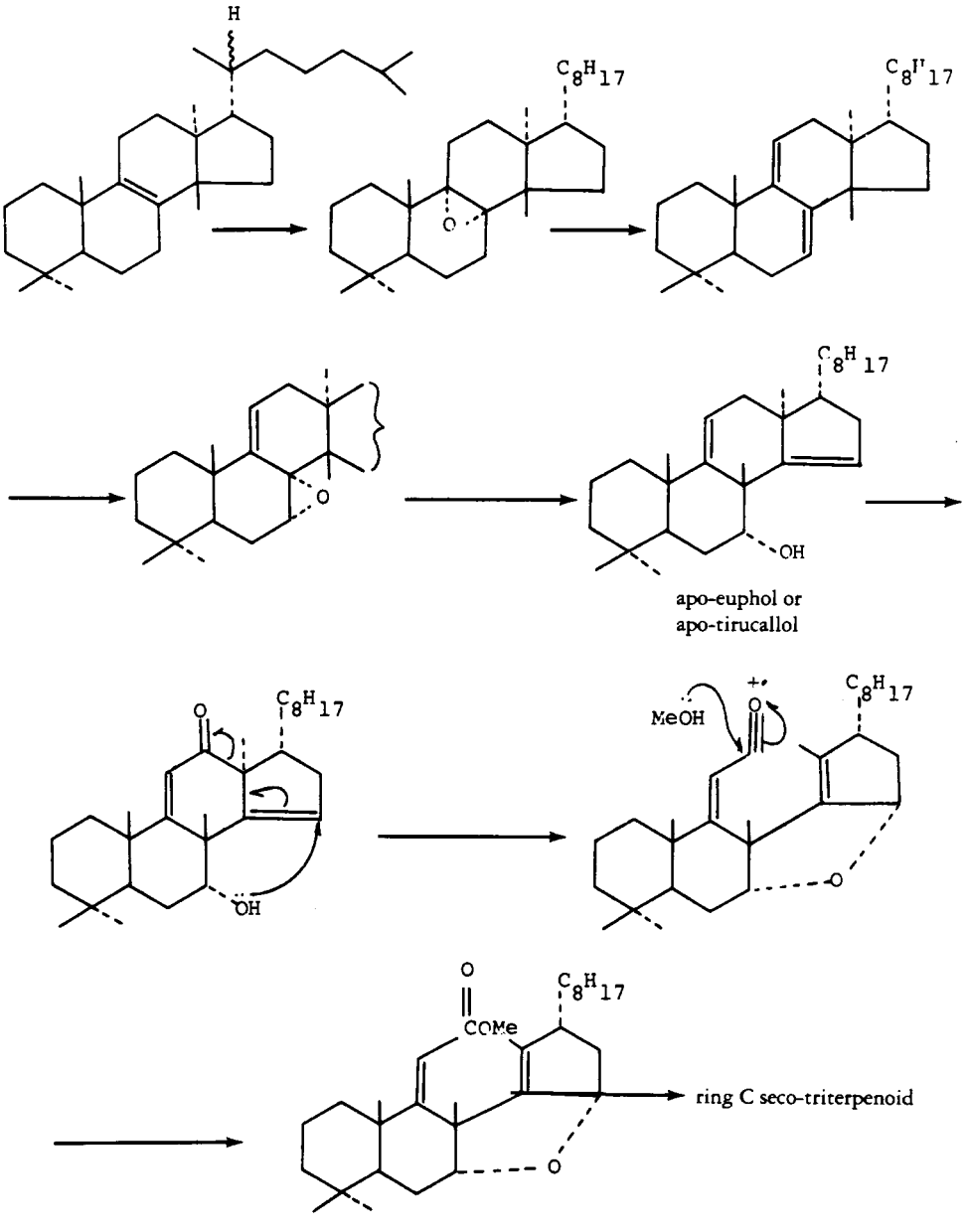
[3]Meliacins or limonoids refer to the tetracyclic triterpenoids possessing the apo-euphol (or apo-tirucallol) skeleton from which four carbons of the C-8 side chain have been degraded. The term limonoid is derived from limonin, the first tetranortriterpenoid isolated from citrus bitter principle in 1841 (35).

