Let the numbers c_{ij} be defined by

$$c_{ij} = \sum_{k=1}^{n} b_{ik}\, b_{jk} \quad (i = 1, \ldots, n;\ j = 1, \ldots, n). \tag{2}$$

If, for $i = 1, \ldots, n$ and $j = 1, \ldots, n$,

$$\left.\begin{array}{ll} c_{ij} = 1 & \text{if } i - j = 0 \\ |c_{ij}| < 1 & \text{if } |i - j| = 1 \\ c_{ij} = 0 & \text{if } |i - j| \geqq 2 \end{array}\right\}, \tag{3}$$

then the $(n-1)$-dimensional content of the point set defined by (1) is given by

$$\left.\begin{array}{l} (\pi/2)^m \cdot \prod_{k=1}^{m-1} (n - 2k)^{-1} \cdot \sum_{s=0}^{m} (2/\pi)^s \cdot I_s, \text{ where} \\ m = [\tfrac{1}{2} n],\ I_0 = 1, \text{ and for } 0 < s \leqq m \\ I_s = \sum_{i_1, i_2, \ldots, i_s} \underbrace{\int_0 \cdots \int_0}_{s}^{c_{i_1 j_1}} \cdots \int^{c_{i_s j_s}} \\ \left(D^{i_1 j_1 i_2 j_2 \ldots i_s j_s}_{i_1 j_1 i_2 j_2 \ldots i_s j_s}\right)^{-\frac{1}{2}} d\gamma_{i_1 j_1} d\gamma_{i_2 j_2} \ldots d\gamma_{i_s j_s} \end{array}\right\} \tag{4}$$

In the sum defining I_s (for $0 < s \leqq m$):

(a) $j_p = i_p + 1$ $(p = 1, \ldots, s)$,

(b) $i_1, i_2, \ldots, i_s$ is any set of s integers with $i_1 < i_2 < \ldots < i_s$ chosen from the whole numbers 1 up to $(n-1)$ inclusive in such a way that for each pair (i_p, i_q) of integers in the set the inequality $|i_p - i_q| \geqq 2$ holds good,

(c) summation is over all sets $i_1, i_2, \ldots, i_q$ satisfying this description,

(d) $D^{i_1 j_1 i_2 j_2 \ldots i_s j_s}_{i_1 j_1 i_2 j_2 \ldots i_s j_s}$ stands for the determinant of the $2s \times 2s$ square symmetrical matrix $\|e_{gh}\|$ in which the elements e_{gh} (g and h running, each of them, through $i_1, j_1, i_2, j_2, \ldots, i_s, j_s$) are given by

$$\left.\begin{array}{l} e_{gh} = \gamma_{gh} \text{ if } g = i_p \text{ and } h = j_p = i_p + 1 \ (p = 1, \ldots, s), \\ \text{and} \\ e_{gh} = c_{gh} \text{ otherwise } [c_{gh} \text{ was defined in (3)}]. \end{array}\right\}$$

If in (1) $\sum_{k=1}^{n} z_k^2 = 1$ is replaced by $\sum_{k=1}^{n} z_k^2 \leqq 1$, the result (4) is to be multiplied by $1/n$, of course.

The $(n-1)$-dimensional content of the point set defined by (1) occurred in a problem in statistics[1]. It had been investigated, however, as early as 1852 by SCHLÄFLI[2] who gave a number of theorems on it, but nothing like a general result by which this content should be explicitly determined. COXETER[3] gave a rather complicated series development for the content of orthoschemes (see below) in case $n = 4$; there is no hint at our result (4) in his paper; moreover, (4) holds with any (integer) value of n $(\geqq 2)$.

If $c_{ij} = 0$ for each pair (i, j) with $|i - j| \geqq 2$ $(i = 1, \ldots, n;\ j = 1, \ldots, n)$, the point set defined by (1) is called an n-spherical orthoscheme by SCHLÄFLI[1] (l.c., p. 74); if this equality does not hold true for each pair (i, j) with $|i - j| \geqq 2$, the point set defined by (1) is called an n-spherical plagioscheme by SCHLÄFLI (l.c., p. 58); I would prefer the terms $(n-1)$-dimensional spherical orthoscheme, and plagioscheme, respectively. The result (4) obtains for orthoschemes only. Research on plagioschemes is in progress, as is research on the expansion of I_s in a particular, relatively simple, multiple series.

