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ALKALOIDS FROM *VINCA HERBACEA* W.K.—X*

THE STRUCTURES AND STEREOCHEMISTRY OF MAJDINE AND ISOMAJDINE†

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Abstract—The alkaloids A-5 and A-4 first obtained from *Vinca herbacea* W.K. are identical with the alkaloids majdine, later isolated from *Vinca major* L. and with its isomer isomajdine. The spectral and chemical evidence, leading to the structural elucidation of these two bases, is presented so that majdine can be represented by expression I and isomajdine by II.

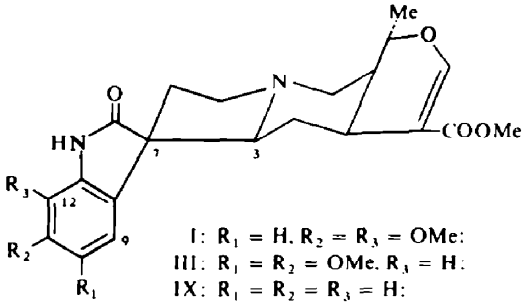
IN THE course of studies on the alkaloidal constituents of *Vinca herbacea* W.K., the identity of the following eight alkaloids has been established, namely (—)-herbaceine,[1] herbaline,[2] herbaine,[3] hervine,[4] reserpinine,[5] (−)-tabersonine, 16-methoxy-(−)-tabersonine and lochnerinine.[6]

Recently, one of us (I.O.) has reported the isolation of two isomeric bases, previously named A-4 and A-5, from the middle polar fraction of the total alkaloidal extract of this plant.[5] In a subsequent short communication Abdurakhimova *et al.* described the isolation of majdine, $C_{23}H_{28}N_2O_6$, m.p. 192–194°, $[\alpha]_D^{MeOH}$ −141° from *V. major* L.[7] This compound when heated in acetic anhydride isomerizes to isomajdine, m.p. 204–206°, $[\alpha]_D^{CHCl_3}$ −90 . Based upon spectral evidence it was claimed that majdine is a diastereomer of carapanaubine (III), while isomajdine differs from majdine by the configuration at C-4.[7]

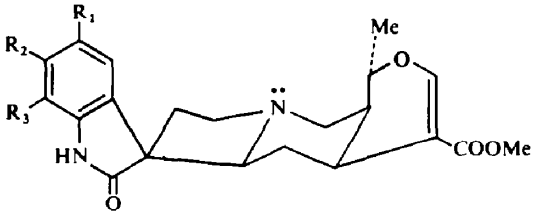
The presence of majdine in *V. major* L. has very recently been confirmed by Kaul and Trojánek,[8] and our direct comparisons by means of TLC and IR show that majdine corresponds to A-5, while A-4 is identical with isomajdine obtained by isomerization of majdine. Accordingly, we propose to drop the names A-5 and A-4 in favour of majdine and isomajdine respectively, and additionally we present evidence to show that majdine can be represented by expression I and isomajdine by II.

* Part IX. M. Shamma, I. Ognyanov, B. Pyuskyulev, J. A. Weiss and R. J. Shine, *Chem. Commun.* 579 (1967).

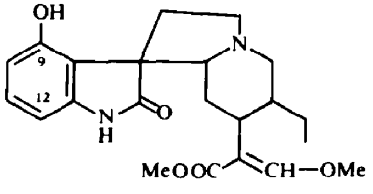
† A short paper is given in *Z. für Naturforschung*.



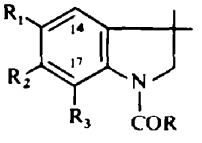
I: $R_1 = H$, $R_2 = R_3 = OMe$;
III: $R_1 = R_2 = OMe$, $R_3 = H$;
IX: $R_1 = R_2 = R_3 = H$;



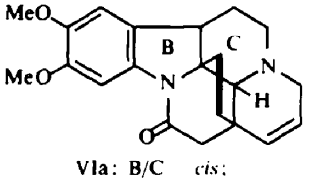
II: $R_1 = H$, $R_2 = R_3 = OMe$;
X: $R_1 = R_2 = R_3 = H$;
XI: $R_1 = R_2 = OMe$; $R_3 = H$;



