pure alkaloid encountered by us in *A. pyricollum* Muell.-Arg. proved to be ulein[4], as demonstrated by direct comparison with a specimen kindly provided by Dr. J. SCHMUTZ. The following three species yielded several new alkaloids, of which four have been isolated in pure form. The empirical formulas given below are consistent with the analytical data, but they should only be considered as tentative ($\pm$ CH_2) until more extensive degradative work has been completed.

Aspidosperma cylindrocarpon Muell.-Arg. furnished *cylindrocarpine* (Table) after purification through the crystalline perchlorate and regeneration of the alkaloid. All oxygen functions are accounted for by a N-cinnamoyl-7-methoxy-dihydroindole grouping and one carbomethoxy function. Their presence was established by acid hydrolysis (yielding cinnamic acid), by hydrogenation to dihydrocylindrocarpine (yielding dihydrocinnamic acid), whose ultraviolet absorption spectrum was practically superimposable upon that of aspidospermine[5], and by alkaline hydrolysis of dihydrocylindrocarpine to the amino acid dihydrocylindrocarpic acid, which could be remethylated with diazomethane to dihydrocylindrocarpine.

Aspidosperma refractum Mart. extract gave after chromatography of the weakly basic fraction *refractine* (Table). The extreme similarity of the ultraviolet absorption spectrum with that of aspidospermine coupled with the N-acetylanalysis indicates the presence[5] of a N-acetyl-7-methoxy-dihydroindole moiety, while the infrared band at 5·74 μ, the methoxyl analysis and the saponification results show that the other two oxygen atoms form part of a carbomethoxy group.

Aspidosperma pyrifolium Mart. furnished the two alkaloids *pyrifoline* and *pyrifolidine* which were separated by fractional crystallization of the perchlorates from the nonphenolic alkaloid fraction. The analytical, spectral and infrared data of pyrifoline indicate the presence of a N-acetyl-7-methoxy-dihydroindole chromophore and of an aliphatically bound methoxyl function.

Work is now under way in our laboratories on the structure elucidation of these alkaloids as well as on the isolation of additional alkaloids from the above-mentioned *Aspidosperma* species.

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[4] J. SCHMUTZ, F. HUNZIKER, and R. HIRT, Helv. chim. Acta *40*, 1189 (1957). – G. BÜCHI and E. W. WARNHOFF, J. Am. Chem. Soc. *81*, 4433 (1959).

[5] The presence of a N-acetyl-7-methoxy-dihydroindole chromophore in aspidospermine was demonstrated by J. R. CHALMERS, H. T. OPENSHAW, and G. F. SMITH, J. chem. Soc. *1957*, 1115.

[6] Postdoctorate research fellow 1958–1959 (Wayne State University); 1959–1960 (Stanford University).

Zusammenfassung

Die Isolierung von vier neuen *Aspidosperma*-Alkaloiden ergab *Cylindrocarpin* (erstes N-Cinnamoyl-dihydroindolderivat) sowie *Refractin*, *Pyrifolin* und *Pyrifolidin* (alles N-Acetyl-dihydroindole), die alle vier eine Methoxylgruppe im Dihydroindolsystem besitzen.

Triterpene Acids from *Commiphora glandulosa* Schinz[1]

The chemistry of the genus *Commiphora* Jacq. (= *Balsamodendron* Kunth), natural order Burseraceae, has not been extensively studied; earlier references are given by WEHMER[2]. Myrrh, usually obtained from *C. abyssinica* (Berg) Engl., *C. molmol* Engl. and *C. opobalsamum* (L.) Engl., has been found to consist of volatile oils, mostly mono- and sesquiterpenes, gums, and unidentified resins, but the presence of triterpenes has never been suggested[3], and it was therefore of interest to find that the resin of *C. glandulosa* Schinz[4], a tree growing in the arid parts of Southern Africa, is a rich source of triterpene acids, both free and combined as glycosides. From two samples of resin collected for us by Dr. I. B. POLE EVANS at different times from the same tree, we found that the free acids were present in roughly the same proportions, but that the glycosides in one case yielded mainly 'aglycone E' and in the other 'aglyconec' (see below for nomenclature).