ponding derivative containing a double bond at C-14,15, affording a Δ^{14}-16-ketone which, upon subsequent oxidation, would lead to the 14,15-epoxy-16-keto derivative. Finally, the desired epoxylactone could be obtained through Baeyer-Villiger oxidation of the epoxyketone. This postulation was supported by the isolation of azadirone [**11**], azadiradione [**12**], and epoxyazadiradione [**2**] from the seed oil of neem (36) along with gedunin [**13**] reported earlier (37), each representing various steps in the biosynthetic pathway. Their relationship was also demonstrated by their in vitro interconversion through stepwise oxidation (36). Later on, C-7 benzoates of 7-deacetylazadiradione [**14**], epoxyazadiradione [**15**], and gedunin [**16**] were also reported, which are the first benzoyl derivatives from neem (38). The precursor of these, namely nimocin [**17**], has recently been obtained from the fruits (39) along with the 7-deacetyl-7-hydroxy-azadiradione (nimbocinol [**18**]) (40). It may be noted that epoxyazadiradione (36) appears to be identical with nimbinin [**2**] isolated in 1942 (7) and the structure established in 1967–68 (41,42), although their specific rotations differ widely. Several 6α-



SCHEME 1

oxygenated derivatives of azadirone such as meldenin [**19**] (42), vepinin [**20**] (43), isomeldenin [**21**] (44), meldenin diol [**22**] (44), nimocinol [**23**] (45), and 4α,6α-dihydroxy-A-homoazadirone [**24**] (46) have also been reported from different parts of the tree. The latter is worth mentioning as it has a seven-membered ring A with a new bond between C-3 and C-28. Preliminary tests of nimocinol [**23**] and its mother fraction against houseflies (*Musca domestica*) have shown that they possess insect growth regulat-



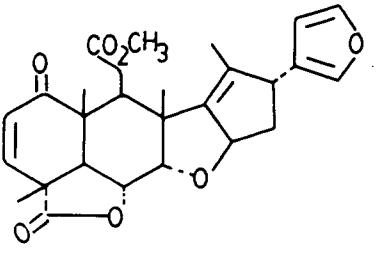
SCHEME 2[a]

[a]There is no record in literature of the isolation of a ring C seco-triterpenoid with an intact C_8 side chain; it is still to be decided whether both oxidations (of the side chain and ring C) take place simultaneously or one follows the other.

ing properties (47). Nimbolin A [**25**] (48), the first example of a triterpenoid from neem with a cinnamate function, was obtained from trunk wood, whereas vilasinin [**26**] (49), 1,3-diacetylvilasinin [**27**] (50), and 1-tigolyl-3-acetylvilasinin [**28**] (51)–all derivatives of azadirone–were isolated from seed oil. The latter two compounds possess quite good insect antifeeding activity (50,51). Vilasinin [**26**] is a possible biogenetic precursor of the ring C seco-meliacins salannin [**10**] and nimbin [**1**] (49). 17β-Hydroxyazadiradione [**29**], isolated from neem fruits (52,53), is the first example from any source of a meliacin having a hydroxyl function at C-17. Another example is nimolicinol [**30**] (54), from fresh fruits, in which the configuration of the furan ring was confirmed through nOe experiments. The first 17-*epi* compound of this series, 17-*epi*-azadiradione (53), was isolated from dried fruits, and the β configuration of the furan ring was decided through nOe difference experiments. A 17-acetoxy meliacin, isonimolicinolide [**31**] (55) has also been isolated, possessing a γ-hydroxybutenolide side chain at C-17 instead of the usual furan ring. C-17 substituted tetranortriterpenoids are very rare in nature (29, 52–54), and **31** is the first 17-acetoxy derivative from any source. 1α-Methoxy-1,2-dihydro-epoxyazadiradione [**32**], 1β,2β-diepoxy-azadiradione [**33**], and 7-acetylneotrichilenone [**34**] (38) were isolated from neem seeds, and their stereochemistry was determined through nOe difference measurements. Compound **34**, the structure of which was confirmed by X-ray structural analysis, possesses anticancer activity in vitro (56). Recently a structurally interesting tetranortriterpenoid, azadirachtanin [**35**], has been reported from the leaves (57); this is the only example of a meliacin with a C-19, C-29 epoxide from neem and is also the first instance of a naturally occurring tetranortriterpenoid with a C-19, C-29 epoxide lacking an epoxide ring between C-14 and C-15.