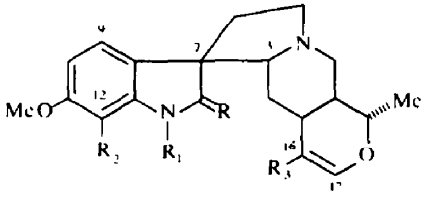
IV a, b, c



Va: R = Et, $R_1 = R_2 = OMe$, $R_3 = OH$;
Vb: R = Et, $R_1 = R_2 = R_3 = OMe$;
Vc: R = Me, $R_1 = H$, $R_2 = OMe$, $R_3 = OH$;
Vd: R = Me, $R_1 = H$, $R_2 = R_3 = OMe$;
Ve: R = Me, $R_1 = R_2 = R_3 = H$;
Vf: R = Et, $R_1 = R_2 = R_3 = H$;



VIa: B/C *cis*;
VIb: B/C – *trans*;



VIIa: R = H_2, $R_1 = H$, $R_2 = OMe$, $R_3 = CH_2OH$;
VIIb: 16,17-dihydro-VIIa.
VIIc: R = H_2, $R_1 = COMe$, $R_2 = OMe$, $R_3 = CH_2OCOMe$;
VIII: R = O, $R_1 = R_2 = H$, $R_3 = COOMe$.

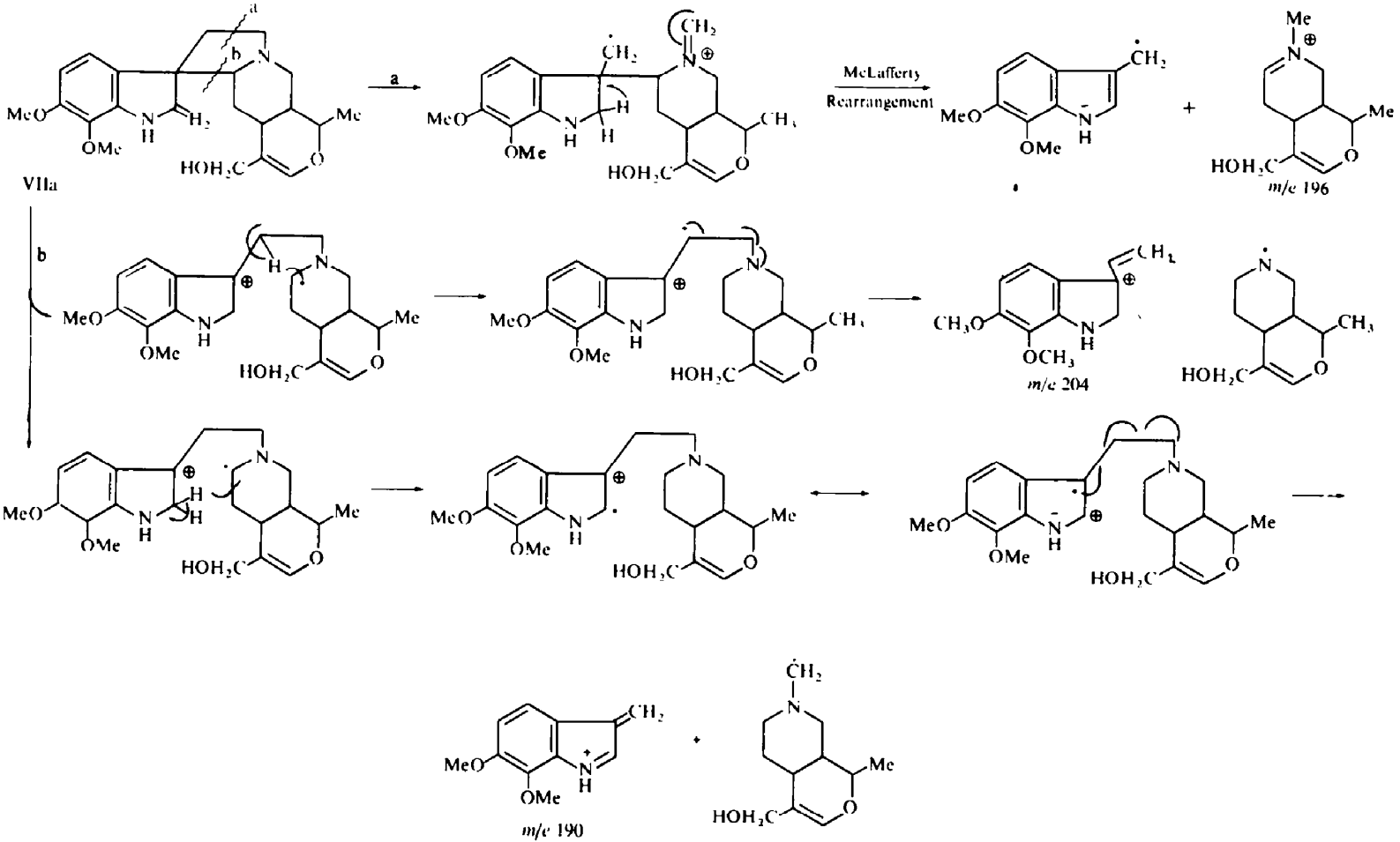
Majdine (I) and isomajdine (II) show a molecular ion peak at *m/e* 428, a base peak at *m/e* 223, and other strong peaks at *m/e* 219, 208, 206, 205, 204 and 180, i.e. the same as for carapanaubine[9] (III).