The resin of *C. glandulosa* is soluble in cold ether to an extent of about 50%. The free acids (about 25% of original resin) were isolated from the ethereal solution through the barium salts, then methylated with diazomethane, and the methyl esters separated on a column of neutral alumina (activity III, according to BROCKMANN[5]). Extraction of the residual resin with ether or methanol at reflux temperature yielded the crude crystalline glycosides (about 10% of original resin).

Five methyl esters could be separated by this method; these will be designated methyl commate A, B, C, D, E, following the order in which they were eluted, graded solvents from ether-chloroform (1:1) through chloroform to chloroform-methanol (9:1) being used. Esters A, B, and C were purified by recrystallization from methanol and E was recrystallized from chloroform. Ester D could not be freed from C using methanol as a solvent, but recrystallization from methylene chloride, in which C dissolves readily, gave an apparently homogeneous product.

[1] We are indebted to Dr. H. HÜRLIMANN for supplying the botanical information in this paper.

[2] C. WEHMER, *Die Pflanzenstoffe*, 2. Aufl., II (Jena 1931), p. 647.

[3] Triterpenes are well known from other genera of the order Burseraceae, e.g. *Canarium* (Elemi resin), *Boswellia* etc.

[4] *C. glandulosa* belongs to the group of *C. pyracanthoides* Engl. s. lat., as pointed out by J. P. M. BRENAN, Kew Bull. *1953*, 104. This author regards *C. lugardae* N. E. Br., *C. seineri* Engl. and *C. berberidifolia* Engl. as synonyms of *C. glandulosa*. The species seems to be distributed over a wide area of Southern Africa, from Mozambique through the Rhodesias to Bechuanaland, Transvaal, and South-West Africa. – It is noteworthy that we found the resins of *C. roxburghii* (Stocks) Engl. (= *C. mukul*) and of *C. viminea* Burtt-Davy, a species still somewhat related to *C. pyracanthoides* (BRENAN), to be completely devoid of triterpene acids both free and combined as glycosides.

[5] H. BROCKMANN and H. SCHODDER, Ber. dtsch. chem. Ges. *74*, 73 (1941).

The IR. spectra (Table IV) and the physical properties (Tables I–III) indicated that the compounds were distinct and different. Homogeneity of the esters was checked by chromatoplate chromatography[6] developing with chloroform-ethyl acetate (4:1) and detecting with concentrated sulphuric acid. Single spots were observed in the case of each of the five esters, R_f values being 0·70 for esters A and B, 0·18 for esters C and D, and 0·07 for ester E. In this solvent system betulinic, oleanolic, and ursolic acid methyl esters ran with the solvent front. Methoxyl determination on esters B–E showed that these were monoesters of C_{30} acids. The properties of the esters are given in Table I, together with the approximate percentage in which they occurred in the original acid mixture.

Acetylation of the methyl esters in pyridine gave the methyl ester acetates, the properties of which are listed in Table II.

Reduction with lithium aluminium hydride in ether or tetrahydrofuran (for methyl commate-A and -E) gave the corresponding alcohols, the commols, the properties of which are shown in Table III.

[6] E. DEMOLE, J. Chromatography *1*, 24 (1958). – We are indebted to Mr. E. von Arx for carrying out these determinations.

All methyl commates gave a positive tetranitromethane test in chloroform except methyl commate-E which is very sparingly soluble in this solvent; its diacetate was positive in the test. The optical rotational values of the methyl esters and their acetates, the high melting points of all the compounds (particularly the methyl esters) and the results of the combustion analyses strongly suggest that these compounds must be classed with the pentacyclic triterpenes.

Methyl commate-A is considered to be an artefact arising by overmethylation of another ester. This suggestion is made to account for the following facts. In contrast to esters B–E, which occurred in about the same percentages in all the batches worked up, the content of ester A varied from 0–1·0% of the mixture. Methyl commate-A contains one acetylateable hydroxyl group, the ester acetate showing no OH absorption in the I. R., and, since the ester itself possesses a single sharp band in the carbonyl region ($\lambda_{max}^{CH_2Cl_2}$ 5·77 μ), it is presumed that the fourth oxygen is present in an ether group. The microanalytical results on ester, ester acetate, and diol fit the formula $C_{32}H_{52}O_4$ for the ester. The diol was found to contain a methoxyl group [found $(O)CH_3$ 3·23%, $C_{31}H_{52}O_3$ requires 3·18% for one $(O)CH_3$] so that the

