vitamin antagonists or antimetabolites. It is significant that, in most instances where a vitamin deficiency has a teratogenic effect, the vitamins in question belong to the B group, including particularly riboflavin and folic acid. A deficiency of the latter, or their blockade by antagonists such as galactoflavin, x-methyl-folic acid, or amethopterin, leads to severe malformations affecting the limbs and various organs. Among the antimetabolites, the glutamine antagonists azaserine (o-diazoacetyl-*L*-serine) and DON (6-diazo-5-oxo-*L*-norleucine) have attracted particular interest as potent teratogenic factors[109].

Although proof is still lacking that the neurotoxic and possible embryotoxic effects of thalidomide or its metabolites are due to faulty glutamic acid metabolism, this assumption would appear to offer an attractive working hypothesis.

Zusammenfassung. In einer vergleichenden Betrachtung werden die chemische Struktur, die pharmakologischen und toxikologischen Eigenschaften von Thalidomid diskutiert. Dabei zeigt sich, dass Thalidomid unter den heute bekannten Sedativa und Hypnotica eine besondere Stellung einnimmt.

Für die beschriebenen Tierversuche wurde ein mit ^{14}C markiertes Präparat verwendet. Bei Ratten wurde die Resorption, die Verteilung in den einzelnen Organen und die Ausscheidungsgeschwindigkeit nach einmaliger wie auch nach chronischer oraler Verabreichung studiert. Von der verabreichten Radioaktivität werden ca. 40% resorbiert. Die resorbierte Menge verteilt sich rasch in allen Organen und wird in verhältnismässig kurzer Zeit ausgeschieden. Eine Ausnahme bildet die Elimination aus den Blutkörperchen, die auffallend langsam vor sich geht.

Die chemischen Veränderungen, die Thalidomid im tierischen Organismus erfährt, konnten weitgehend aufgeklärt werden. Beim Hund werden ca. $^2/_3$ des verabreichten Präparates unverändert mit den Faeces eliminiert. Die im Urin ausgeschiedene Radioaktivität liegt zur Hauptsache in Form von Metaboliten vor. Von diesen konnten bisher 6 Substanzen, entsprechend 60% der im Urin vorhandenen Radioaktivität, quantitativ erfasst und identifiziert werden. Alle diese Verbindungen sind Glutaminsäurederivate, die aus Thalidomid durch hydrolytische Aufspaltung entstanden sind. Der Abbau von Thalidomid im Organismus führt daher zu einer Anzahl von Stoffwechselprodukten, die Derivate einer biogenen Aminosäure sind. Auf Grund dieser Feststellung werden verschiedene Hypothesen über die möglichen Ursachen der Nebenwirkungen von Thalidomid diskutiert.

Brèves communications – Kurze Mitteilungen – Brevi comunicazioni – Brief Reports

Alkaloid Studies[1]. The Structure of Aspidofiline

Three alkaloids–pyrifolidine (I)[2], pyrifoline (II)[2], and aspidofiline[3]–have been isolated from the Brazilian tree *Aspidosperma pyrifolium* Mart. and the structures of the first two (I, II) have recently been elucidated[4,5]. We should now like to report evidence which leads to the assignment of expression III to aspidofiline.

Earlier studies[3] attributed the empirical formula $C_{20}H_{22}N_2O_2$ to aspidofiline and also indicated the presence of an N-acyldihydroindole moiety and of a strongly hydrogen-bonded phenolic group. The presence of these two structural features was confirmed by the n.m.r. spectrum[6], which exhibited a signal at 2.30 ppm due to the N-acetyl grouping and one at 10.13 ppm associated with a hydrogen-bonded C-17 phenolic grouping (see aspidocarpine[7] and spegazzinidine[8]). Furthermore, the n.m.r. spectrum established the absence of an ethyl group or of the C-2 hydrogen (quartet in the 3.8–4.5 ppm region[9]) typical of alkaloids based on the aspidospermine skeleton (e.g. I), but it did show signals in the 6.70–7.35 ppm region for the three aromatic protons. Chemical confirmation for the presence of the phenolic grouping was adduced by acetylation (20 h refluxing with acetic anhydride in benzene) to 0-acetylaspidofiline (IV) (m.p. 179–181°, $[\alpha]_D^{30} + 53°$ (all rotations in chloroform)) or methylation (diazomethane in methanol; 24 days at 0°) to 0-methylaspidofiline (V) (colorless glass distilled at

[1] This paper represents part XXXVII. For preceding paper see H. Vorbrueggen and C. Djerassi, J. Amer. chem. Soc. *84*, in press (1962).