The result (4) can be proved by two widely different methods, one of them being a straightforward solution of the system of linear partial differential equations of the first order given by SCHLÄFLI[1] (l.c., p. 65). Both methods are somewhat lengthy, but fairly elementary.

H. R. VAN DER VAART

Zoological Laboratory of University, Leiden, November 22, 1952.

Zusammenfassung

In kurzer Form wird der Inhalt gewisser (orthoschematischer) sphärischer Polyeder für eine willkürliche Dimensionenzahl mitgeteilt. Diese Formel bildet die Lösung eines von SCHLÄFLI aufgestellten Systems linearer partieller Differentialgleichungen erster Ordnung.

[1] H. R. VAN DER VAART, Proc. Kon. Ned. Akad. Wet. *53*, 494, 507 (1950); Indagationes Mathematicae *12*, 146, 159 (1950).

[2] J. H. GRAF, Mitt. Bern. Naturfor. Ges. *1896*, 77. – L. SCHLÄFLI (hg. v. J. H. GRAF), *Neue Denkschriften der allgemeinen schweizerischen Gesellschaft für die gesamten Naturwissenschaften*, Bd. *38* (1901), IV und 239 S.

[3] H. S. M. COXETER, Quart. J. Math., Oxf. Ser. *6*, 13 (1935).

[1] L. SCHLÄFLI (hg. v. J. H. GRAF), *Neue Denkschriften der allgemeinen schweizerischen Gesellschaft für die gesamten Naturwissenschaften*, Bd. *38* (1901), IV u. 239 S.

Notes on the Alkaloids of *Picralima*

The alkaloids of *Picralima nitida* occur in the seeds and have been studied by HENRY and SHARP[1] and HENRY[2], as well as by RAYMOND-HAMET[3] who has given a review of the subject[4].

Akuammine[5].—The formula attributed to the base by HENRY and SHARP[1] was $C_{22}H_{28}O_4N_2$, but the results did not exclude $C_{22}H_{26}O_4N_2$. 16 analyses of 12 different specimens (all decomposing at 254–259°) gave as average C, 69·02; H, 6·88%. 10 results within ±0·3% of the mean gave C, 68·98%, and 13 results within ±0·1% of the mean gave H, 6·88%. The average of 6 results gave N, 7·18%. $C_{22}H_{26}O_4N_2$ requires C, 69·09; H, 6·85; N, 7·33%. $C_{22}H_{28}O_4N_2$ requires C, 68·73; H, 7·34; N, 7·29%. The formula with H_{26} is evidently preferable.

The groups known to be present are 1 OMe, 1 NMe, 1 OH which we have confirmed. 1 CMe is also present (found, Me, 2·89%). Akuammine is a strong base, pK_a, 7·5 (strychnine, 7·6) and electrometric titration with alkali gave a curve with no inflection up to pH 10. This

[1] T. A. HENRY and T. M. SHARP, J. Chem. Soc. *1927* (1950).

[2] T. A. HENRY, J. Chem. Soc. *1932*, 2759.

[3] M. RAYMOND-HAMET, C. r. Acad. Sci. *211*, 125 (1940); Arch. exp. Path. Pharm. *199*, 399 (1942); C. r. Soc. Biol. *137*, 404 (1943); *138*, 199 (1944); C. r. Acad. Sci. *221*, 699 (1945); *230*, 1183 (1950); Rev. Int. bot. app. Agric. trop. *31*, 465 (1951); C. r. Acad. Sci. *233*, 560 (1951).

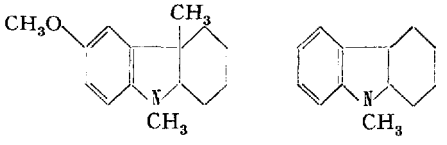
[4] M. RAYMOND-HAMET, Rev. Int. bot. app. Agric. trop. *31*, 465 (1951).

[5] The initiation of the present investigation was the result of the good offices of Professor E. SCHLITTLER who put us in touch with Dr. A. UFFER of Ciba, Ltd. Dr. UFFER separated the alkaloidal content of seeds of *Picralima nitida* collected in Kumasi (August, 1947) and very kindly sent us substantial quantities of akuammine and fractions obtained in the course of his work. We are also deeply indebted to Dr. T. M. SHARP of the Wellcome Research Laboratories for specimens of akuammine and some of its congeners. The akuammine was derived from *Picralima Klaineana* and was found by comparison of I. R. spectra to be identical with that from *Picralima nitida*.

was not in agreement with our preconception that the base was a readily hydrolysable lactone. This idea was linked with the postulation of a methoxyl group in the benzene nucleus which appeared to be supported by the behaviour of model compounds.

