*Chemistry of Natural Compounds, Vol. 31, No. 6, 1995*

# TERPENOIDS OF PLANTS OF THE *Ferula* GENUS. I. NATURAL CAROTANE DERIVATIVES

**A. I. Saidkhodzhaev and A. U. Mamatkhanov**

UDC 547.983:582.89

*This review, generalizing information up to 1993, is devoted to the chemistry and spectral properties of natural carotane compounds.*

Since 1970, a study of the chemical composition of various plants of the *Ferula* genus growing on the territory of Uzbekistan and adjacent republics been conducted in the Institute of the Chemistry of Plant Substances of the Republic of Uzbekistan Academy of Sciences. Problems of the systematic investigation of the terpenoids of *Ferula* plants have been solved, methods have been developed for their isolation and separation, their structures and stereochemistries have been determined, new drugs have been created from them, and attempts have been made to answer a number of questions connected with the biosynthesis of the terpenoids and with the chemotaxonomy of the *Ferula* genus.

Up to now, more than 50 species of the *Ferula* genus have been subjected to chemical study, and more than 250 terpenoids have been isolated from them. We were the first to show that plants of the *Ferula* genus contain, in addition to terpenoid coumarins and sesquiterpene lactones, a new group of natural compounds characteristic for this genus — esters of terpenoid alcohols with aromatic and aliphatic acids.

The structures and stereochemistries of about 100 new terpenoids belonging to the acyclo-, monocyclo-, and bicyclofarnesane, germacrane, humulane, guaiane, carotane, himachalane, and camphane types have been established. Terpenoids with carotane, humulane, and himachalane skeletons have been isolated form the Uzbekistan flora for the first time.

We have studied the dynamics of the accumulation of terpenoids in each organ of *Ferula* plants as functions of the growth site and of the vegetation period. The results of these investigations have enabled us to select the period and site of the growth of a plant in the optimum manner, to isolate the maximum number of terpenoids, and to attempt to reveal the laws of their accumulation in the organs of the plant. It has been found that, with a variation in the ecological–geographical conditions, the terpenoids in plants change more rapidly than the morphological characteristics of the plants. Consequently, one and the same plant species may contain different terpenoids under different growth conditions.

The present review is devoted to one of the most widespread types of giant fennel (*Ferula*) terpenoids — derivatives of carotane (daucane).

Carotane derivatives form a new group of natural compounds the majority of which have been detected and studied during the last two decades. Their structure is based on the carbon skeleton of a bicyclic sesquiterpene — 4-isopropyl-1,8-dimethylbicyclo[0.3.5]decane (**1**), which has acquired the name of "carotane" or "daucane." Both terms were formed from the name of the plant *Dauca carota*, components of the essential oil of which — the alcohols carotol (**2**) and daucol (**3**) — were the first representatives of this class of compounds.

## METHODS OF ISOLATING AND SEPARATING CAROTANES

More than 100 natural carotane derivatives have been described in the literature (Table 1). It must be mentioned that compounds of this type are characteristic mainly of plants of the Apiaceae family, only a few cases of their isolation from other sources being known.

---

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, Tashkent, fax (3712) 89 14 75. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 767-780, November-December, 1995. Original article submitted July 4, 1994.

0009-3130/95/3106-0645$12.50 

TABLE 1. Natural Carotane Derivatives

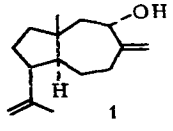
| Compound, composition, mp, $[\alpha]_D$ | Producer | Literature |
|---|---|---|
| **I. *tran*-Carotane Derivatives** | | |
| 1. Dauca-8(14),11(13)-dien-9-ol $C_{15}H_{24}O$ | Fokienia hodgisii | 1, 2 |
| 2. Dauc-11-ene-9-ol $C_{15}H_{24}O$ | Fokienia hodgisii | 1, 2 |
| 3. Jaeschkeanadiol (ferutinol, chimgandiol) $C_{15}H_{26}O_2$, 91-92°C, +38.8° | Ferula jaeschkeana, F. tenuisecta, F. tschimganica | 3-6 |
| 4. Angeloyljaschkeanadiol $C_{20}H_{32}O_3$ | F. elaechytrys | 7 |
| 5. Teferidin $C_{22}H_{30}O_3$ | F. tenuisecta | 8 |
| 6. Ferutinin $C_{22}H_{30}O_4$, 121-122°, +66.1° | F. tenuisecta | 4, 9 |
| 7. Salicyloyljaeschkeanadiol $C_{22}H_{30}O_4$ | F. elaechytrys | 7 |
| 8. Ferutidin $C_{23}H_{32}O_4$, 102-103°C, +103.5° | F. ovina | 10 |
| 9. Akiferidin $C_{22}H_{32}O_5$, 53-54°C, +28.5° | F. akitschkensis | 11 |
| 10. Ferutin $C_{23}H_{32}O_5$, 130-131°C, +101.8° | F. tenuisecta | 4, 12 |
| 11. Teferin $C_{23}H_{32}O_5$, 78-80°C, +86.5° | F. tenuisecta | 13 |
| 12. Akiferin, $C_{24}H_{34}O_5$, 102-103°C, +69.1° | F. akitschkensis | 14 |
| 13. Palliferidin, $C_{25}H_{36}O_6$, 115-116°C, +71.4° | F. pallida | 15 |
| 14. *trans*-Cinnamoyljaeschkeanadiol $C_{24}H_{32}O_3$ | F. rigidula | 16 |
| 15. *p*-Coumaroyljaeschkeanadiol $C_{24}H_{32}O_4$ | F. rigidula | 16 |
| 16. *p*-Acetoxycoumaryljaeschkeanadiol $C_{26}H_{34}O_6$ | F. rigidula | 16 |
| 17. Isovaleroylepoxyjaschkeanadiol $C_{20}H_{34}O_4$, 86-88°C | F. linkii | 17 |
| 18. *p*-Hydroxybenzoylepoxyjaeschkeanadiol (tenuferidin) $C_{22}H_{30}O_5$, 134-135°C, +75° | F. linkii, F. tenuisecta | 17-19 |
| 19. *p*-Methoxybenzoylepoxyjaeschkeanadiol $C_{23}H_{32}O_5$, 145-148°C | F. lancerottensis | 17 |
| 20. Vanilloylepoxyjaeschkeanadiol $C_{23}H_{32}O_6$, 104-105°C, +11.2° | F. linkii, F. tenuisecta | 17-19 |
| 21. Isovanilloylepoxyjaeschkeanadiol $C_{23}H_{32}O_6$, 176-178°C, +134.6° | F. tenuisecta | 18, 19 |
| 22. Veratroylepoxyjaeschkeanadiol $C_{24}H_{34}O_6$, 187-190°C | F. linkii | 17 |
| 23. *trans*-Cinnamoylepoxyjaeschkeanadiol $C_{23}H_{32}O_4$ | F. rigidula | 16 |
| 24. Lapidin $C_{20}H_{30}O_4$, 80-81°C, +166.1° | F. lapidosa | 20, 21 |
| 25. Vanilloyllapidol $C_{23}H_{30}O_6$, 176-178°C | F. latypinna | 22 |
| 26. *p*-Hydroxybenzoyllapidol $C_{22}H_{28}O_5$ | F. sinaica | 23 |
| 27. Palliferin $C_{25}H_{34}O_7$, 133-134°C, +201° | F. pallida | 24 |
| 28. Palliferidin $C_{24}H_{30}O_7$ | F. pallida | 24 |
| 29. Ferugin $C_{22}H_{30}O_5$, 140°C, +15° | F. jaeschkeana | 25, 26 |
| 30. Feruginidin $C_{22}H_{30}O_5$, 130°C, +6° | F. jaeschkeana | 25, 26 |
| 31. 14-*p*-Anisoyloxydauca-4,8-diene $C_{23}H_{30}O_3$ | F. tingitana | 27 |
| 32. Feruone $C_{15}H_{24}O_3$, +1.5° | F. jaeschkeana | 28 |
| 33. Lancerodiol $C_{15}H_{24}O_3$ | F. lancerottensis | 29 |
| 34. *p*-Hydroxybenzoyllancerodiol $C_{22}H_{28}O_5$, 227-228°C | F. rigidula, F. lancerottensis | 16, 29 |
| 35. *p*-Methoxybenzoyllancerodiol $C_{23}H_{30}O_5$ | F. lancerottensis | 29 |
| 36. Vanilloyllancerodiol $C_{23}H_{30}O_6$ | F. lancerottensis, F. rigidula | 16, 30 |
| 37. *trans*-Cinnamoyllancerodiol $C_{24}H_{30}O_4$ | F. rigidula | 16 |
| 38. *p*-Coumaroyllancerodiol $C_{24}H_{30}O_5$ | F. rigidula | 16 |
| 39. 2$\beta$-Hydroxy-6$\alpha$-*p*-benzoyllancerodiol $C_{22}H_{28}O_6$ | F. sinaica | 23 |
| 40. 6-Isovaleroylisolancerotriol $C_{20}H_{34}O_4$, 84-86° | F. linkii | 31 |
| 41. 6-Isovaleroylferutriol $C_{20}H_{34}O_4$, 54-56°C | F. linkii | 31 |
| 42. *p*-Hydroxybenzoylferutriol $C_{22}H_{30}O_5$, 74°C | F. jaeschkeana | 28 |
| 43. Jaeschferin $C_{23}H_{32}O_5$, +35° | F. jaeschkeana | 32 |
| 44. Akichenin $C_{27}H_{36}O_6$, 162-163°C, −8.3° | F. akitschkensis | 33 |