Tetranortriterpenoid-γ-hydroxybutenolides.—Nimocinolide [**36**] and isonimocinolide [**37**] obtained from the fresh neem leaves (39) are the first γ-hydroxybutenolides (α,β-unsaturated-γ-hydroxy-γ-lactones) from neem with an apo-euphane (or apo-tirucallane) intact carbocyclic skeleton. They possess insect growth regulating properties and affect fecundity in houseflies (*M. domestica*) at a dosage of 100–500 ppm. They show mutagenic properties in mosquitoes (*Aedes aegypti*), producing larval-pupal intermediates. Photo-oxidation of nimocinol [**23**] afforded only **36**, showing that they are genuine natural products and not derived from photo-oxidation of the furan ring (58). Nimbocinolide [**38**] (59) and isonimbocinolide [**39**] (60), also obtained from the same source, bear a 2-methyl-2-hydroxypropionate function at C-11; their mother fraction is capable of disturbing the metamorphic growth of mosquitoes (*A. aegypti*) and produces larval-pupal intermediates (47).

Ring C seco-tetranortriterpenoids.—Nimbin [**1**] (7) is the first representative of ring C seco-tetranortriterpenoids from neem, the structure of which was finally established in



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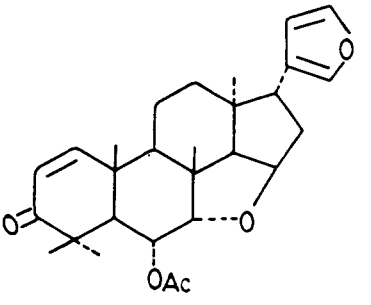

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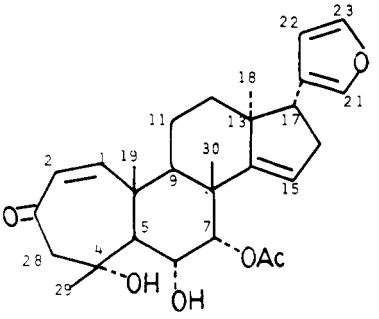

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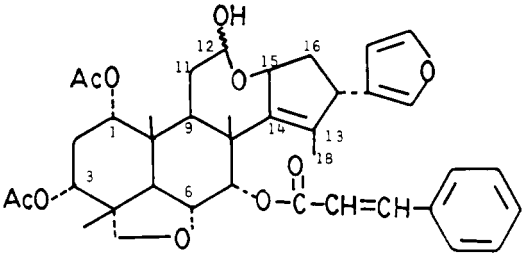

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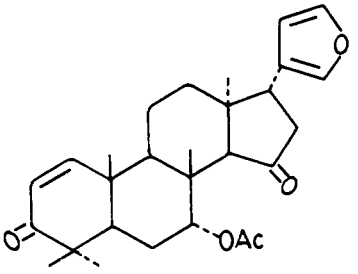

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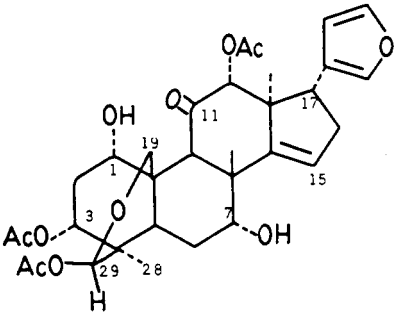

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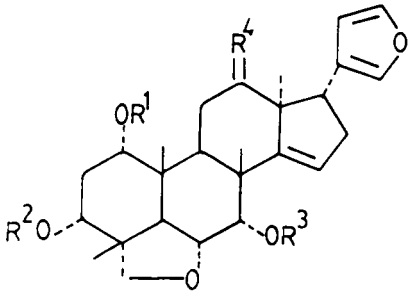
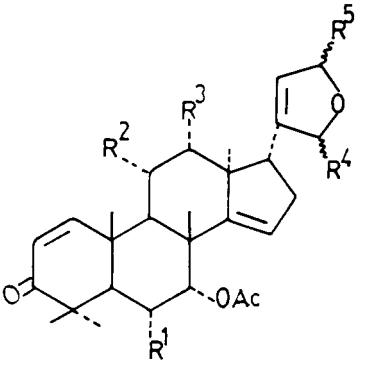


9 $R^1=R^2=R^3=H$, $R^4=O$
25 $R^1=R^2=Ac$, $R^3=COCH=CHPh$, $R^4=H_2$
26 $R^1=R^2=R^3=H$, $R^4=H_2$
27 $R^1=R^2=Ac$, $R^3=H$, $R^4=H_2$

28 $R^1=$  , $R^2=Ac$, $R^3=H$, $R^4=H_2$



36 $R^1=OH$, $R^2=R^3=H$, $R^4=O$, $R^5=OH$
37 $R^1=OH$, $R^2=R^3=H$, $R^4=OH$, $R^5=O$
38 $R^1=H$, $R^2=OCOC(Me)_2OH$, $R^3=OH$, $R^4=O$, $R^5=OH$
39 $R^1=H$, $R^2=OCOC(Me)_2OH$, $R^3=OH$, $R^4=OH$, $R^5=O$

