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PYRINDANE ALKALOIDS FROM *TECOMA STANS*[1]

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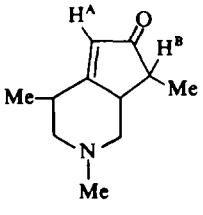
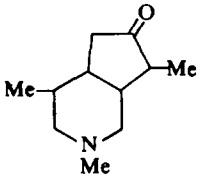
Abstract—The isolation of six alkaloids from *Tecoma stans* is described. The structures of four have been established; tecomanine (I), 4-noractinidine (XI), an N-nor-methyl skytanthine (VIII) and boschniakine (XIII). The fifth and sixth alkaloids are tertiary alcohols, possibly (XV) and (XVI).

SINCE the first report of alkaloids in *Tecoma stans* Juss. in 1899,[2] and the isolation of the first alkaloid in 1959,[3] a number of pyrindane alkaloids of obvious monoterpene relationship have been isolated from the plant and the structures of some of them determined.[1 4–6] Over the same period a number of related alkaloids have been isolated, notably from *Skytanthus acutus*,[7–12] *Actinidia polygama*,[13] and *Boshniakia rossica*,[14] indicating considerable variations in oxidation level both of the ring and of the attached Me groups. We report here the results of examination of alkaloidal extracts from *Tecoma stans*, from samples obtained in Cuba, Florida and Mexico. We have isolated one known alkaloid (tecomanine) and five which have not been previously reported in *Tecoma stans*. The alkaloids were isolated from the volatile fraction (b.p. 80–120° at 1 mm) of the total basic extract and were separated by a combination of fractional precipitation as picrates, column chromatography on Florisil, and preparative VPC. A major difficulty in the early work was the instability of the major alkaloid, tecomanine, but the picrate has been found to be stable and has been kept for some years without appreciable deterioration.



I



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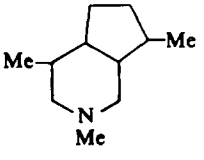

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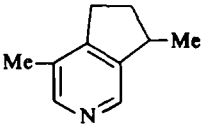

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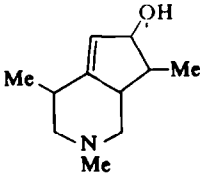
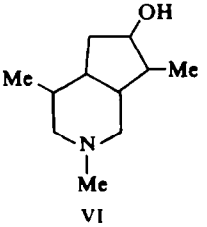
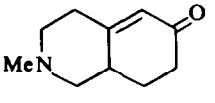


V



VI



VII

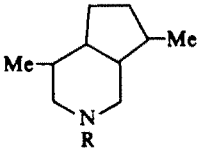
Tecomanine, which was the major alkaloid in all specimens examined, and the only alkaloid found in all samples, isolated from its picrate by passage through a Florisil column and immediately examined gave good spectral data and analyses.

Further analyses on picrate and methiodide established the formula $C_{11}H_{17}NO$ and the structure has been shown, as described below, to be I. The UV absorption showed a maximum at 226 mμ ($\log_{10}\varepsilon$ 4·1) with a blue shift to 223 mμ on acidification. The calculated maximum for a 3-alkylcyclopentenone would be 231 mμ, but the shift to shorter wavelength, increased on acidification, parallels that shown by the hexahydroisoquinoline (VII)[15] (though of small magnitude). The IR maxima at 1700 and 1620 cm^{-1} of approximately equal intensity again indicate a cyclopentenone system;[16] the NMR spectrum in acidic $CDCl_3$ showed an olefinic proton (H^A) at 5·95 ppm (all shifts are reported in ppm from internal TMS) in good agreement with that expected for the α-proton of a cyclopentenone system, with broadening due to some allylic coupling, an N-Me singlet at 2·75 ppm, and two C-Me doublets centred at 1·02 and 1·12 ppm respectively. In non-acidic media these two C-Me signals were virtually super-imposed. We assign the Me signal at lower field in the protonated tecomanine to the Me group on the piperidine ring; hence the signal at 1·02 ppm is due to that adjacent to the CO group. That one of the C-Me groups was coupled to a methine proton adjacent to the CO group was shown by heating a $CDCl_3/CD_3CO_2D$ mixture containing tecomanine when the expected exchange of H^B occurred and the doublet centred at 1·02 ppm collapsed to a singlet. The physical evidence thus suggested a structure related to the pyrindane alkaloids and this was confirmed by conversion of tecomanine into actinidine.[13]