Actually akuammine is a phenol as shown by its immediate solubility in methanolic alkali (it is only sparingly soluble in methanol) and recoverability on addition of acid (identical I.R. spectra), by its coupling with *p*-nitrobenzenediazonium salts to an azo-compound which dissolves in alcoholic alkali to a blue solution, and finally by its reaction with 2:6-dichloroquinone-chloroimide in warm acetic acid solution to a reddish violet dye which becomes pure blue on the addition of sodium hydroxide. The latter reaction resembles that exhibited by *p*-methylaminophenol (metol).

Akuammine develops at once a characteristic orange red colouration with ferric chloride in very dilute cold hydrochloric acid solution. After acetylation no colour is developed, even on keeping for some hours. Exactly the same colour is somewhat more slowly developed under these conditions by the model substance (I), but not by any other of the three isomers in which the methoxyl occupies one of the alternative positions in the benzene nucleus.



(I) (II)

This model behaves similarly to akuammine in other reactions and it is likely that the methoxyl group of (I) is easily eliminated in oxidative processes.

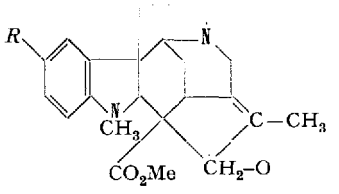
RAYMOND-HAMET[1] found that the U.V. absorption spectrum indicated a hydro-indole structure, and this we have confirmed. The I.R. absorption shows bands at 3·06 μ (OH or NH), 5·76 μ (ester or lactone unconjugated with C=C), and 12·33 μ (probably 1:2:4-trisubstituted benzene) supported by absence of bands at 13·3 μ (1:2-disubstituted benzene) and 12·8 μ (1:2:3-trisubstituted benzene).

The instability of akuammine under certain conditions in hot alcoholic solution is now understandable since it is a derivative of *p*-aminophenol. Before we knew this, a considerable loss of material occurred in a final recrystallisation. The product was distilled with zinc dust (WITKOP's technique) and afforded 3-ethylpyridine and (probably) skatole. The 3-ethylpyridine was identical with a synthetic specimen.

Akuammine is only slowly hydrogenated (palladised charcoal or ADAM's catalyst in ethanol), and appears to afford a dihydro-derivative which requires further study. The hydrochloride had m.p. 232–233° and crystallised with one C_2H_6O. Models of type (II) show oxidation colour reactions quite different from those of type (I) due to dehydrogenation of the hydro-indole nucleus. Akuammine behaves like a 2:3:3-trisubstituted dihydroindole and thus must be classified as a strychnine (β) rather than a yohimbine (α) type[2].

The constitution (III) fits all the known facts including the pharmacological findings of RAYMOND-HAMET that akuammine resembles cocaine in its action.

The position of the double bond is the most doubtful feature. It is provisionally placed to accomodate the fact that akuammine gives the iodoform reaction.



(III) R=OH
(IV) R=H

(III) and (IV)

Pseudo-akuammigine.—This base[1] has the formula $C_{22}H_{26}O_3N_2$, H_2O, it contains 1 OMe and 1 NMe. Unlike akuammine it has no reducing properties towards ammoniacal silver solutions and the I.R. absorption shows no band corresponding to OH or NH below 3·28 μ where the absorption by the paraffin paste commences. There is a band (ester C=O) at 5·76 μ, exactly the same frequency as with akuammine, and a band at 13·26 μ indicating a disubstituted benzene derivative. Otherwise the I.R. spectrum is very similar to that of akuammine.

The formula (IV) is indicated, that is akuammine less the phenolic hydroxyl, but there are two difficulties; in the first place, the oxidative colour with ferric chloride is developed reluctantly; this could be attributed to the proximity of the ester group to the methylimino group. Secondly, the (C)Me determination indicates two such groups. Whilst this result can be accomodated by modification of (IV), it is also possible that some $-CO_2Me$ has become $-CO_2Et$ in the course of working up the bases using ethanolic solutions. Very little material is available, and we hope to return to this point.