[2] B. Gilbert, L. D. Antonaccio, A. A. P. G. Archer, and C. Djerassi, Exper. *16*, 61 (1960).

[3] L. D. Antonaccio, J. org. Chem. *25*, 1262 (1960).

[4] C. Djerassi, A. A. P. G. Archer, T. George, B. Gilbert, and L. D. Antonaccio, Tetrahedron *16*, 212 (1961).

[5] B. Gilbert, J. M. Ferreira, R. J. Owellen, C. E. Swanholm, H. Budzikiewicz, L. J. Durham, and C. Djerassi, Tetrahedron Letters 59 (1962).

[6] Measured with a Varian A-60 spectrometer in $CDCl_3$ solution with tetramethylsilane as internal standard ($\delta = 0.0$ ppm). All signals are reported in ppm as δ units (δ = cps/60).

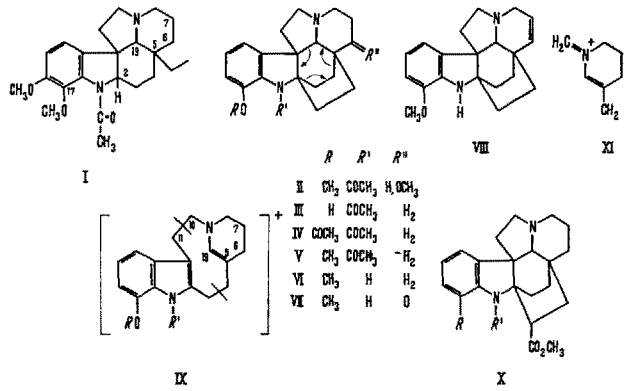
[7] S. McLean, K. Palmer, and L. Marion, Can. J. Chem. *38*, 1547 (1960).

[8] C. Djerassi, H. W. Brewer, H. Budzikiewicz, O. O. Orazi, and R. A. Corral, Exper. *18*, 113 (1962).

[9] C. Djerassi, A. A. P. G. Archer, T. George, B. Gilbert, J. N. Shoolery, and L. F. Johnson, Exper. *16*, 532 (1960).

175°/7 × 10^{-6} mm), which was cleaved by heating for 1 h with 50% hydrochloric acid to 0-methyldeacetylaspidofiline (VI) (m.p. 129–131°, $[\alpha]_D^{27}$ −6.4°, λ_{max}^{EtOH} 244 and 287 mμ, log ε 3.79 and 3.34, unchanged in alkaline solution).

The empirical formula of aspidofiline (m.p. 190–191°, $[\alpha]_D^{20}$ −174°, $\lambda_{max}^{EtOH-KOH}$ 231 and 308 mμ, log ε 3.76 and 4.31) was shown to be $C_{21}H_{26}N_2O_2$ (338)–rather than the earlier[3] assumed $C_{20}H_{22}N_2O_2$–by mass spectrometry of the parent alkaloid (molecular ion at *m/e* 338) and its three transformation products, IV (mol. ion 380), V (mol. ion 352) and VI (mol. ion 310). Most importantly, the mass spectra of aspidofiline (III) and its derivatives (IV–VI) all showed a strong M-28 peak (IX), analogous to the expulsion (see arrows in II) of ethylene in aspidoperminelike alkaloids[10], and a base peak at *m/e* 109. The latter was encountered first in the mass spectra of refractine (X, $R = OCH_3$; $R' = CHO$)[11], aspidofractine (X, $R = H$; $R' = CHO$)[11] and kopsinine (X, $R = R' = H$)[12] and attributed to species XI.