TABLE 1 (continued)

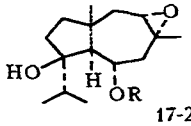
| Compound, composition, mp, $[\alpha]_D$ | Producer | Literature |
|---|---|---|
| 45. Akiferidinin $C_{27}H_{36}O_7$, 66-67°C, +46° | F. akitschkensis | 11 |
| 46. 2β-Hydroxy-6α-anisoyloxyjaeschkeanadiol $C_{22}H_{32}O_5$, +14° | F. sinaica | 23 |
| 47. 2α-Acetoxy-6α-benzoyloxyjaeschkeanadiol $C_{24}H_{32}O_5$ | F. communis | 34 |
| 48. 2α-Acetoxy-6α-*p*-hydroxybenzoyloxyjaeschkeanadiol $C_{24}H_{32}O_6$, +5.9° | F. communis | 35 |
| 49. 2α-Acetoxy-6α-*p*-anisoyloxyjaeschkeanadiol $C_{25}H_{34}O_6$ | F. communis | 34 |
| 50. Pallidin $C_{25}H_{38}O_5$, 79-80°C, −148.5° | F. pallida | 36 |
| 51. 10-Acetyl-6-isovaleroylferulinkiol $C_{22}H_{36}O_5$ | F. linkii | 28 |
| 52. 10-Hydroxy-6-angeloyljaeschkeanadiol $C_{20}H_{32}O_4$, −57.8° | F. communis | 35 |
| 53. $C_{23}H_{32}O_5$ | F. communis | 34 |
| 54. $C_{27}H_{36}O_5$ | F. communis | 34 |
| 55. $C_{25}H_{34}O_6$ | F. communis | 34 |
| 56. $C_{25}H_{38}O_6$ | F. communis | 34 |
| 57. $C_{29}H_{40}O_7$ | F. communis | 34 |
| 58. Lapiferol $C_{15}H_{26}O_4$, 112-114°C, +15.4° | F. latipinna, F. soongorica | 22, 37 |
| 59. Lapiferin $C_{22}H_{34}O_6$, 137-138°C, −41.6° | F. lapidosa | 38 |
| 60. $C_{22}H_{36}O_6$, 115-116° | F. linkii | 28 |
| 61. 10-Acetyllapiferol $C_{17}H_{28}O_5$, 106-108° | F. linkii | 28 |
| 62. Isolancerotriol $C_{15}H_{26}O_3$, +63° | F. sinaica | 39 |
| 63. 4β,9β-Dihydroxy-6α-*p*-hydroxybenzoyldauc-8(14)-ene $C_{22}H_{32}O_5$, +21.9° | F. sinaica | 23 |
| 64. 4β,6α,8β-Trihydroxy-9α-*p*-hydroxybenzoyldaucane $C_{22}H_{32}O_6$, −15.4° | F. sinaica | 23 |
| 65. 4β,8β,9α-Trihydroxy-6α-*p*-hydroxybenzoyldaucane $C_{22}H_{32}O_6$, +15.8° | F. sinaica | 23 |
| 66. 6-Isovaleroylisolancerotetrol $C_{20}H_{34}O_4$, 84-86°C | F. linkii | 40 |
| 67. 6-Isovaleroylepoxylancerotetrol $C_{20}H_{34}O_6$ | F. linkii | 40 |
| 68. Lapiferinin $C_{26}H_{36}O_8$, 157-158°C, +63° | F. lapidosa | 41 |
| 69. Tingitanol $C_{25}H_{38}O_6$ | F. tingitana | 42 |
| 70. Acetyltingitanol $C_{27}H_{40}O_7$, 141-143°C | F. tingitana | 27 |
| 71. 2β,6α-Diangeloyloxy-4β-hydroxydauc-8-ene-10-one $C_{25}H_{36}O_6$ | F. sinaica | 23 |
| 72. $C_{25}H_{34}O_7$, 152-154°C | F. communis | 34 |
| 73. $C_{27}H_{36}O_8$ | F. communis | 34 |
| 74. $C_{27}H_{36}O_8$ | F. communis | 34 |
| 75. $C_{28}H_{38}O_9$ | F. communis | 34 |
| 76. Lapidolin $C_{24}H_{36}O_8$, 187-189°C, +27.7° | F. lapidosa | 43 |
| 77. Lapidolinin $C_{26}H_{36}O_9$, 163-164°C, +26.7° | F. lapidosa | 44 |
| 78. Lapidolinin $C_{28}H_{38}O_{10}$, 182-183°C, +54.5° | F. lapidosa | 43 |
| 79. Laserpitin $C_{25}H_{38}O_7$, 116-117°C, +118° | Laserpitium latifolium | 45, 46 |
| 80. Monoangeloyllaserol $C_{20}H_{32}O_6$, 145-146°C, +105° | L. latifolium | 47 |
| 81. Laserpitinol $C_{25}H_{40}O_7$, 138-139°C | L. latifolium | 47 |
| 82. Isolaserpitin $C_{25}H_{38}O_7$, 159°C, −28° | L. latifolium | 47 |
| 83. Deoxodehydrolaserpitin $C_{25}H_{38}O_6$, 59-60°C | L. latifolium | 47 |
| 84. Acetyldeoxodehydrolaserpitin $C_{27}H_{40}O_7$ | L. latifolium | 27 |
| 85. 6-Deangeloyl-6-isobutanoyllaserpitin $C_{27}H_{36}O_8$ | L. latifolium | 27 |
| 86. 9β-Hydroxy-7,8-epoxyjaeschkeanadiol $C_{15}H_{26}O_4$, +47° | F. jaeschkeana | 48 |
| 87. $C_{20}H_{26}O_5$, 90°C, −466° | F. jaeschkeana | 49 |
| 88. Hercenolactone (fastigiolide) $C_{15}H_{20}O_2$, −31° | Barbilophorallycopides, | 50, 51 |
| 89. CAF — 603, $C_{15}H_{26}O_2$, 82-83°C | Ageratum gastugiatum | 52 |
| 90. Pyrosal $C_{15}H_{22}O_4$, 145-147°C, +183° | Aspergillus oryzae | 53 |
| | Rosa rugoza | |