The U.V. absorption[2] indicates a dihydro-indole constitution. We have confirmed this, but note that the shape of the curve is somewhat anomalous for an N-methylhexahydrocarbazole, and this may once more be due to the proximity of $-CO_2Me$ to NMe.

Akuammidine ($C_{21}H_{24}O_3N_2$, H_2O).—This base contains 1 OMe (NMe absent) and affords an acetyl and a benzoyl derivative[1]. RAYMOND-HAMET detected two active hydrogen atoms[3] and we find (C)Me, 5·3%, [2(C)Me requires 8·2%].

The U.V. spectrum[4] shows that the base is a true indole derivative and it thus belongs to the α-series. Largely on pharmacological grounds, but also on account of hydrolysis to the amphoteric akuammidinic acid, RAYMOND-HAMET[3] proposed the constitution of a dide-hydroyohimbine. This fits the occurrence of two active H atoms but not the (C)Me determination. It is hard to reconcile these results and the problem requires further study.

Akuammigine ($C_{22}H_{26}O_3N_2$,H_2O) is also an indole derivative (U.V. spectrum)[5] containing 1 OMe but no NMe[1].

[1] M. RAYMOND-HAMET, C. r. Acad. Sci. *230*, 1183 (1950).

[2] The expressions "strychnine" and "yohimbine" types are not very satisfactory. Taking cognisance of the well established biogenesis we could speak of the α-series and β-series (yohimbine and strychnine respectively) which indicate the coupling of the α- or β-positions of tryptamine with the second amino-acid component (e.g. dihydroxyphenylalanine).

[1] T. A. HENRY, J. Chem. Soc. *1932*, 2759.

[2] M. RAYMOND-HAMET, C. r. Acad. Sci. *230*, 1183 (1950).

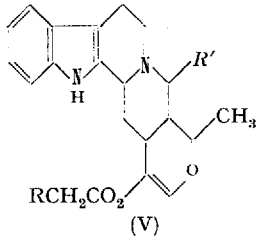
[3] M. RAYMOND-HAMET, Rev. Int. bot. app. Agric. trop. *31*, 465 (1951); cf. Bull. Soc. Pharm. Bordeaux *90*, 178 (1952).

[4] M. RAYMOND-HAMET, C. r. Acad. Sci. *221*, 699 (1945).

[5] M. RAYMOND-HAMET, C. r. Acad. Sci. *221*, 699 (1945); *332*, 560 (1951).

We find (C)Me 5·78, 6·37%; active H, 0·62% [2(C)Me requires 7·7 and 2 H requires 0·52%].

The I.R. absorption spectrum includes bands at 2·82, 3·00 and 3·28 μ (OH and NH), 5·86 μ and 5·94 μ (ester or ketone carbonyl group conjugated with a double bond), 6·14 μ (asymmetrically substituted double bond) and 13·50 μ (o-disubstituted benzene nucleus). This evidence, together with the U.V. is consistent with the presence of $MeO_2C—C=C—O—$, although the extra conjugated carbonyl peak in the I.R. is an unusual feature. There is an "extra" carbon atom, probably corresponding to a (C)Me, and the constitution (V) is feasible (R = H, R' = Me, or R = Me, R' = H), this structure also showing the suggested[1] relation to mayumbine.



(V)

Akuammiline ($C_{22}H_{24}O_4N_2$) contains 1 OMe and no NMe[2]. It appears to contain two (C)Me groups (7·0%, theory, 7·9%), and its U.V. spectrum is in the main like that of an indole, although it presents some slight variations. The first maximum at 2,200 A (logε, 4·25) is about 50 A shorter, and the second peak ($\lambda_{max.}$ 2,400 A; logε, 3·54) is rather broader than usual. The I.R. absorption shows a broad and very weak band at 2·9 μ (OH or NH or not significant), bands at 5·76 μ (C = O of unconjugated ester type), at 6·16 μ (probably C = C but could be C = N), at 6·26 μ (more conjugated C = C), at 13·29 μ (o-disubstituted benzene, but this is uncertain because bands at 12·90 and 13·21 μ are also observed).

Akuammiline could be a keto-akuammigine or a hydroxydehydroakuammigine. The modified indole spectrum suggests that a functional group is attached to the indole nucleus. The base gives a bright crimson red Otto reaction which is characteristic.