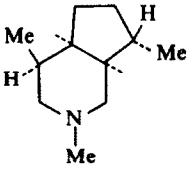
Reduction of tecomanine with palladium charcoal in ethanol gave an uptake of one molar equivalent of hydrogen; gas chromatography of the reduction mixture showed four peaks of which the major product could be isolated by repeated recrystallization of the picrate. This dihydrotecomanine (II) isolated from the pure picrate had no major absorption above 220 mμ and had a single maximum in the CO region at 1740 cm^{-1} (cyclopentanone). The NMR spectrum of dihydrotecomanine confirmed the absence of unsaturation (no olefinic proton) and the upfield shift of one C-Me doublet to 0·9 ppm also indicated the removal of the double bond β to this Me group. The pure dihydrotecomanine (II) formed a hydrazone in 95% ethanol; the residue after evaporation of the ethanol gave a single oxygen-free base when heated with sodium hydroxide in diethylene glycol. The picrate of this base (III) gave a correct analysis for a skytanthine picrate but comparison of the mixed m.p. determinations with the picrates of the known skytanthines[17] supplied by Professor Eisenbraun showed marked depression. To confirm the presence of the pyrindane skeleton in tecomanine the mixture of dihydrotecomanines was subjected to Huang-Minlon reduction and the mixed skytanthines were dehydrogenated. Separation of the pyridine bases after dehydrogenation was accomplished by preparative VPC and the major product was a base (IV) whose picrate was identical with a sample of D,L-actinidine picrate supplied by Professor Djerassi. Unfortunately, no deductions on the stereochemistry of tecomanine are possible on the available evidence because of the possibility of isomerization at various points during the conversion I → IV.

Reduction of tecomanine with sodium borohydride in methanol gave a mixture of two alcohols, separated by chromatography on Florisil, and shown by analyses of their picrates to be the unsaturated alcohol (V) ($\nu^{OH}_{CCl_4}$ 3603, 3630 cm^{-1} and $\nu^{CH}_{CCl_4}$ 3055 cm^{-1} unsaturated cyclic alcohol) and the saturated alcohol (VI) ($\nu^{OH}_{CCl_4}$ at 3633 cm^{-1}; no unsaturated CH).

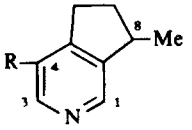
The second alkaloid isolated as a picrate from the Florida samples of *Tecoma stans* was shown by analysis and molecular ion (153) to have formula $C_{10}H_{19}N$. The IR spectrum showed NH stretching in the region of 3000 cm^{-1} and the NMR spectrum showed two C-Me doublets but no N-Me absorption. The alkaloid formed an N-benzoyl derivative (IX) and the suspicion that it was an N-normethylskytanthine (VIII) was confirmed by dehydrogenation to D,L-actinidine (IV) identified as its picrate, and by Clarke–Eschweiler methylation to a skytanthine (III). The skytanthine had $[\alpha]_D^{22}$ +5·5° and the picrate had m.p. 142–143°. The skytanthines with physical constants in closest agreement with these are the δ-skytanthine (X) of known stereochemistry and that derived from tecostanine, of unknown stereochemistry.[5] Comparison of the picrate of our N-methylated compound with δ-skytanthine picrate supplied by Dr. Casinovi showed them to be different. We were unable to obtain a specimen of the picrate from the "tecostanine" skytanthine but comparison of the mass spectral breakdown patterns of our base and that of the "tecostanine" skytanthine (supplied by Professor Le Men) showed much similarity.