Table I. Methyl Esters

	Formula	Found		Calculated		m. p.* °C	$[\alpha]_D$ /$CHCl_3$	% (approx.)
		C	H	C	H			
A	$C_{32}H_{52}O_4$	76·79	10·52	76·75	10·47	200–201	+77°	0–1·0
B	$C_{31}H_{50}O_3$	78·93	10·60	79·10	10·71	239–241	+39°	1·0
C	$C_{31}H_{50}O_4$	76·15	10·54	76·50	10·36	239–242	+84°	together
D	$C_{31}H_{50}O_4$	76·28	10·24	76·50	10·36	268–271	+76°	50·0
E	$C_{31}H_{50}O_5$	74·18	10·04	74·06	10·03	293–295	+72° (dioxan)	20·0

* All m.p.s. are corrected.

Table II. Methyl Ester Acetates

	Formula	Found		Calculated		m. p.* °C	$[\alpha]_D$ /$CHCl_3$
		C	H	C	H		
A	$C_{34}H_{54}O_5$	74·87	9·85	75·23	10·03	175–176	+34°
B	$C_{33}H_{52}O_4$	77·01	10·40	77·29	10·22	236–237	+39°
C	$C_{35}H_{54}O_6$	73·55	9·47	73·64	9·54	189–190	+46°
D	$C_{35}H_{54}O_6$	73·85	9·61	73·64	9·54	170–171	+49°
E	$C_{35}H_{54}O_7$	71·75	9·45	71·64	9·28	215–216	+62°

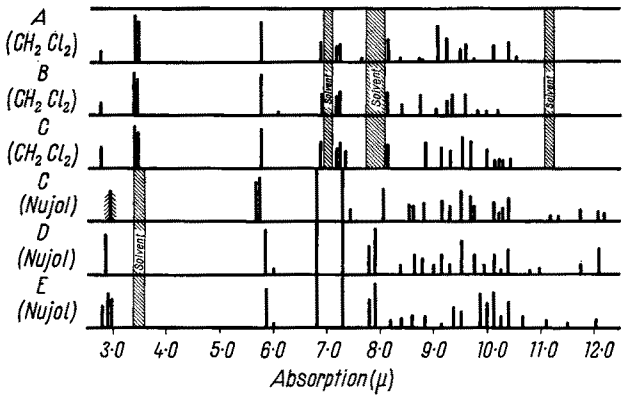
* All m.p.s. are corrected.

Table III. Commols

	Formula	Found		Calculated		m. p.* °C	$[\alpha]_D$
		C	H	C	H		
A	$C_{31}H_{52}O_3$	79·03	10·92	78·76	11·09	294–298	+76° (tetrahydrofuran)
B	$C_{30}H_{50}O_2$	81·39	11·32	81·39	11·38	230–232	+38° (chloroform)
C	$C_{30}H_{50}O_3$	78·43	10·81	78·55	10·99	258–259	+81° (dioxan)
D	$C_{30}H_{50}O_3$	78·63	11·06	78·55	10·99	246–247	+79° (chloroform)
E	$C_{30}H_{50}O_4$	75·79	10·78	75·90	10·62	245–246	+63° (ethanol)

* All m.p.s. are corrected

Table IV. I. R. Spectra of Esters



commic acid-A skeleton calls for C_{30} and 5 rings with one double bond. Methyl commate-B contains one acetylateable hydroxyl group. Methyl commate-C and -D each contain two acetylateable hydroxyl groups, as does methyl commate-E, but the latter has an additional hindered hydroxyl group that appears in the I. R. spectrum of the diacetate ($\lambda_{max}^{CH_2Cl_2}$ 2·78 μ).

Further work on the chemistry of these substances will be reported elsewhere.

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Zusammenfassung

Die Isolierung von fünf neuen Triterpensäuren («Commisäure-A bis -E», englisch «commic acid-A to -E») als Methylester aus *Commiphora glandulosa* Harz wird beschrieben. Sie wurden als Acetate bzw. als die entsprechenden Alkohole charakterisiert.