The IR spectra of majdine and isomajdine differ mainly in the finger-print region and resemble that for carapanaubine.[9] The IR spectrum of majdine (in $CHCl_3$) shows an absorption maximum at 3440 cm^{-1} (3440) (data in parenthesis refer to isomajdine), corresponding to the free NH of the lactam group. Strong peaks due to the aromatic portion of the molecule are situated at 1480 and 1515 cm^{-1} (1475 and 1515), while an ether group is indicated by bands at 1098 cm^{-1} (1090). Maxima due to the MeOOC—CH=CH—O— moiety are found at 1725 and 1625 cm^{-1} (1725 and 1630), and the absorption of the lactam carbonyl is at 1705 cm^{-1} (1680). The out-of-plane bending aromatic C—H vibrations are at 768 and 785 cm^{-1} (770 and 790), being different from that for carapanaubine (III) which is at 767 cm^{-1}, indicating that majdine and isomajdine differ from carapanaubine (III) in the substitution pattern of ring A.

The NMR spectra of majdine and isomajdine (Table 1) show, that the two aromatic hydrogens in ring A in both compounds exhibit an AB splitting pattern (J = 8 c/s) which clearly excludes the Abdurakhimova proposal,[7] and requires that these hydrogens have an *ortho* relationship. The two aromatic OMe groups in majdine and isomajdine must thus be either at the 9,10 or the 11,12 positions. Substitution at positions 9 and 12 is considered to be very improbable because such cases have not been described among the natural indole alkaloids.

The NMR data (Table 1) alone cannot determine the position of the two OMe groups, since the signals of the aromatic protons in ring A of all known methoxylated indole and oxindole alkaloids, independent of the number and position of the substituents, appear in the 6·20–7·20 δ region. It is known however, that in all $N_{(a)}$-acylated indole alkaloids the C-12 proton is strongly deshielded in the presence of an acyl group and produces a downfield signal higher than 7·50 δ. For example the signal from C-12 proton in the C-9 substituted oxindole alkaloids speciofoline (IVa),[10] rotundifoline (IV)b)[10] and stipulatine (IVc)[11] is shifted from 6·40–6·60 δ to 7·74–7·75 δ after $N_{(a)}$-acetylation. In addition all 16,17-disubstituted $N_{(a)}$-acylindole alkaloids (corresponding to 11,12-disubstituted oxindoles) show two typical aromatic doublets at 6·50–7·10 δ (J_{14-15} = 8–9 c/s) for both the C-14 and C-15 protons; the first one gives a signal at higher δ-values (see for example aspidoalbine (Va),[12] O-methylaspidoalbine (b),[12] aspidocarpine (Vc)[13] and O-methylaspidocarpine (Vd).[13] If the position at C-17 is not substituted, the signal of the corresponding C-17 proton appears at 7·50–8·50 δ [see demethoxyaspidospermine, (Ve),[14] demethoxypalosine, (Vf),[15] schizogamine, (VIa) and isoschizogamine, (VIb)[16]].