In view of these mass spectrometric and n.m.r. properties and the co-occurrence of aspidofiline and pyrifoline (II)[5] in the same plant, structure III appeared to be the most plausible alternative for aspidofiline, formation of the *m/e* 109 ion being rationalized readily by rupture (wavy lines in IX) of the allylically activated centers in the M-28 species (IX), this path being substantiated by the appearance of a metastable peak at *m/e* 41.5. Chemical confirmation of this supposition could be provided by the following direct interrelation with pyrifoline (II).

The conversion of pyrifoline (II) into N-deacetyl-6-demethyl-6-dehydropyrifoline (VII) has already been described earlier[5]. Clemmensen reduction of VII and separation of the complex reaction mixture by preparative thinlayer chromatography on silica gel (developed with a mixture of 10% ethanol (95%)–45% benzene–45% ethylacetate) yielded 0-methyl-deacetyl-6-dehydroaspidofiline (VIII) (mol. ion at *m/e* 308, no *m/e* 109 peak (XI), M-28 (IX, $R = CH_3$; $R' = H$ with 6–7 double bond) and *m/e* 107 (XI with additional double bond) peaks of equal intensity, base peak at *m/e* 188)[13]. Catalytic hydrogenation of VIII with palladized charcoal catalyst in ethyl acetate solution provided 0-methyldeacetylaspidofiline (VI) (m.p. 128–129°, $[\alpha]_D^{27}$ −7.7°), which was shown to be identical with the naturally derived material by infrared, ultraviolet, n.m.r. and mass spectrometry as well as by thinlayer chromatographic mobility.

Aspidofiline thus represents the first alkaloid of the hexacyclic class encompassed by pyrifoline[5], refractine[11], kopsinine[12] and their congeners, where the hydroaromatic portion of the molecule bears no functional groups[14].

Zusammenfassung: Auf Grund von Protonresonanz und massenspektrometrischen Messungen sowie durch direkte Verbindung mit Pyrifolin (II) wird für das *Aspidosperma*-Alkaloid Aspidofilin die Struktur III vorgeschlagen.

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[10] K. BIEMANN, M. FRIEDMANN-SPITELLER, and G. SPITELLER, Tetrahedron Letters 485 (1961).

[11] C. DJERASSI, T. GEORGE, N. FINCH, H. F. LODISH, H. BUDZIKIEWICZ, and B. GILBERT, J. Amer. chem. Soc. *84*, 1499 (1962).

[12] W. G. KUMP, D. J. LE COUNT, A. R. BATTERSBY, and H. SCHMID, Helv. chim. Acta *45*, 854 (1962).

[13] This *m/e* 188 peak, which is also encountered in less intense form in the mass spectra of V and VI—and at *m/e* 174 in aspidofiline (III)—is almost certainly due to rupture of the molecule at positions 5, 10, and 19.

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Über eine neue Synthese von 18-Hydroxy- und 18-Oxo-progesteron[1,2]

Im Verlaufe von Untersuchungen über biogenetische Zusammenhänge in der Reihe der Corticosteroide[3] wurden in den letzten Jahren in unserem Laboratorium mehrere potentielle Vorläufer des Aldosterons synthetisiert[4]. Neben den von uns bereits beschriebenen, in Stellung 18 oxigenierten Derivaten des Cortexons[5], 11β-Hydroxyprogesterons und Corticosterons, kommt den entspre-

[1] Über Steroide, 188. Mitt.

[2] 187. Mitt. s. CH. MEYSTRE, K. HEUSLER, J. KALVODA, P. WIELAND, G. Anner und A. WETTSTEIN, Helv. chim. Acta *45*, 1317 (1962).

[3] Zusammenfassende Darstellung s. A. WETTSTEIN, Exper. *17*, 329 (1961); vgl. ferner das Übersichtsreferat über «Die Chemie des Aldosterons» vom gleichen Autor, Verhandlungen der Deutschen Gesellschaft für innere Medizin, *68*, (1962), im Druck.

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[5] F. W. KAHNT, R. NEHER und A. WETTSTEIN, Helv. chim. Acta *38*, 1237 (1955).