TABLE 1 (continued)

| Compound, composition, mp, $[\alpha]_D$ | Producer | Literature |
|---|---|---|
| **II. *cis*-Carotane Derivatives** | | |
| 91. Carotol $C_{15}H_{26}O$, +30.4° | Daucus carota | 54-62 |
| 92. Daucol $C_{15}H_{26}O_2$, 113-115°C −16.9° | D. carota | 55-59 |
| 93. Vaginatin $C_{20}H_{30}O_4$, 77-78°C, −266.7° | Selenum vaginatum | 29, 63-65 |
| 94. 10α-Cinnamoyl-1,2-dehydrocarotol $C_{24}H_{30}O_3$, −198° | F. linkii | 66 |
| 95. 10α-Cinnamoylcarotol $C_{24}H_{32}O_3$, −77° | F. linkii | 66 |
| 96. Fercomin $C_{23}H_{30}O_5$, 130-132°C | F. communis | 67 |
| 97. Fercolide $C_{23}H_{26}O_6$ | F. communis | 67 |
| 98. Angeloylfelikiol $C_{20}H_{32}O_4$, 106-108°C | F. linkii | 31 |
| 99. Epoxyangeloylwebol $C_{20}H_{28}O_5$, 82-84°C | F. linkii | 31 |
| 100. Angeloylwebol $C_{20}H_{28}O_4$ | F. linkii | 31 |
| 101. *p*-Methoxybenzoyllinkitriol $C_{23}H_{34}O_5$ | F. lancerottensis | 29 |
| 102. Pallidin $C_{25}H_{38}O_7$, 109.5-110°C, −27.9° | F. pallida | 68 |
| 103. Acetylcarotdiol $C_{17}H_{28}O_3$ | F. linkii | 69 |
| 104. Veratroylcarotdiol $C_{24}H_{34}O_5$ | F. linkii | 69 |
| 105. Angeloyllasidiol $C_{20}H_{32}O_3$ | Lasianthus fruticosa | 70 |
| 106. Carotane 1,4-oxide $C_{15}H_{26}O$ | D. carota | 71 |
| 107. Diangeloyltorosol $C_{25}H_{36}O_5$ | F. rigidula | 16 |
| 108. 13-Vanilloyldaucol $C_{22}H_{32}O_6$ | F. rigidula | 16 |

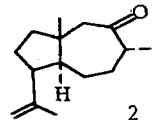


1

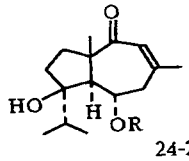


17-23

17. R = isovaleroyl
18. R = *p*-hydroxybenzoyl
19. R = *p*-anisoyl
20. R = vanilloyl
21. R = isovanilloyl
22. R = veratroyl
23. R = *trans*-cinnamoyl

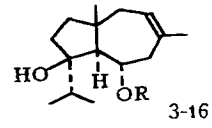


2



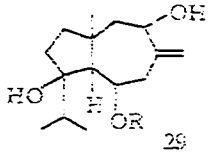
24-28

24. R = angeloyl
25. R = vanilloyl
26. R = *p*-hydroxybenzoyl
27. R = 3,4,5-trimethoxybenzoyl
28. R = 3-methoxy-4,5-methylenedioxybenzoyl



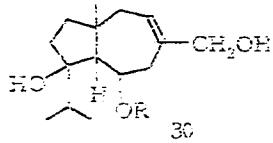
3-16

3. R = H
4. R = angeloyl
5. R = benzoyl
6. R = *p*-hydroxybenzoyl
7. R = salicyloyl
8. R = *p*-anisoyl
9. R = 3,4-dihydroxybenzoyl
10. R = isovanilloyl
11. R = vanilloyl
12. R = veratroyl
13. R = 3,4,5-trimethoxybenzoyl
14. R = *trans*-cinnamoyl
15. R = *p*-coumaroyl
16. R = *p*-acetoxycoumaroyl



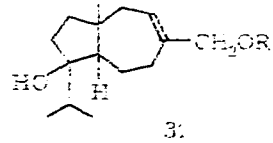
29

29. R = *p*-hydroxybenzoyl



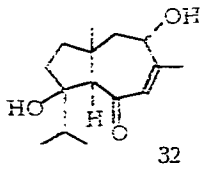
30

30. R = *p*-hydroxybenzoyl

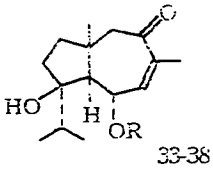


31

31. R = *p*-anisoyl

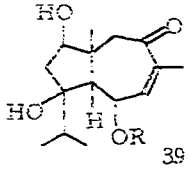


32



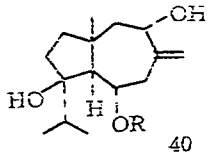
33-38

33. R = H
34. R = *p*-hydroxybenzoyl
35. R = *p*-anisoyl
36. R = vanilloyl
37. R = *trans*-cinnamoyl
38. R = *p*-coumaroyl