As this analogical determination of the position of the both aromatic OMe groups is impossible due to the fact that majdine and isomajdine do not react with acetic anhydride,[7] majdine was reduced with LAH in dioxan. 2-Deoxy-2-dihydromajdinol (VIIa) was obtained together with a small amount of the 16,17-dihydro derivative (VIIb). In the spectrum of VIIa the C-9 and C-10 aromatic hydrogen peaks are at 6·79 and at 6·38 δ. After acetylation of VIIa to $N_{(a)}$, O-diacetyl-2-deoxy-2-dihydromajdinol (VIIc) the signals of the same protons are at 7·12 and at 6·95 δ (J_{9-10} = 9 c/s) respectively. This relatively small downfield shift upon $N_{(a)}$ acetylation is in a good agreement with the signals of protons at C-14 and C-15 in e.g. Vc and Vd, which are


VIIa
a
b
McLafferty Rearrangement
m/e 196
m/e 204
m/e 190

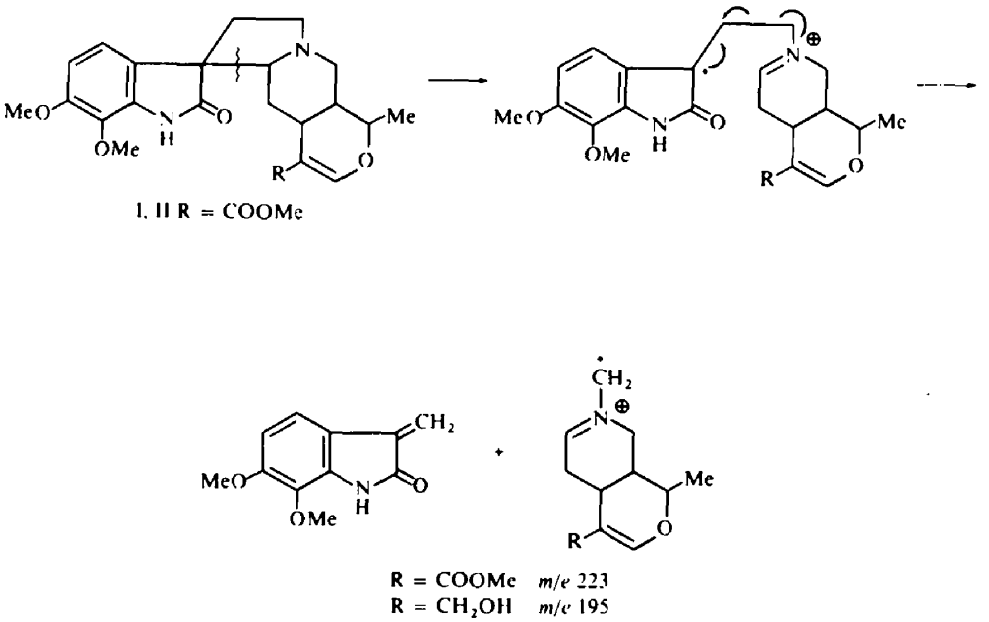


CHART I. Interpretation of Mass Spectrum of 2-deoxy-2-dihydro-majdinol (VIIa)

at 7·09 and 6·73 δ respectively.[13] These results are, therefore, in favour of the 11,12-disubstitution pattern in majdine and isomajdine.*

Majdine when refluxed in 10% acetic acid gave mainly unchanged starting material, while heating in pyridine yielded isomajdine as the principal product. Majdine (I) must therefore belong to the *syn* series (lactam oxygen and the pair of electrons on $N_{(b)}$-atom on the same side), while isomajdine (II) must be *anti*.[17] In addition, the pK'_a values for majdine (4·8) and isomajdine (4·4) (in 66% DMF) indicate that majdine is more basic and must be the *syn* isomer.