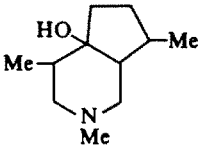
VIII: R = H
IX: R = CoPh



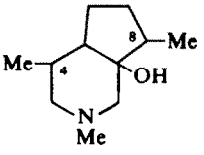
X



XI: R = H
XII: R = CH_2OH
XIII: R = CHO
XIV: R = CO_2H



XV



XVI

After removal of most of the tecomanine picrate from the Cuban extract of *Tecoma stans*, the residue was chromatographed on Florisil, giving three major fractions, A, B (tecomanine), and C. The alkaloid A had a pungent odour; analysis on the picrate showed a formula $C_9H_{11}N$ for the base. The UV absorption showed maxima at 259·5 and 267 mμ ($\log_{10}$ ε 3·05, 2·98) doubling in intensity on acidification and strongly resembling those reported for 3,4-di-alkylpyridines.[18] The NMR spectrum of alkaloid A picrate in $CDCl_3$ showed three aromatic protons, a pyridine α-proton doublet at 8·85 ppm with a superimposed singlet at 8·8 ppm (protons 1 and 3 in formula XI) and a β-proton doublet (proton 4) at 8·03 ppm. A C-Me doublet at 1·6 ppm and groups of multiplets at 3·2–3·8 ppm (three protons), 2·5–3·0 ppm (one proton) and 2·0–2·4 ppm (one proton) confirmed the structure XI—a 4-noractinidine—for alkaloid A. A mixed m.p. of alkaloid A picrate with a sample of 8-epi-4-noractinidine picrate derived from asperuloside[19] supplied by Professor L. H. Briggs showed no depression. Our alkaloid A concludes an interesting oxidation sequence in the pyrindane group—from actinidine (IV),[13] through tecostidine

(XII),[20] boschniakine (XIII)[14] (see below also), boschniakinic acid (XIV)[14] to 4-noractinidine (XI).

The third base, C, eluted from the Florisil column again formed a crystalline picrate, m.p. 168–170° from which on analysis a formula $C_{10}H_{21}NO$ was deduced for the parent alkaloid (confirmed by the mass spectrum molecular ion). The base, regenerated from pure picrate, was a solid which after sublimation had m.p. 91–92°. No absorption was observed in the UV above 220 mμ, and the main feature of the IR spectrum was a tertiary alcohol OH stretching at 3609 cm^{-1} (no intramolecular H-bonding). The base C was isomeric with tecostanine,[5] and with the two reported hydroxyskytanthines from *Skytanthus acutus*.[10,12] Tecostanine is a primary alcohol, while the hydroxyskytanthines were both tertiary and one had m.p. 94–95°, close to that of base C. However, both previously reported hydroxyskytanthines are substituted on the carbon bearing a Me group which therefore shows as a singlet in the NMR spectrum; the spectrum of base C clearly shows two C-Me doublets and hence the OH group must occupy a bridgehead position. The O-benzoyl derivative of base C showed a single peak at very low retention time in the gas chromatograph (comparable to that of a skytanthine) and it is apparent that ready elimination is taking place to give a single isomer but this does not allow any deductions as to the position of the OH group. The absence of H-bonding between OH and nitrogen[21] leads us to suggest tentatively the structure XV rather than XVI for base C.

An isomeric solid alkaloid $C_{10}H_{21}NO$, m.p. 82–94°, was isolated from a second sample of *Tecoma stans* from Florida by preparative GPC and characterized as its methiodide m.p. 310–312°. Again the NMR spectrum showed that the OH group was not attached to the C atoms (4 or 8) carrying the Me groups since both Me groups appeared as doublets. In the absence of any low field protons attributable to oxygen-bearing methine or methylene groups the OH group was again assumed to be tertiary. Unlike base C, the isomeric alcohol showed evidence of intramolecular H-bonding in the IR spectrum and on this basis is tentatively formulated as XVI.

Finally, preparative gas chromatography of the basic fraction from a *Tecoma stans* sample of Mexican origin gave in addition to 4-noractinidine (XI) and an incompletely characterized hydroxyskytanthine, a sample of boschniakine (XIII). Confirmation of the structure was obtained by comparison of the semicarbazone with a sample of boschniakine semicarbazone[14] kindly supplied by Professor Sakan.

It is interesting to tabulate the pattern of occurrence of the various pyrindane alkaloids with the origin of the specimens (Table 1); the only common factor to date is the universal occurrence of tecomanine as the major alkaloid in all samples. Noteworthy also was the virtual absence of other alkaloids in the roots of the Mexican sample (the only case where separate extractions could be made of roots and of leaves and twigs).