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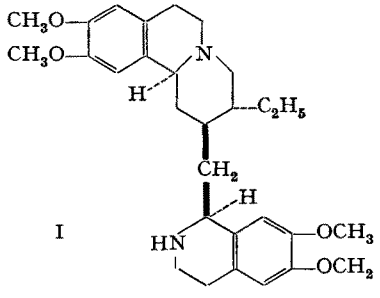
Stereospezifität der Wirkung von Emetin

Die amöbicide Wirkung und Toxizität von totalsynthetisch hergestelltem rac. Emetin, rac. Isometin (I)[1] und der beiden optischen Antipoden (−)-Emetin (II) und (+)-Emetin (Spiegelbild von II)[2] wurden *in vitro* und *in vivo* bestimmt und mit natürlichem Emetin[3] verglichen. Sämtliche Präparate wurden als Dihydrochlorid-hydrate geprüft.

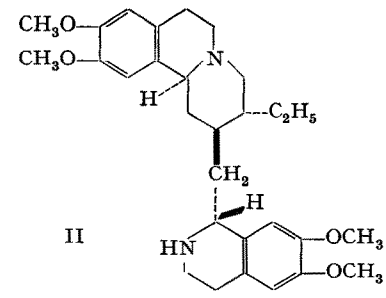


I

[1] Die Formel entspricht einem der beiden opt. Antipoden des Racemates.

[2] A. BROSSI, M. BAUMANN und O. SCHNIDER, Helv. chim. Acta *42*, 1516 (1959).

[3] Emetin-hydrochlorid, Ph. H. V. (Sandoz AG., Basel).



II

Technik. Unsere Versuche wurden mit *Entamoeba histolytica*, Stamm Moore, gehalten auf einem diphasischen Nährboden, bestehend aus Eikoagulat und Stones-Locke-Lösung, zusätzlich einer Polybakterien-Flora, durchgeführt. Die Aktivität *in vitro* wurde im Shaffer-Frye-Medium bestimmt und entspricht der minimalen Präparate-Konzentration, bei der mikroskopisch nach 24stündiger Bebrütung in der Nährflüssigkeit keine lebenden Amöben mehr gefunden wurden. Die Aktivität *in vivo* wurde nach der Technik von JONES (modifiziert) bestimmt und entspricht der Menge des einmalig oral gegebenen Präparates in mg/kg, die 6 Tage nach Verabreichung bei 50% der Ratten zum Verschwinden des Erregers führt. Die Toxizität wurde an der Ratte nach der Probitmethode, bei Verwendung von 4 Tieren pro Dosis und einer Beobachtungszeit von 10 Tagen bestimmt.

Resultate

Präparat	Toxizität	Aktivität *in vitro*	Aktivität *in vivo*
	DL_{50} Ratte s. c. mg/kg	Endwert in γ/ml	CD_{50} Ratte oral mg/kg
Nat. Emetin	25	10	9,5
(−)-Emetin (II) . . .	17	10	6,0
(+)-Emetin*	700	1000	170,0
Rac. Emetin	35	20	13,0
Rac. Isoemetin (I)[1] . .	1400	1000	200,0

Diskussion. Aus diesen Untersuchungen geht hervor, dass totalsynthetisch hergestelltes (−)-Emetin (II) die gleiche akute Toxizität und amöbicide Wirkung aufweist wie das natürliche Alkaloid. Das unnatürliche (+)-Emetin ist hingegen unwirksam, aber auch wenig toxisch. Dementsprechend ist rac. Emetin etwas weniger toxisch und weniger wirksam als (−)-Emetin (II). Das rac. Isoemetin (I)[1] ist wenig toxisch, aber auch unwirksam, was für seinen (−)-Antipoden in orientierenden klinischen Versuchen bestätigt wurde[4]. Demnach ist die amöbicide Wirkung von Verbindungen aus der Emetinreihe konfigurationsspezifisch.

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*Forschungsabteilung der F. Hoffmann-La Roche & Co., A.G., Basel und * Instituto Nacional de Endemias Rurais, Belo Horizonte (Brasilien), 8. September 1959.*

[4] T. A. HENRY, *The Plant Alkaloids* 4th ed. (J. & A. Churchill, London 1949), p. 402.