Based on the stereochemistry of pentacyclic oxindole alkaloids,[17,19] it is evident that majdine must possess the same *allo* stereochemistry as pteropodine (IX) and carapanaubine (III). The IR spectra of the three alkaloids (in CS_2 solution) are extremely close in the critical region near 1190 cm^{-1} in accordance with ref. 20, and the similarity in the NMR chemical shifts given in Table 1. The spin decoupled J_{19-20} value for majdine (I) obtained by irradiation of the C-19 Me group is 10 c/s, corresponding to a dihedral angle of 165° as required by expression I.

An interesting NMR feature is that the C-9 aromatic hydrogen in majdine is at 6·72 δ and in isomajdine at 6·84 δ. The downfield shift in the second case being caused by the proximity of the hydrogen in question to $N_{(k)}$. The same downfield trend occurs when going from carapanaubine (III) to isocarapanaubine (XI) where the corresponding values for the C-9 hydrogens are 6·76 and 6·94 δ respectively.

The mass spectrum of 2-deoxy-2-dihydromajdinol (VIIa; Chart I) shows a molecular ion peak at *m/e* 386, corresponding to the loss of 42 mass units from majdine as a result of the reduction of the lactam to an amine and the ester to a carbinol. Peaks originating from rings A and B are found at *m/e* 190 and 204. The base peak was originally expected to be at *m/e* 195, assuming the mode of cleavage of ring C to parallel that of majdine and isomajdine. However, the base peak was found at *m/e* 196, and a suggested mechanism for the genesis of this ion can be found in Chart II. The mass spectra of compounds VIIb and VIIc are analogous with signals corresponding to those of VIIa (Experimental).

EXPERIMENTAL

All UV spectra were measured in EtOH on a JASCO UV/ORD-5 spectrometer. The IR spectra in KBr discs were run on Zeiss UR-10 and Beckmann IR-5A instruments, and the mass spectra were determined with an Atlas CH-4 and an MCH-6 (USSR) mass spectrometer at an ionizing potential of 70 eV. The samples were introduced into the electron beam directly at 80–90°. The NMR spectra were measured on a Varian HA-100 in $CDCl_3$ using TMS as an internal standard. The pK'_a values were determined in 66% DMF by titration with 0·01N HCl.

The isolation of majdine and isomajdine has been described.[5] *Majdine* (I): m.p. 190–192°, $[\alpha]_D^{24}$ $-108 \pm 2°$ (Py), TLC R_f 0·35 on Woelm G acid alumina using benzene–ether–EtOH 35:14:1; pK'_a 4·8; λ_{max} 225, 248 sh, 285 sh mμ (4·57, 4·23, 3·16); *m/e* (%) 428 (M^+ 100), 413(2), 411(3), 397(3), 223(46), 208(13), 206(4), 205(5), 204(6), 180(9), 59(35).

Isomajdine (II). M.p. 208–210°, $[\alpha]_D^{24}$ $-111 \pm 2°$ (Py), TLC R_f 0·42 on Woelm G acid alumina; pK'_a 4·4; λ_{max} 225, 248 sh, 285 sh mμ (4·53, 4·16, 3·04). Mass spectrum close to that of majdine.

Isomerization of majdine (I) *to isomajdine* (II). Majdine (10·8 mg) was refluxed in pyridine (1 ml) for 24hr.

* Recently, on the basis of the same reasons (probably) the structure VIII was suggested for the C-4 isomeric pair of 11-methoxylated oxindole vinerine and vineridine; the signal of C-12 proton in $N_{(a)}$-acetylvinerine is at 7·70 δ (doublet).[18]