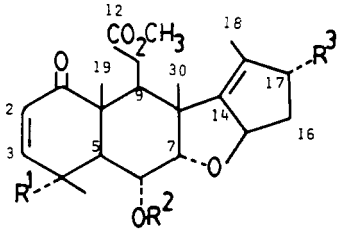
1968 (61). It has been shown to inhibit the growth of potato virus "X" in vitro (62). Salannin [**10**] (34), 3-deacetylsalannin [**40**] (50), salannol [**41**] (50), and salannol acetate [**42**] (51), all constituents of neem oil, show strong antifeedant activity, comparable to that of azadirachtin (51,63). In this series the activity is apparently not dependent on the nature of the ester groups attached at C-1 and C-3. A similar activity was found in **43** and **44**, isolated from neem seeds, which are the first triterpenoids where the C-17 furyl group is replaced by an unsaturated lactam group (51,64). In salannin [**10**], which is structurally related to nimbin [**1**], the relative positions of the tiglate

and acetate functions were assigned on the basis of ^{1}H-nmr data and the hydrolysis of the less-hindered acetate at C-3 to 3-deacetylsalannin [**40**] (34). Compound **40** obtained earlier through the alkaline hydrolysis of salannin [**10**] followed by methylation (34) has now also been isolated from a natural source (51). 2′,3′-Dehydrosalannol [**45**] isolated from the leaves (65); desacetylnimbin [**46**] obtained from the seeds, bark, and twigs (66,67); nimbolide [**8**] (32) from fresh leaves; and nimbolin B [**47**] from trunk wood (48) are all related to nimbin [**1**] and represent various stages in the biosynthetic pathway. Nimbolide [**8**] is the only compound from neem possessing a lactone ring between C-6 and C-28.

Azadirachtin, the most potent insect antifeedant and insect growth regulating agent, was isolated in 1968 from neem and *M. azedarach* seeds, using a feeding inhibition test (68,69). Its structure elucidation presented a great deal of difficulty due to its unstable nature and failure to crystallize the triterpenoid itself or any of its derivatives. As a result of detailed nmr studies by various groups of workers (63,68,70), the structure **48** was elucidated in 1975; however, some doubt remained about certain parts of the structure. Particularly, the ^{13}C-nmr signals of C-13 (δ 69.69) and C-14 (δ 68.53) should appear at lower field if they were connected to tertiary hydroxy or alkoxy groups. Extensive nOe experiments, homodecoupling experiments, ^{13}C deuterium isotope shifts, and C,H long-range coupling measurements carried out in recent years (51, 71–73) finally led to structure **49** for azadirachtin. The ^{13}C deuterium isotope effects observed on C-7, C-11, and C-20 confirmed the assigned structure, with C-11 as a hemiacetal, the chemical shifts of C-13 and C-14 being explained as typical of quaternary oxirane carbons (51,72). Further, the nOe's are consistent with the revised structure **49**, which has also been confirmed through X-ray crystallographic studies of 3-detigloyldihydroazadirachtin obtained through catalytic hydrogenation of azadirachtin followed by detigloylation (71). A related compound, 22,23-dihydro-23β-methoxyazadirachtin [**50**], isolated from seeds (72), was found to impair the development of larvae of *Epilachna varivestis* and *Spodoptera littoralis* (51). Deacetylazadirachtinol from fresh fruits proved as potent as azadirachtin in inhibition of insect ecdysis and about 2.5-fold less active as an insect growth inhibitor, when fed in artificial diet to larvae of tobacco bud worm (*Heliothis viressens*) (74). In the light of the revised structure of azadirachtin and detailed ^{1}H- and ^{13}C-nmr and nOe experiments, the structure of deacetylazadirachtinol has been reassigned as 3-tigloylazadirachtol [**51**] (75). In an attempt to study the functional groups responsible for the activity of azadirachtin, a stereocontrolled synthesis of the hydroxydihydrofuran acetal fragment of azadirachtin, which proved to be a potent insect antifeedant, has been reported in the current year (76).