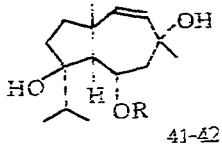
39

39. R = *p*-hydroxybenzoyl



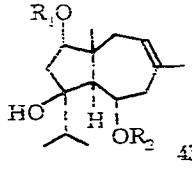
40

40. R = isovaleroyl



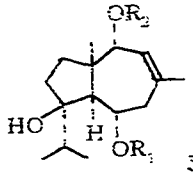
41-42

41. R = isovaleroyl
42. R = *p*-hydroxybenzoyl



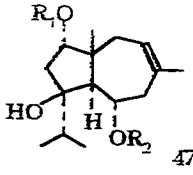
43-46

43. $R_1$ = H, $R_2$ = vanilloyl
44. $R_1$ = angeloyl, $R_2$ = *p*-hydroxybenzoyl
45. $R_1$ = angeloyl, $R_2$ = 3,4-dihydroxybenzoyl
46. $R_1$ = H, $R_2$ = *p*-anisoyl



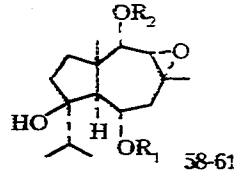
50-57

50. $R_1$ = $R_2$ = angeloyl
51. $R_1$ = isovaleroyl, $R_2$ = acetyl
52. $R_1$ = angeloyl, $R_2$ = H
53. $R_1$ = *p*-anisoyl, $R_2$ = H
54. $R_1$ = benzoyl, $R_2$ = angeloyl
55. $R_1$ = *p*-anisoyl, $R_2$ = acetyl
56. $R_1$ = *p*-anisoyl, $R_2$ = angeloyl
57. $R_1$ = veratroyl, $R_2$ = angeloyl



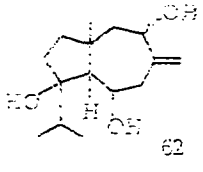
47-49

47. $R_1$ = acetyl, $R_2$ = benzoyl
48. $R_1$ = acetyl, $R_2$ = *p*-hydroxybenzoyl
49. $R_1$ = acetyl, $R_2$ = *p*-anisoyl

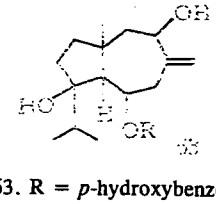


58-61

58. $R_1$ = $R_2$ = H
59. $R_1$ = angeloyl, $R_2$ = acetyl
60. $R_1$ = isovaleroyl, $R_2$ = acetyl
61. $R_1$ = H, $R_2$ = acetyl

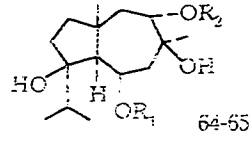


62



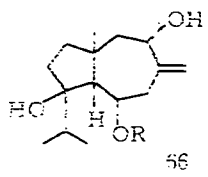
63

63. R = *p*-hydroxybenzoyl

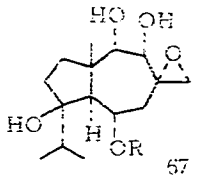


64-65

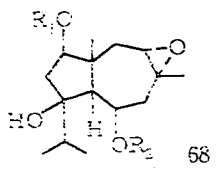
64. $R_1$ = H, $R_2$ = *p*-hydroxybenzoyl
65. $R_1$ = *p*-hydroxybenzoyl, $R_2$ = H



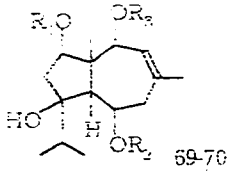
66. R = isovaleroyl



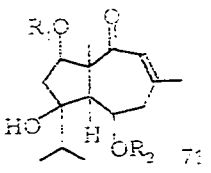
67. R = isovaleroyl



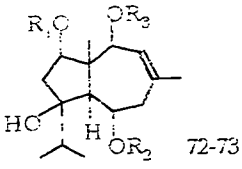
68. $R_1$ = acetyl, $R_2$ = veratroyl



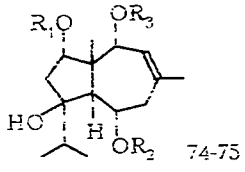
69. $R_1$ = H, $R_2$ = $R_3$ = angeloyl
70. $R_1$ = acetyl, $R_2$ = $R_3$ = angeloyl



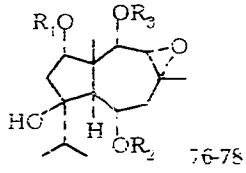
71. $R_1$ = $R_2$ = angeloyl



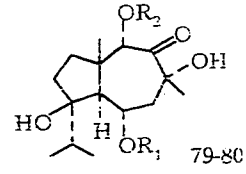
72. $R_1$ = acetyl, $R_2$ = *p*-anisoyl, $R_3$ = H
73. $R_1$ = $R_3$ = acetyl, $R_2$ = *p*-anisoyl



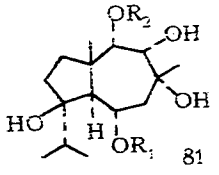
74. $R_1$ = $R_3$ = acetyl, $R_2$ = *p*-anisoyl
75. $R_1$ = $R_3$ = acetyl, $R_2$ = veratroyl



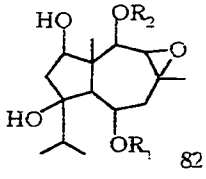
76. $R_1$ = $R_3$ = acetyl, $R_2$ = angeloyl
77. $R_1$ = acetyl, $R_2$ = veratroyl, $R_3$ = H
78. $R_1$ = $R_3$ = acetyl, $R_2$ = veratroyl



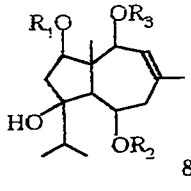
79. $R_1$ = $R_2$ = angeloyl
80. $R_1$ = H, $R_2$ = angeloyl



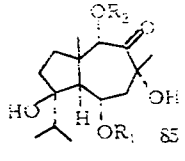
81. $R_1$ = $R_2$ = angeloyl



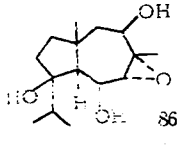
82. $R_1$ = $R_2$ = angeloyl



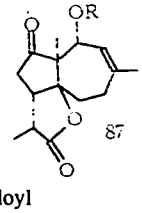
83. $R_1$ = H, $R_2$ = $R_3$ = angeloyl
84. $R_1$ = acetyl, $R_2$ = $R_3$ = angeloyl