EXPERIMENTAL

M.ps were determined on a hot stage and are uncorrected. IR spectra were determined on a Beckman IR-7 or Perkin–Elmer 221 machine, UV spectra on a Carey spectrometer, NMR spectra on a Varian H-60 or Perkin–Elmer R10 60 Mc. machine.

Extraction procedure. The ground plant material (20 kg) was exhaustively extracted with hot EtOH or MeOH, the extract concentrated *in vacuo* and absorbed on to Celite. The Celite was stirred with successive portions of water (once), and dil HCl until extracts gave no further test with Meyers reagent. Basification of the acid extracts (with dil NH_4OH or Na_2CO_3 aq) and extraction with $CHCl_3$ gave a dark extract which

TABLE 1

Alkaloid	Cuba	Mexico		Florida I	Florida II	Egypt
		Roots	Leaves			
Tecomanine	+ +	+ +	+ +	+ +	+ +	+ +
N-Norskytanthine			+	+		
4-Noractinidine	+	Trace	+			
Base C (XV)	+			+		
Hydroxyskytanthine (XVI)					+	
Boschniakine		Trace	+			
Tecostanine[5]						+
Tecostidine (XII)						+

was evaporated and distilled. The fraction b.p. 80–120°/1 mm (20·1 g) was dissolved in absolute alcohol (~150 ml) and treated with alcoholic picric acid to give crude alkaloid Al picrate (6·2 g). The filtrate was diluted to 500–600 ml and treated with further alcoholic picric acid to give tecomanine picrate (8·46 g). The residue after separation of tecomanine picrate was evaporated, basified, and extracted with $CHCl_3$. The $CHCl_3$ extracts were evaporated and the residue chromatographed on Florisil. A typical chromatogram is described below:

8·5 g of mixed alkaloids in 500 g Florisil

Solvent	Fractions (100 ml)	Weight	Retention time* at 122°	Alkaloid
Benzene	6	100 mg	—	Non-basics
Benzene	14	2·1 g	1·2 min	A
10% Ethyl acetate	16	1·8 g	4·3 min	Tecomanine
25% Ethyl acetate	10	Total 2 g	2·6, 4·3	Mixture
50% Ethyl acetate	10		2·6, 4·3	Mixture
Ethyl acetate	14	1·1 g	2·6 min	C

Tecomanine (I). The crude picrate after precipitation was recrystallized from EtOH to give pure *tecomanine picrate*,† m.p. 179·5–180·5°. A $CHCl_3$ soln of the picrate, percolated through a Florisil column evaporated and distilled, gave pure *tecomanine* (I),† b.p. 125°/0·1 mm, $[\alpha]_D^{24}$ −175° (*c* 1·17, $CHCl_3$). The *methiodide*,† m.p. 240–242°.

Dihydrotecomanine (II) (a) Tecomanine (100 mg) in EtOH, with 5% Pd–C catalyst hydrogenated to completion at NTP. Uptake at 25·8° and 752 mm was 12·9 ml (theory 13·8 ml). Evaporation of the filtered soln to small volume and treatment with alcoholic picric acid gave crude dihydrotecomanine picrate. Gas chromatography of the picrate (injected in acetone) showed three peaks. Five recrystallizations from MeOH gave pure *dihydrotecomanine picrate*,† m.p. 189·5–191·5°. The pure base, regenerated from the picrate by treatment with lithium hydroxide, had b.p. 80°/0·1 mm (bulb tube).

(b) Hydrogenation in AcOH with Adams catalyst gave a mixture of three products with the same retention times on GPC as the above but with a lower proportion of the major component, and more difficult to purify via the picrate.

* On a 9 ft column ¾% SE-30 gum on Gaschrome P.

† Analyses have been reported in Ref. 1.

Huang-Minlon reduction of dihydrotecomanine. A mixture of pure II (84 mg) and 100% hydrazine (35 mg) in EtOH (1 ml) was heated on the steam bath for 1 hr. The dihydrotecomanine peak * (retention time 4·75 min at 122°) was entirely replaced by a hydrazone peak at 15·6 min. Evaporation of the EtOH gave a low melting solid which was heated with diethylene glycol (1 ml) and NaOH (6·2 g) at 190° for 4 hr. The cooled mixture was steam distilled and the steam distillate extracted with ether; the ether soln showed only one peak on the gas chromatograph. The *picrate*, prepared in ether and recrystallized from EtOH, had m.p. 152–153°†. A mixed m.p. with α-, β-, γ- and δ-skytanthines supplied by Professor Eisenbraun, all showed depression. The *skytanthine* (III) had $[\alpha]_D^{24}$ −13° (*c*, 0·68 in $CHCl_3$).