Akuammicine ($C_{19}H_{22}O_2N_2$) is said to contain 1 OMe and no NMe (but *v.infra*). In many ways it is *sui generis* with the remarkably high rotatory power $[\alpha]_D$ – 737·5° (in alcohol)[2]. Its Otto reaction is an intense and persistent royal blue colour.

The U.V. spectrum differs fundamentally from the spectra of the congeneric alkaloids. It is almost identical with that given by echitamidine[3] (which also has a high rotatory power[4]) and suggests considerable conjugation.

Among strychnine derivatives, benzylidenestrychnine exhibits a deep blue Otto reaction, and high rotatory powers are observed with a number of substances in the group which have double bonds in conjugation with the amide carbonyl. We may be sure that akuammicine contains the part structure —N—CO—C=C, with an asymmetric centre vicinal to an unsaturated group.

(C)Me determination gave Me 6·15, 6·6% [2(C)Me requires 9·68%].

The I.R. absorption spectrum has bands at 2·99 μ (OH or more probably NH), 6·03 μ (typical amide carbonyl, probably with further conjugation), 6·24 μ (probably armoatic double bond), 13·39 μ (o-disubstituted benzene, supported by absence of bands at 12·3 and 12·8 μ).

In the case of echitamidine[1] about half of the methyl was obtained as OMe (Zeisel) and half as NMe (Herzig-Meyer), but there is only one methyl group, and hence the (O)Me is unusually hard to remove, or the (N)Me is unusually labile. We prefer the latter hypothesis, which was noted by Goodson as a possibility, because COOMe cannot be present in akuammicine and it is hard to accomodate a methoxyl group otherwise.

M. F. Millson, R. Robinson and A. F. Thomas

The Dyson Perrins Laboratory University of Oxford, December 17, 1952.

Zusammenfassung

Für das Alkaloid *Akuammin* wird die neue Bruttoformel $C_{22}H_{26}O_4N_2$ aufgestellt und durch Vergleich verschiedener UV.- und IR.-Spektren und Reaktionen das Vorliegen einer 5-Hydroxydihydroindol-Verbindung abgeleitet. Die Zinkstaubdestillation liefert 3-Äthyl-Pyridin und vermutlich Skatol. Als Arbeitshypothese wird für *Akuammin* die Formel (III) vorgeschlagen. Die UV.- und IR.-Spektren und Reaktionen von Pseudo-akuammigin, Akuammigin, Akuammilin und Akuammicin sind gleichfalls diskutiert.

[1] J. A. Goodson, J. Chem. Soc. *1932*, 2626.

The Origin of Steric Hindrance in Cyclohexane Derivatives

Hassel[1] and Pitzer[2] and coworkers have pointed out that in the stable or "chair" form of cyclohexane there are two types of bonds, so-called equatorial ($\varkappa$ or e) and polar (ε or p) bonds. On the basis of this concept, Barton[3] has been able to make important and far-reaching predictions on the reactivity of substituted cyclohexanes and natural products containing cyclohexane rings. One of these predictions is concerned with the relative ease of esterification of hydroxyl groups and ease of hydrolysis of ester groups in polar and equatorial positions. Hydroxyl groups are esterified more easily and ester groups hydrolyzed more easily when in the *equatorial* than when in the *polar* position, due to the greater steric hindrance in the latter. The reason for this might be twofold. It is possible that an ester group in the polar position of a substituted cyclohexane has to stay in this position during hydrolysis and that the resulting crowded transition state (crowded due to steric interference of non-adjacent polar substituents) accounts for the relatively slow rate (reaction path A). On the other hand, it is also possible that prior to reaction the molecule is forced into a different conformation in which the ester group is now in the equatorial position (and some other, more bulky group in the polar position), and that the slower rate is due to the extra energy required to bring about the conformational transformation (reaction path B).

[1] M. Raymond-Hamet, C. r. Acad. Sci. *233*, 560 (1951).
[2] T. A. Henry, J. Chem. Soc. *1932*, 2759.
[3] M. Raymond-Hamet, C. r. Acad. Sci. *233*, 560 (1951).
[4] J. A. Goodson, J. Chem. Soc. *1932*, 2626.

[1] O. Hassel *et al.*, Acta Chem. Scand. *1*, 149, 929 (1947), and earlier papers.
[2] C. W. Beckett, K. S. Pitzer, and R. Spitzer, J. Amer. Chem. Soc. *69*, 2488 (1947).
[3] D. H. R. Barton, Exper. *6*, 316 (1950).