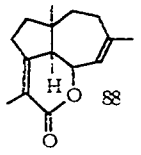
85. $R_1$ = isobutanoyl,
$R_2$ = angeloyl

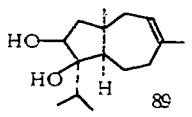


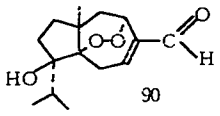
86

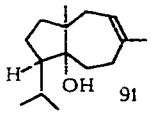


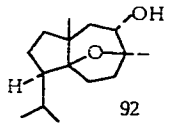
87. R = angeloyl

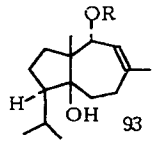

88

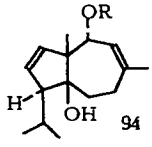

89

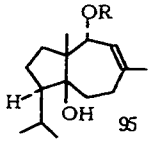

90

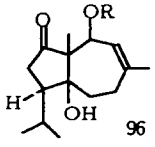

91

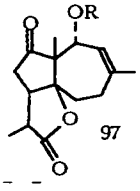

92

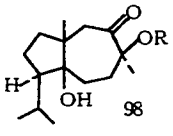

93. R = angeloyl

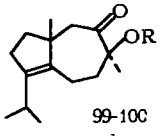

94. R = *trans*-cinnamoyl

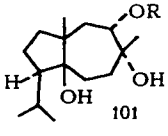

95. R = *trans*-cinnamoyl

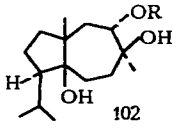

96. R = *p*-anisoyl

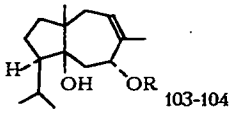

97. R = *p*-anisoyl

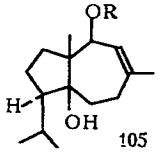

98. R = angeloyl

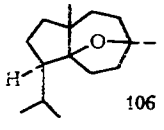

99. R = epoxyangeloyl
100. R = angeloyl

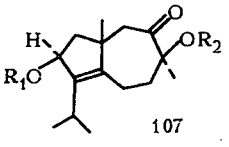

101. R = *p*-anisoyl

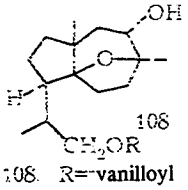

102. R = 3,4,5-trimethoxybenzoyl


103. R = acetyl
104. R = veratroyl

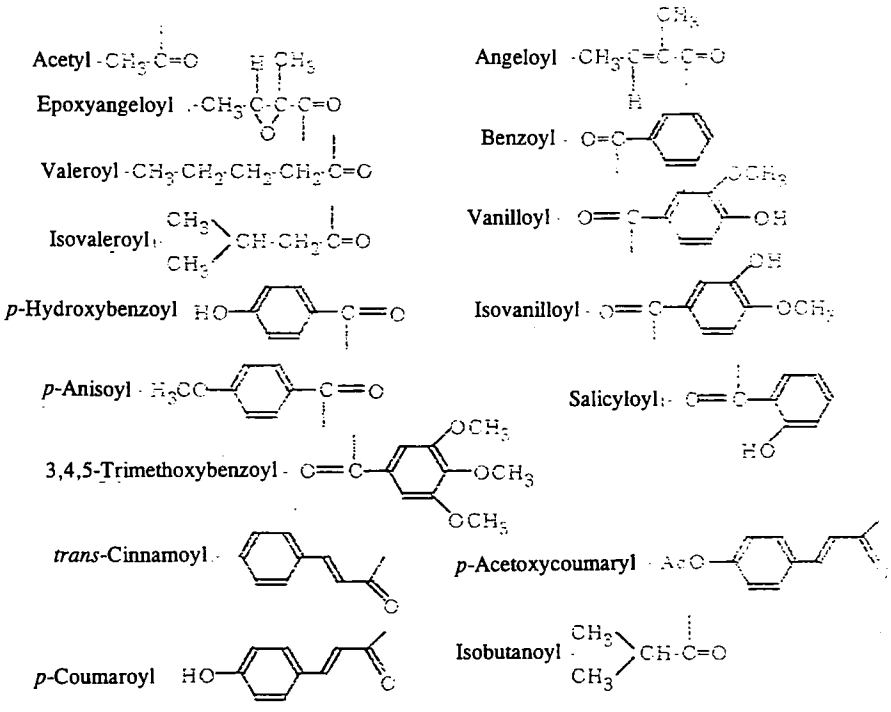

105. R = angeloyl


106


107. $R_1 = R_2$ = angeloyl


108. R=vanilloyl

**Conventional names**




Carotanes are particularly widespread in plants of the genus *Ferula*, which, by their qualitative and quantitative compositions, are the most promising sources of these compounds. It is only quite rarely that carotane derivatives are found in plants in the form of free alcohols. The majority of them are in the form of esters with aromatic and aliphatic acids.

The general scheme for isolating this class of compounds does not differ basically from the methods for isolating other classes of water-insoluble natural compounds. The only condition is the use of methods not affecting the ester bond in order to prevent hydrolysis during isolation.

The comminuted raw material is extracted with a suitable organic solvent: methanol, acetone, chloroform, or ethanol. The extract is treated with solvents of different polarities — from hexane to water — and then the terpenoid-containing fractions are chromatographed on column of neutral alumina or silica gel. In order to prevent various rearrangements and cyclizations, labile substances are chromatographed on silica gel impregnated with silver nitrate. It must be mentioned that only sesquiterpene alcohols and acids were isolated at first from many *Ferula* species in which esters were later detected [5], this being possibly connected with the use of alkaline solutions in the isolation process.

For separating the neutral and the phenolic fractions of sesquiterpene esters, use is made of the capacity of phenols for forming salts — phenolates. The general scheme of separation appears as follows: the ester-containing fractions are treated with a 2-5% solution of sodium carbonate to eliminate free organic acids. Then the phenolic components are extracted from the residue with a 0.5-1.0% solution of sodium hydroxide, and the neutral substances remain in the mother liquor. The alkaline solution is acidified, and the substances are extracted with a suitable solvent and, after elimination of the solvent, are separated on a column of adsorbent [8-12].

Carotane esters are also isolated by extracting the raw material with various solvents: petroleum ether, chloroform and ethanol or gasoline, benzene, and methanol, successively. Each of the fractions obtained is separated on columns of silica gel or Sephadex LH-20 with elution by various solvent mixtures [26, 29].