Conversion of tecomanine into actinidine. The mixture of dihydrotecomanines obtained by hydrogenation with Adams catalyst (270 mg) was subjected to Huang-Minlon reduction as described above, giving mixed skytanthines (170 mg). Distillation of the skytanthine mixture from Pd/C gave a mixture showing pyridine absorption in the UV. Separation of the mixture by preparative gas chromatography (a 4% SE-30 on Gaschrome P column, programmed from 75° at 2°/min) gave one fraction having the spectral characteristics of actinidine, and yielding a *picrate* m.p. 138–140°, showing no depression with a sample of D,L-actinidine picrate supplied by Professor Djerassi.

Sodium borohydride reduction of tecomanine. Pure I (350 mg) in MeOH was treated with excess $NaBH_4$ and allowed to stand at room temp until all the absorption above 220 mμ had disappeared (several hr). The mixture was diluted, extracted with $CHCl_3$, the $CHCl_3$ soln dried and evaporated. The residual oil showed two major peaks on GPC and was chromatographed on Florisil; benzene–EtOAc mixtures brought off one component (70 mg) forming a *picrate*, m.p. 154–156° (from H_2O). (Found: C, 49·55; H, 5·4; N, 13·25. $C_{17}H_{22}N_4O_8$ requires: C, 49·75; H, 5·4; N, 13·65%). The free *base* V had b.p. 110°/0·25 mm (bulb tube).

Pure EtOAc eluted a second component (VI; ~100 mg) forming a *picrate*, m.p. 168–170° (from H_2O). (Found: C, 49·25; H, 6·0; N, 13·3. $C_{17}H_{24}N_4O_8$ requires: C, 49·5; H, 5·85; N, 13·6%).

Alkaloid A1 (*nor*-N-*methylskytanthine*) (VIII). The crude picrate from the Florida sample of *Tecoma stans* was recrystallized from MeOH, and had m.p. 179–180°. (Found: C, 50·5; H, 5·5; N, 14·5. $C_{16}H_{22}N_4O_7$ requires: C, 50·25; H, 5·8; N, 14·65%); M^+ = 153. The *free base* VIII had b.p. 125–130°/13 mm $[\alpha]_D^{22}$ +35°; NMR peaks at 0·9 ppm (doublet, J = 6·5 c/s) and 1·02 ppm (doublet, J = 6·5 c/s) with no other prominent singlet.

Dehydrogenation of alkaloid A1. Alkaloid A1 (200 mg) was distilled with Pd–C (500 mg, 10%) at 750 mm press. The oil which distilled was converted into a *picrate*, m.p. 139–140°, identical with D,L-actinidine picrate.

Methylation of alkaloid A1 *to a skytanthine* (III). The alkaloid A1 (170 mg) regenerated from the picrate was heated for 13 hr with a mixture of formaldehyde (2 ml, 40%) and formic acid (3·1 ml, 88%). Evaporation, basification and extraction with ether gave, after evaporation and treatment with ethereal picric acid, a *skytanthine picrate*; recrystallized from EtOH, m.p. 142–143°. (Found: C, 51·2; H, 5·95; N, 13·8. $C_{17}H_{24}N_4O_7$ requires: C, 51·5; H, 6·1; N, 14·15%). The *skytanthine* recovered from the picrate had b.p. 105/15 mm (bulb tube). (Found: C, 78·6; H, 12·95; N, 8·7. $C_{11}H_{21}N$ requires: C, 78·15; H, 12·65; N, 8·35%), $[\alpha]_D^{22}$ +5·5° (*c*, 3·3; $CHCl_3$); the NMR spectrum showed three proton doublets at 0·85 and 0·95 ppm, and a three proton singlet (N-Me) at 2·25 ppm. A mixture of the picrate with a sample of X picrate supplied by Dr. Casinovi melted at 130–133°.