Ring C seco-tetranortriterpenoid-γ-hydroxybutenolides.—Salannolide [**52**], isolated from the total bitter principle of seed oil (77), represents the first tetranortriterpenoid from neem with a γ-hydroxybutenolide side chain at C-17. Other such derivatives are isoazadirolide [**53**] from leaves (78) and desacetylnimbinolide [**54**], desacetylisonimbinolide [**55**] (67), margosinolide [**56**], and isomargosinolide [**57**] (79) isolated from fresh twigs. Compounds **56** and **57** represent the first constituents so far reported from twigs. The unique feature of these is the ether linkage between C-6 and C-28 with a 1-en-3-one ring A. Compounds **56** and **57** are of biological significance inasmuch as growth inhibiting activity of ring C seco-limonoids is enhanced by the presence of an α,β-unsaturated ketone system in ring A (74).

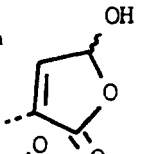
It may be noted that most of the triterpenoidal constituents reported from neem are azadirone [**11**] derivatives that further support the postulated biosynthetic pathway. The biosynthesis of α,β-unsaturated-γ-hydroxybutenolides, several of which have been isolated from neem and other sources (58,80,81), may proceed through photo-



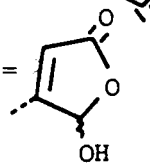
1 R^1=CO_2Me, R^2=Ac, R^3=furan

46 R^1=CO_2Me, R^2=H, R^3=furan

54 R^1=CO_2Me, R^2=H, R^3=



55 R^1=CO_2Me, R^2=H, R^3=



60 R^1=OH, R^2=H, R^3=furan
61 R^1=OH, R^2=Ac, R^3=furan

oxidation of furans. However, the reverse pathway, i.e., the reduction of the butenolides to the cyclic hemiacetal followed by the formation of furan, seems likely because various hemiacetals [**3**, **6**, **7**] and a lactone [**5**] as well as dihydrofuran [**4**] derivatives with a C-4 side chain at C-23 have also been obtained. Thus, **36–39** represent intermediates in the biosynthesis of azadirone [**11**] and its derivatives; while **54–57** and **52–53** may be regarded as intermediates in the biosynthesis of nimbin [**1**] and salannin [**10**] derivatives, respectively. On the other hand, **31** may be an intermediate in the biosynthetic pathway of azadiradione [**12**] derivatives. It may further be noted that all the γ-hydroxybutenolides (including ring C seco derivatives) were detected in fresh plant extracts, demonstrating that they are genuine natural products.

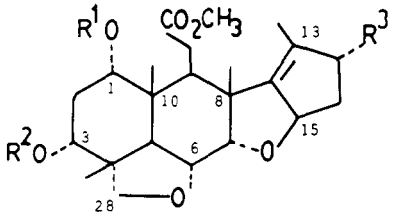
PENTANORTRITERPENOIDS.—Recently four pentanortriterpenoids, nimbinene [**58**], 6-deacetylnimbinene [**59**], nimbandiol [**60**], and 6-*O*-acetylnimbandiol [**61**], have been reported from neem (82) in which one of the C-4 methyls has been lost along with the four carbons of the side chain.

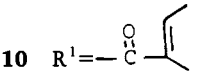
HEXANORTRITERPENOID.—Nimolicinoic acid [**62**] (55), the only hexanortriterpenoid from neem, is the first instance of isolation of a naturally occurring hexanortriterpenoid with an apo-euphane (or apo-tirucallane) skeleton. Only a few hexanortriterpenoids have been reported from other sources, but they possess cucurbitacin (83,84), dammarane (85), and lanostane skeletons (86). Compound **62** is also the first example of a hexanortriterpenoidal acid isolated from any source.

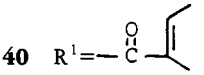
In respect to the biosynthetic precursors of the triterpenoids of neem, it may be noted that **3** and **5** are tirucallane derivatives (C-20*S*), whereas the rest have an undefined configuration at C-20.

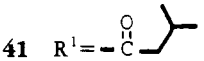
The mother fraction of **5**, **6**, **7**, **31**, and **62** showed insect growth regulating properties against pulse beetle (*Cellasobruchus analis*). The LD_{50} value was found to be 50 g/cm^2, as compared to the LD_{50} value of diflubenzuron (dimilin), 20 g/cm^2, determined by the contact method (47,55).