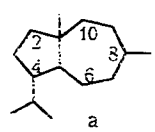
The plants are placed in a Soxhlet apparatus and extracted with benzene. The concentrated benzene extract is added to a column of silica gel or Sephadex LH-20 [35].

The raw material is extracted with gasoline in a Soxhlet apparatus, and the extract obtained is separated on Sephadex LH-20 [42].

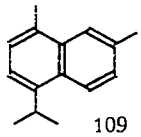
Analysis of the methods of isolating esters from plants that have been described in the literature permit the conclusion that the most suitable is one based on separating the total extractive substances into neutral, acid, and phenolic fractions, since this method provides the possibility of predicting the natures of the substances isolated from the fractions [8-12].

## CHEMICAL PROPERTIES AND METHODS OF ESTABLISHING THE STRUCTURES AND STEREOCHEMISTRIES OF CAROTANES

The study of the structures of the first representatives of the carotanes — carotol (**91**), daucol (**92**), and laserpitin (**93**) — took many years because of the formation of a naphthalene derivative — daucalene (**109**) — on their dehydrogenation. It was then found that, in addition to the main component, daucalene, dehydrogenation also formed azulene derivatives [60]. This fact showed that carotane was based on a carbon skeleton consisting of five- and seven-membered rings.



a


109

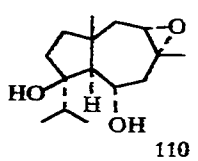
The presence of the seven-membered ring in carotane was shown by two independent methods based on chemical transformations.

The esters contain residues of both aliphatic and aromatic organic acids. The following aliphatic acids have been identified: acetic, angelic, valeric, isovaleric, and epoxyangelic. The aromatic acids are more diverse, numbering more than ten: benzoic salicylic, *p*-hydroxybenzoic, *p*-methoxybenzoic, 3,4-dihydroxybenzoic, vanillic, isovanillic, veratric, 3,4,5-trihydroxybenzoic, 3,4,5-trimethoxybenzoic, 5-methoxy-3,4-methylenedioxybenzoic, *p*-hydroxycinnamic, and *p*-coumaric.

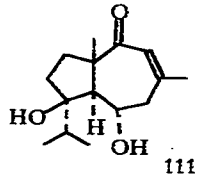
The wide structural diversity of natural carotane compounds is due to the conformation of the terpenoid bicycle (*cis*- or *trans*- linkage) and, in considerable degree, to the set of functional groups, the possibilities of their attachment in various positions of the sesquiterpene skeleton, and their mutual orientation.

Definite regularities are observed in the positions of the substituents in the carbon skeleton of carotane which are fully explicable on the basis of the derivation of these compounds from farnesol. Since the double bond in farnesol itself is located at $C_3$-$C_4$, in the majority of carotanes the double bonds an the epoxide and tertiary hydroxy groups occupy these positions in the carbon atoms of the isoprenyl units.

Characteristic for the majority of carotanes is the presence of substituting groups at $C_8$-$C_9$, which may be represented by a double bond (ferutinol (**3**)), an epoxy ring (tenuferol (**110**)), or two oxygen-containing functions (laserpitinol (**81**)). The latter are most probably the result of the opening of an epoxide ring. Then the secondary hydroxy group may be oxidized in nature to a ketone (**111**) or be acylated (**24**). The tertiary hydroxy group is capable of forming an epoxide ring (**92**) [71] and, by being split out, may produce a new exomethylene group (**40**) [39] or an olefinic bond (**33**) [29].



110

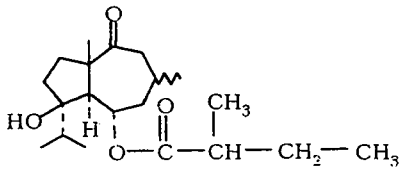


111

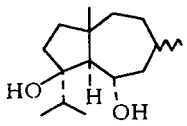
According to their type of linkage, carotanes are subdivided into derivatives of *cis*-carotane and of *trans*-carotane. In the majority of the *trans*-carotane derivatives there is a $\beta$-oriented tertiary hydroxy group at $C_4$ and an $\alpha$-oriented secondary hydroxy group at $C_6$. *cis*-Carotane derivatives are characterized by the presence of a $\beta$-oriented tertiary hydroxy group at $C_5$ (vaginatin (**93**)) or a $\beta$-oriented oxide ring at $C_5$-$C_8$ (daucol (**92**)). In the case of *cis*-carotane compounds not having these groups, the presence of a double bond at $C_4$-$C_5$ is unfailing (angeloylwebiol (**100**)). The relationship that we have discovered has been traced in all natural carotane compounds and no exceptions to it have so far been reported.

Carotane structures are studied mainly by the chemical methods developed for terpene compounds, in combination with modern instrumental methods.

Analysis of the proposed structures of carotane alcohols isolated from plants of the *Ferula* genus has revealed the following correlations between them, and these have been used in proving their structures and stereochemistries. The Huang–Minlon reduction of tetrahydrolapidin (**112**) gave dihydroferutinol (dihydrojaeschkeanadiol (**113**)), the structure and stereochemistry of which had been showed earlier [3], and thereby established the absolute configuration of lapidin (**24**) [20].

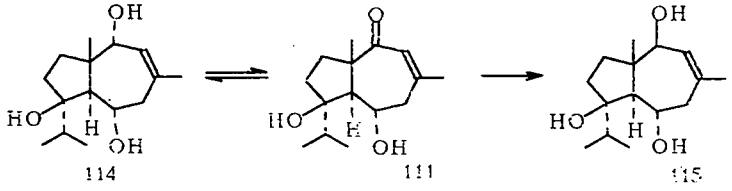


112



113

The sesquiterpene alcohol pallinol (**114**), a component of the ester pallinin (**50**) [36], proved to be dihydrolapidol, the structure of which was proved by two methods: a) by reducing lapidol with sodium tetrahydroborate in methanol, which led to two dihydrolapidols (**114**, **115**) from which pallinol (**114**) was isolated chromatographically; and b) by the oxidation of pallinol with chromic anhydride in pyridine, which gave a monoketone of pallinol, identical with lapidol (**111**) [20]. In this way the interrelationship between ferutinol (jaeschkeanadiol (**3**)), lapidol (**111**), and pallinol (**114**) was shown.

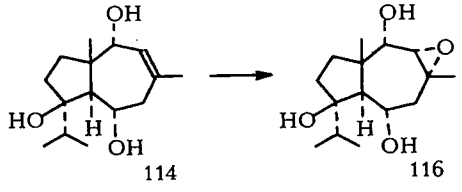


114 111 115

The structure and stereochemistry of lapiferol (**116**) were shown by its formation from pallinol on epoxidation with perphthalic acid [37].

The epoxidation of ferutinin (**6**), ferutin (**10**), and teferin (**11**) gave the corresponding epoxy derivatives (**18**, **20**, **21**), which were subsequently isolated from natural sources [18].