TABLE 1. NMR CHEMICAL SHIFTS AND PHYSICAL CONSTANTS OF SOME ALLO-HETEROYOHIMBINE OXINDOLES

Group	Majdine (I)	Pteropodine (IX)[17]	Isomajdine (II)	Isopteropodine (X)[17]	Carapanaubine (III)[9]
C-19-Me	1·38	1·35	1·37	1·38	1·38
COO-Me	3·58	3·55	3·58	3·56	3·58
Ar-OMe	3·80	—	3·80, 3·83	-	3·85
C=CH —O—	7·41	7·70	7·40	7·72	7·46
Ar—H	6·50, 6·74[a]	7·30	6·50, 6·84[a]	7·28	6·62, 6·76[b]
C-19—H	4·30	4·49	4·30	4·31	4·46
J_{19-20} (Found)	10 c/s	9 c/s	9 c/s	9 c/s	10 c/s
J_{19-20} (Calc)	10 c/s	10 c/s	10 c/s	10 c/s	10 c/s
$[\alpha]_D^{CHCl_3}$	−108°·[c]	−103°	−111°·[c]	−111°	−115°
M.p.	190–192°[c]	217–219°	208–210°[c]	209–211°	221–223°
pK_a'	4·8	4·8	4·4	4·0	

[a] Two doublets: (I) J = 8 c/s; (II) J = 10 c/s.
[b] Two singlets.
[c] Measured in pyridine.

The solvent was evaporated off under reduced press and the residue subjected to preparative TLC in the Woelm G system described above. The bands R_f 0·35 and 0·42 were collected and eluted, and afforded 2·4 mg of isomajdine and 4·0 mg of the starting material.

Isomerization of isomajdine (II) *to majdine* (I). Isomajdine (5 mg) was refluxed in 10% HOAc (2 ml) for 2 hr. The soln was made alkaline with ammonia, extracted with ether, and the combined extracts dried. TLC of the residue under standard conditions gave majdine as the major product together with a little isomajdine.

Reduction of majdine (I) *with LAH*. Majdine (200 mg) was continuously extracted into a suspension of LAH (500 mg) in dry dioxan (20 ml) and refluxed under N_2 for 3 hr. After cooling, a saturated soln of Seignet salt (20 ml) was added, and the mixture evaporated to dryness *in vacuo*. The residue was dissolved in water (10 ml), made alkaline with ammonia and extracted with ether (3 × 50 ml). The ether soln was dried and the solvent distilled off. Column chromatography of the crude product (166 mg) on neutral alumina (activity II, 30 g) was carried out using ether–acetone–MeOH (47:2:1) and afforded two homogeneous substances, namely VIIa which was the major product and VIIb. The major product (VIIa) crystallized from ether, m.p. 162–164°, (22 mg), R_f 0·25, (TLC on Woelm G alumina, ether–acetone–MeOH 49:08:02); λ_{max} 215, 247 infl., 292 sh mμ (4·45, 3·70 and 3·44); γ_{max} ($CHCl_3$) 1390, 1625, 1100, 1670, 3410 and 3610. The NMR signals were at 1·45 (3H), 3·90 (3H), 3·93 (3H), 6·38 and 6·79 (2H, J = 6 c/s) and 7·84 δ (1H). The mass spectral peaks were at *m/e* (%): 386(M^+, 30), 371(5), 224(4), 204(7), 198(4), 196(100), 194(5), 190(8), 180(21).

The minor product (VIIb) exhibited λ_{max} 215, 250 sh., 294 mμ (4·54, 3·60 and 3·41); R_f 0·15. The mass spectral peaks were at *m/e* (%): 388 (M^+, 15), 373(5), 204(6), 198(100), 190(8) and 180(13).

Acetylation of 2-deoxy-2-dihydromajdinol (VIIa). The substance (10 mg) was dissolved in a mixture of dry pyridine (1 ml) and Ac_2O and left 48 hr at room temp. A small sample of the reaction mixture was evaporated to dryness, dissolved twice in dry EtOH (1 ml) and again evaporated to dryness. To the residue 5% ammonia (2 ml) was added and extracted with ether (3 × 10 ml). The extract was washed with dilute ammonia, dried and evaporated to dryness. TLC of the product (system as above) showed two spots R_f 0·55 and 0·16. The remaining mixture was refluxed for 10 hr, cooled and worked up as above. The major product VIIc (R_f 0·55) was isolated on preparative TLC as an amorphous substance (4 mg). The mass spectral peaks were at *m/e* (%): 470 (M^+, 27), 455(14), 413(30), 412(30), 238(100), 224(29), 190(13), 180(56).

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