4-*Nor-actinidine* (XI). The first fractions from the Florisil column were shown by gas chromatography to be predominantly one base, and were converted in ether into a picrate. Recrystallization of the picrate from MeOH gave pure *base A* (XI) *picrate*, m.p. 135–137° (unstable to heat, dried at room temp (0·2 mm). (Found: C, 49·4; H, 3·9; N, 15·2. $C_{15}H_{14}N_4O_7$ requires: C, 49·7; H, 3·9; N, 15·5%). A second crystalline modification had m.p. 116–117°. The regenerated pure alkaloid A had $[\alpha]_D^{24}$ +3°, $[\alpha]_{436}^{24}$ +21°, $[\alpha]_{380}^{24}$ +49° (*c*, 2·34 in $CHCl_3$). A mixture of base A picrate and 8-epi-4-noractinidine picrate[19] showed no depression of m.p.

Alkaloid C (XV). The later fractions from the Florisil column were mixtures with predominantly one peak on gas chromatography. From the purer fractions it was possible to obtain a *picrate* (prepared in ether, crystallized from water) m.p. 170–170·5°. (Found: C, 49·25; 49·45; H, 5·82, 5·85; N, 13·27, 13·52. $C_{17}H_{24}N_4O_8$ requires: C, 49·5; H, 5·85; N, 13·6%). The *methiodide* needles from EtOH had m.p. 293–295°. (Found: C, 44·5; H, 7·5; N, 4·15; I, 38·6. $C_{12}H_{24}INO$ requires: C, 44·3; H, 7·45; N, 4·3; I, 39·0%). The *free base*, regenerated from pure picrate and sublimed at 110°/0·25 mm had m.p. 91–92°. The O-*benzoyl*

* On a 9 ft column ¾% SE-30 gum on Gaschrome P.

† Analyses have been reported in Ref. 1.

derivative, prepared in pyridine at room temp, had m.p. 60–65° (from aqueous EtOH). (Found: C, 74·9; H, 8·65; N, 5·0. $C_{18}H_{25}NO_2$ requires: C, 75·2; H, 8·8; N, 4·9%); $\nu_{max}^{CHCl_3}$ 1720, 1275, 1115 cm^{-1}; NMR shows overlapping doublets at 0·9 and 1·0 ppm, N-Me singlet at 2·3 ppm. and aromatic protons centred at 8·2 (two) and 7·6 (three) ppm ($CO-C_6H_5$). Injection of the benzoate into a gas chromatograph* (flash heater temp 220°) gave a single peak at 3·0 min (column temp 142) compared with 6·2 min for base C and 3·1 min for III indicating clean elimination of benzoic acid.

Boschniakine (XIII). The basic fraction obtained by extraction of the leaves of *Tecoma stans* (of Mexican origin) were submitted to preparative VPC. The early fraction separated was shown to be 4-noractinidine, identical with that from the Cuban sample. The second major fraction was XIII, $\nu_{max}^{CHCl_3}$ 2750 (aldehyde CH), 1700 (aldehyde C=O) cm^{-1}; NMR peaks at 1·38 (3 proton doublet, CH_3CH), 8·77 (one proton singlet) 8·99 (one proton singlet) and 10·45 (aldehyde CH) ppm. The semicarbazone had m.p. 217–220° (dec) and showed no depression in a mixed m.p. with a sample of boschniakine semicarbazone supplied by Professor Sakan.

Hydroxyskytanthine (XVI). The basic extracts from the second Florida sample of *Tecoma stans* were treated with picric acid to remove tecomanine and separated by preparative VPC. The main product obtained pure was the *hydroxyskytanthine* (XVI), m.p. 87–94°; $\nu_{max}^{CHCl_3}$ 3650, 3580, 3500–3000 (broad, no change on dilution), 1092 cm^{-1}; NMR peaks at 0·95 (three proton doublet), 1·25 (distorted three proton doublets), 2·27 (3-proton singlet, NCH_3). The methiodide, recrystallised from EtOH, had m.p. 310–312° (dec). (Found: C, 44·4; H, 7·25; N, 4·3. $C_{12}H_{24}INO$ requires: C, 44·3; H, 7·4; N, 4·3%). Mass spectrum of XVI showed M^+ at 183 (100% base peak) and at 166, 150, 122, 107, 98, 85, 83, 74 (90% of base peak), 72, 70, 55 (90% base peak).

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