The positions of the acyl residues in mono- and diesters with the same acid residues have been determined by comparing the chemical shifts (CSs) of the signals of the gem-acyl and gem-hydroxy protons in the PMR spectra of the initial compounds and their hydrolysis products [19].

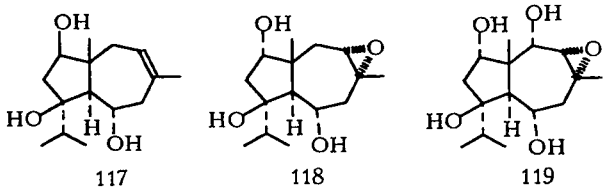


114 116

In the case of mixed di- and triesters, the positions of the acid residues have been established by their stepwise hydrolysis under mild conditions. In all the carotane di- and triesters the acid residue present at $C_6$ is split out first, and this fact has been used to prove the structures of the esters [32, 38, 43, 44].

Analysis of the PMR spectra of *trans*-carotane esters has shown that, on passing from alcohols to esters, in addition to changes in the CSs of gem-hydroxylic protons, the CSs of the signals of C-methyl groups located vicinally to an ester group or spatially close to it also change.

We have directed attention to the changes in the CSs of the signals of secondary methyl groups in isopropyl radicals in the spectra of esters of carotane alcohols — ferutinol (**3**), tenuferol (**110**), lapidol (**111**), pallinol (**114**), lapiferol (**116**), akichenol (**117**), lapiferinol (**118**), and lapidolinol (**119**).



117 118 119

On comparing the PMR spectra of esters of these alcohols we noted that the CSs of the signals of secondary methyl groups are influenced differently by the nature of the ester radical at $C_6$: in the spectra of the sesquiteperne alcohols themselves and their acetyl and angeloyl derivatives at the $C_6$-OH the signals of an isopropyl group are observed in the form of a six-proton doublet or of two three-proton doublets with a difference in the CSs ($\Delta\delta$) of the methyl groups of 0.04-0.06 ppm. When an aromatic acid residue is present at $C_6$ the difference in the CSs of the methyl groups increases ($\Delta\delta$ 0.08-0.2 ppm). This relationship is observed in all *trans*-carotane esters and their derivatives.

As is known, in all carotane esters of the *trans*-carotane type found in plants of the *Ferula* genus there is an $\alpha$-oriented ester group at $C_6$ and the change in the CSs of the signals of the isopropyl group may be caused by the anisotropic influence of the ester carbonyl or the benzene nucleus of an aromatic acid. The fact that such a pattern is observed only in esters with aromatic acids permits a conclusion in favor of the anisotropic influence of a benzene ring.

The relationship found between the nature of the acyloxy group and the CS of the isopropyl radical enables us to determine the positions of the acyl groups in mixed di- and triesters of the carotane type without stepwise hydrolysis [19].

For proving the structures of carotane compounds, ever wider use is being made of $^{13}C$ NMR spectroscopy [7, 16, 23], but up to the present no relationship has been found between the parameters of $^{13}C$ NMR spectra and the structures and stereochemistries of carotane compounds.

## REFERENCES


1. W. P. Korthals, D. Merkel, and M. Muhlstadt, Liebigs Ann. Chem., **745**, 31 (1971).
2. W. P. Korthals, D. Merkel, and M. Muhlstadt, Liebigs Ann. Chem., **745**, 39 (1971).
3. M. C. Sriraman, B. A. Nagasampagi, K. S. Pandey, and S. Dev, Tetrahedron, **29**, No. 7, 985 (1973).
4. A. I. Saikhodzhaev and G. K. Nikonov, Khim. Prir. Soedin., 166 (1974).
5. N. P. Kir'yalov, in: Plants of the Umbelliferae Family as Sources of Biochemically Active Substances [in Russian], Trudy BIN AN SSSR, Ser. 4, 129 (1968).
6. S. V. Serkerov, in: Abstracts of Lectures at the 1st Congress of Azerbaidzhan Pharmacists [in Russian], Baku (1976), p. 5.
7. M. Miski, A. Ulubelen, and T. J. Mabry, Phytochemistry, **22**, 2231 (1983).
8. A. I. Saidkhodzhaev and G. K. Nikonov, Khim. Prir. Soedin., 105 (1976).
9. A. I. Saidkhodzhaev and G. K. Nikonov, Khim. Prir. Soedin., 28 (1973).
10. A. I. Saidkhodzhaev and G. K. Nikonov, Khim. Prir. Soedin., 525 (1974).
11. A. Yu. Kushmuradov, A. Sh. Kadyrov, A. I. Saidkhodzhaev, and V. M. Malikov, Khim. Prir. Soedin., 725 (1978).
12. A. I. Saidkhodzhaev and G. K. Nikonov, Khim. Prir. Soedin., 559 (1972).
13. T. Kh. Khasanov, A. I. Saidkhodzhaev, and G. K. Nikonov, Khim. Prir. Soedin., 528 (1974).
14. A. Sh. Kadyrov, A. I. Saidkhodzhaev, G. K. Nikonov, and U. Rakhmankulov, Khim. Prir. Soedin., 284 (1977).
15. A. Yu. Kushmuradov, A. I. Saidkhodzhaev, and A. Sh. Kadyrov, Khim. Prir. Soedin., 400 (1981).
16. M. Miski and J. Jakupovic, Phytochemistry, **29**, 173 (1990).
17. J. G. Diaz, B. M. Fraga, A. G. Gonzalez, P. Gonzalez, and M. G. Hernandez, Phytochemistry, **23**, 2541 (1984).
18. A. I. Saidkhodzhaev, Khim. Prir. Soedin., 70 (1978).
19. A. I. Saidkhodzhaev, Author's abstract of doctoral dissertation [in Russian] Tashkent (1984).
20. L. A. Golovina and A. I. Saidkhodzhaev, Khim. Prir. Soedin., 318 (1981).
21. A. I. Saidkhodjaev [Saidkhodzhaev], L. A. Golovina, and V. M. Malikov, in: 9th Conference on Isoprenoids. Abstracts of Papers, Prague (1981), p. 74.
22. A. G. Gonzalez, J. Bermejo, A. G. Diaz, and L. Araucibia, J. Nat. Prod., **51**, No. 6, 1140 (1988).
23. Ahmed A. Ahmed, Phytochemistry, **30**, 1207 (1991).
24. S. N. Garg, S. K. Agarwal, V. P. Manojan, and S. N. Pastogi, J. Nat. Prod., **50**, No. 2, 253 (1987).
25. A. Yu. Kushmuradov, A. I. Saidkhodzhaev, and A. Sh. Kadyrov, Khim. Prir. Soedin., 523 (1981).
26. B. M. Fraga, M. G. Hernandez, J. G. Diaz, A. G. Gonzalez, and P. Gonzalez, Phytochemistry, **25**, 2883 (1986).
27. M. Miski and T. J. Mabry, J. Nat. Prod., **49**, No. 4, 657 (1986).
28. S. N. Garg and S. K. Agarwal, Planta Med., **53**, No. 4, 341 (1987).
29. B. M. Fraga, A. G. Gonzalez, P. Gonzalez, M. G. Hernandez, and C. L. Larruga, Phytochemistry, **24**, 501 (1985).