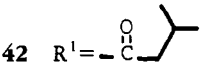
NONTRITERPENOIDAL CONSTITUENTS.—Nontriterpenoidal constituents isolated from different parts of neem include hydrocarbons, fatty acids, diterpenoids,

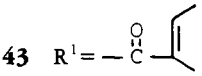
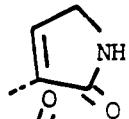


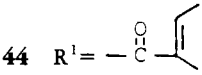
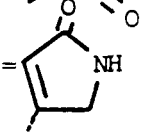
10 R^1=  , R^2=Ac, R^3=furan

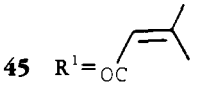
40 R^1=  , R^2=H, R^3=furan

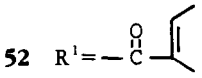
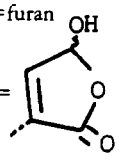
41 R^1=  , R^2=H, R^3=furan

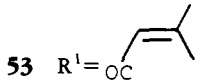
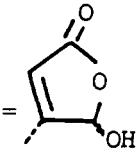
42 R^1=  , R^2=Ac, R^3=furan

43 R^1=  , R^2=Ac, R^3= 

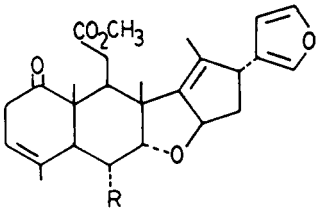
44 R^1=  , R^2=Ac, R^3= 

45 R^1=  , R^2=H, R^3=furan

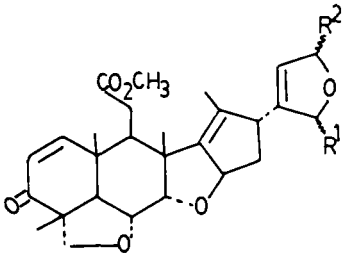
52 R^1=  , R^2=Ac, R^3= 

53 R^1=  , R^2=H, R^3= 

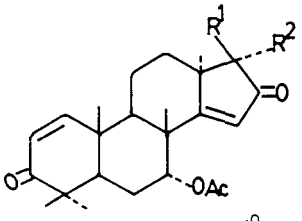
sterols, phenols, flavonoids, glycosides, sugars, amino acids, and carbohydrates (87). Sugiol and nimbiol (88) are the phenolic tricyclic diterpenes isolated from trunk bark. Nimbaflavone (89) isolated from the leaves is the first example of an isoprenyl flavanone from the Meliaceae family. Nimbochalcin, a dihydrochalcone derivative, and nimbocetin, a substituted aromatic ester, were isolated from the hydrolyzate of the main aqueous fraction of the fresh fruits (90). Quercetin, isolated from the leaves (91), acts as an antitumor promoter (92) and also showed an antiaggregating effect (93). Alkane fraction from leaves showed larvicidal activity against mosquitoes (*Culex pipiens fatigans*). Four of these alkanes were identified as $Me(CH_2)_nMe$ (n = 16, 17, 24, and 32) (12). Polysaccharide fractions from neem bark are of particular interest as they possess antitumor and anti-inflammatory properties (94,95). Recently an antineoplastic drug has also been obtained from neem bark (96). Furthermore, scopoletin (97,98) has also been obtained from neem leaves (78) which is the first report of the isolation of a coumarin from any of its various parts, although several coumarins have been isolated from other plants of the Meliaceae family, e.g., the closely related plant *M. azedarach* (99).



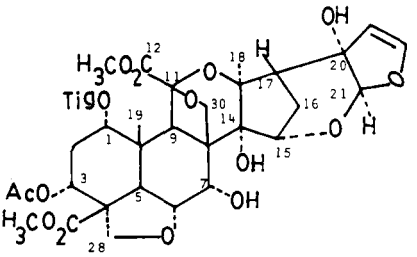
58 R=OAc
59 R=OH



56 R^1=O, R^2=OH
57 R^1=OH, R^2=O

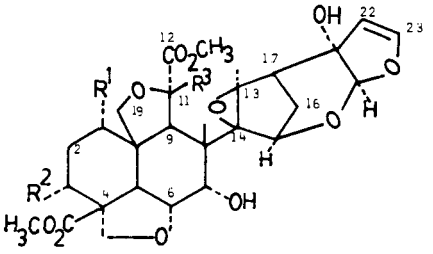


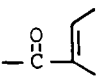
31 R^1=OAc, R^2= 

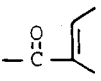


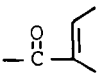
48

62 R^1=H, R^2=CH_2COOH



49 R^1=O—  , R^2=OAc, R^3=OH

50 R^1=O—  , R^2=OAc, R^3=OH;
22,23-dihydro-
23β-methoxy

51 R^1=OH, R^2=O—  , R^3=H

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