30. M. Miski, J. Mabry, and O. Saya, J. Nat. Prod., **50**, No. 5, 829 (1987).
31. J. G. Diaz, B. M. Fraga, A. G. Gonzalez, M. G. Hernandez, and A. Perales, Phytochemistry, **25**, 1161 (1986).
32. K. B. Bizhanova, A. I. Saidkhodzhaev, and V. M. Malikov, Khim. Prir. Soedin., 127 (1980).
33. A. Sh. Kadyrov, A. I. Saidkhodzhaev, and G. K. Nikonov, Khim. Prir. Soedin., 102 (1976).
34. M. Miski and T. J. Mabry, Phytochemistry, **24**, 1735 (1985).
35. D. Lamnaouer, N. T. Martin, D. Molho, and B. Bodo, Phytochemistry, **28**, 2711 (1989).
36. A. Yu. Kushmuradov, A. I. Saidkhodzhaev, and V. M. Malikov, Khim. Prir. Soedin., 53 (1986).
37. L. A. Golovina, A. I. Saidkhodzhaev, V. M. Malikov, and M. G. Pimenov, Khim. Prir. Soedin., 763 (1987).
38. L. A. Golovina, A. I. Saidkhodzhaev, N. D. Abdullaev, V. M. Malikov, and M. R. Yagudaev, Khim. Prir. Soedin., 296 (1983).
39. Ahmed A. Ahmed, J. Nat. Prod., **53**, No. 2, 483 (1990).
40. B. M. Fraga, M. G. Hernandez, J. G. Diaz, A. G. Gonzalez, and P. Gonzalez, Phytochemistry, **25**, 2883 (1986).
41. L. A. Golovina, A. I. Saidkhodzhaev, and V. M. Malikov, Khim. Prir. Soedin., 301 (1983).
42. M. Miski, A. Ulubelen, T. J. Mabry, W. H. Watson, J. Vickovic, and M. Holub, Tetrahedron, No. 40, 5197 (1984).
43. L. A. Golovina, A. I. Saidkhodzhaev, V. M. Malikov, and S. Melibaev, Khim. Prir. Soedin., 787 (1982).
44. L. A. Golovina, A. I. Saidkhodzhaev, and V. M. Malikov, Khim. Prir. Soedin., 713 (1985).
45. M. Holub, Z. Samek, V. Herout, and F. Sorm, Coll. Czech. Chem. Comm., **32**, No. 2, 591 (1967).
46. A. Linea, C. Novak, L. Vesela, and V. Kupcik, Coll. Czech. Chem. Comm., **32**, No. 9, 3437 (1967).
47. M. Holub, Z. Samek, and F. Sorm, Monatsh. Chem., **98**, No. 3, 1138 (1967).
48. P. Moldt, U. W. Smitt, and S. B. Christensen, J. Nat. Prod., **50**, No. 5, 974 (1987).
49. S. N. Garg and S. K. Agarval, J. Nat. Prod., **51**, No. 4, 771 (1988).
50. S. N. Garg, L. H. Misra, S. K. Agarval, V. P. Manajan, and S. N. Pastogi, Phytochemistry, **26**, 449 (1987).
51. S. Huneck, A. F. Cameron, J. D. Connolly, M. Melaren, and D. S. Rucroff, Tetrahedron Lett., No. 38, 3959 (1982).
52. F. Bohlmann, G. W. Ludwig, J. Jakupovic, R. M. King, and H. Robinson, Phytochemistry, **22**, 983 (1983).
53. N. Watanabe, M. Yamaguchi, T. Misutani, H. Kondoh, S. Omura, K. Handda, and K. Kushida, J. Nat. Prod., **53**, No. 5, 1176 (1990).
54. Y. Hashiboko, S. Tahara, and Y. Misatani, Phytochemistry, **28**, 425 (1989).
55. Y. Asahino and T. Tsukamito, J. Pharm. Soc. Jpn., **525**, 261 (1925).
56. V. Sykora, L. Novotny, M. Holub, V. Herout, and F. Sorm, Coll. Czech. Chem. Comm., **26**, 788 (1961).
57. F. Sorm and L. Urbanek, Coll. Czech. Chem. Comm., **13**, No. 1, 49 (1948).
58. F. Sorm and L. Urbanek, Coll. Czech. Chem. Comm., **13**, No. 2, 420 (1948).
59. V. Sykora, L. Novotny, and F. Sorm, Tetrahedron Lett., No. 14, 24 (1959).
60. L. Chuirdoglu and M. Descamps, Chem. Ind., No. 44, 1377 (1954).
61. V. Herout, M. Holub, L. Novotny, F. Sorm, and V. Sykora, Chem. Ind., No. 23, 662 (1960).
62. L. Chuirdoglu and M. Descamps, Tetrahedron, **8**, 271 (1960).
63. L. H. Zalkow, E. Y. Eisenbraun, and J. N. Sholery, J. Org. Chem., **26**, No. 4, 981 (1961).
64. C. K. Mesta, S. K. Paknikar, and S. C. Bhattacharyya, Chem. Comm., 584 (1968).
65. K. Rajendran, S. K. Paknikar, C. K. Trivedi, and S. C. Bhattacharyya, Ind. J. Chem., **16B**, No. 1, 4 (1978).
66. Z. F. Mahmoud, N. A. Abdel Salam, T. M. Sarg, and F. Bohlmann, Phytochemistry, **20**, 735 (1981).
67. O. Hofer, M. Widhaluu, and H. Creyer, Monatsh. Chem., **115**, 1207 (1984).
68. M. Miski and T. J. Mabry, Phytochemistry, **25**, 1673 (1986).
69. A. Yu. Kushmuradov, M. K. Makhmudov, A. I. Saidkhodzhaev, B. Tashkhodzhaev, V. M. Malikov, and M. R. Yagudaev, Khim. Prir. Soedin., 42 (1990).
70. B. M. Fraga, M. G. Hernandez, and J. G. Diaz, Phytochemistry, **28**, 1649 (1989).
71. D. F. Weimer and D. C. Ailes, J. Org. Chem., **46**, No. 26, 5499 (1981).
72. R. S. Dhillon, V. K. Gautam, P. S. Kalsi, and B. R. Chhabra, Phytochemistry, **28**, 639 (1989).