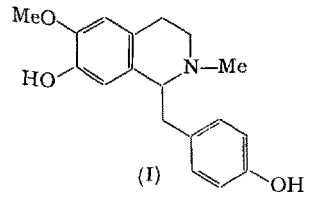
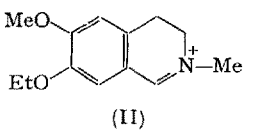
the structure of the phenolic fragment as *l*-*N*-methylcoclaurine (I).

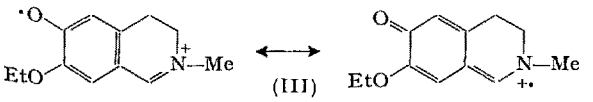
The non-phenolic fragment could also not be crystallized; it was purified by chromatography on alumina (neutral, activity I), gave a single spot on t.l.c. on silica gel and was dextrorotatory. Its p.m.r. spectrum was identical with that of the corresponding non-phenolic fragment obtained from hayatinin ethyl ether[1]. The absence of a signal at τ 6.40–6.50 indicated *O*-ethylation at the 7-position. This assignment was supported by (1) deuteration studies with hayatidin, which showed that there were no protons *ortho* or *para* to the phenolic group, as well as by (2) the mass spectrum, which showed intense peaks at *m/e* 220 and 206. The former corresponded to the ion (II) and the latter to (III) with a hydrogen transfer. The peaks for the other ions were at *m/e* 192, 190, 111, 97 and 91; the molecular ion peak was absent.



(I)



(II)

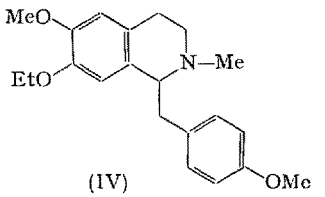


(III)

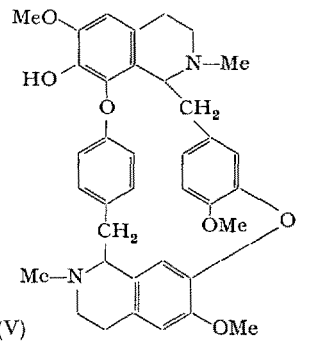
The methiodide of the non-phenolic fragment, m.p. 180°, was identical with that of the corresponding methiodide obtained from the non-phenolic fragment of hayatinin ethyl ether.

All this evidence led to the formulation of the non-phenolic fragment as *d*-1-*p*-methoxybenzyl-6-methoxy-7-ethoxy-2-methyl-tetrahydroisoquinoline (IV).

The assignment of the 2 fragments resulting from sodium and liquid ammonia reduction of hayatidin ethyl ether as (I) and (IV) respectively, clearly established the structure of hayatidin as (+ −)-4″-*O*-methylbebeerine (V). Using the serine convention and the sequence rule, (+) = L = S and (−) = D = R, hayatidin then corresponds to the (S, R) absolute configuration[7,8].



(IV)



(V)

Zusammenfassung. Das Alkaloid Hayatidin, aus Wurzeln von *Cissampelos pareiras* Linn. isoliert, konnte nach Reduktion seines Äthyläthers und Identifikation der Fragmente durch die Darstellung passender Derivate mit protonmagnetischer Resonanz und weiteren Methoden als (+ −)-4″-*O*-Methylbebeerine charakterisiert werden.

A. K. Bhatnagar and S. P. Popli

Central Drug Research Institute, Lucknow (India), 10th October 1966.

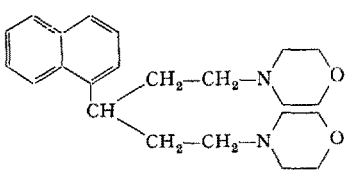
[7] M. Tomita and J. Kunitomo, J. pharm. Soc., Japan *82*, 741 (1962).

[8] The authors thank Prof. A. R. Battersby, Drs. M. L. Dhar and S. Bhattacharji for much useful advice, Dr. R. S. Kapil for mass spectral determinations and Dr. James Walker and Dr. E. J. Herbert for samples of the methiodide of *l*-*O*,*O*′,*N*-trimethylcoclaurine and *O*-ethyl derivative of (+ +)-4″-*O*-methylcurine respectively.

Anti-Arrhythmic Properties of 1,5-Dimorpholino-3-(1-Naphthyl)-Pentane: DA 1686

During investigations performed in the field of naphthalene derivatives, it has been observed that 1,5-dimorpholino-3-(1-naphthyl)-pentane possesses both in vitro and in vivo anti-arrhythmic properties.

The structural formula of DA 1686 is as follows:



molecular weight 368.50

DA 1686 is a brown viscous oil, insoluble in water; the dihydrochloride is a white crystalline compound, very soluble in water.

When tested on isolated guinea-pig auricles at a concentration of $4 \cdot 10^{-6}$, DA 1686 reduces the tachycardic effect of aconitine $1 \cdot 10^{-7}$ and reduces the effect of the increased frequency of electrical stimulation. In this latter test DA 1686 is 1.8 times more active than quinidine and 9 times more active than procainamide.

DA 1686 at 2% concentration has a local anaesthetic activity similar to that of quinidine but higher than that of procainamide when tested in vivo in mice (tail-pinch method adapted for testing local anaesthetics). The compound has a considerable effect at 2% concentration when tested on the cornea of guinea-pigs.

In dogs anaesthetized with morphine and pentobarbital, DA 1686 slowly infused at a dose of 20 mg/kg protects the animals from death induced by a rapid i.v. administration of adrenalin during inhalation of benzol.

DA 1686 protects rats from the arrhythmia induced by aconitine (34 µg/kg, i.v.) and in guinea-pigs delays the

onset of arrhythmia, ventricular fibrillation and cardiac arrest provoked by a slow infusion of ouabain (8 μg/kg every 90 sec).

In rabbits, the compound reduces the tachycardic effect of prolonged thyroxine treatment (0.2 mg/day/rabbit for 10 days).

The pressor activity of adrenalin and of occlusion of the carotids in anaesthetized rabbits is not modified by the compound just as the hypotensive action of acetylcholine remains unchanged. By contrast, the hypotensive effect of the stimulation of the peripheral stump of the vagus is reduced.

In anaesthetized rabbits, DA 1686 provokes bradycardia, widening of the QRS and mild hypotension. The effect on the cardiac frequency is greater than that exerted by quinidine and procainamide, while the effect on the QRS and pressure is minor.

The compound is well absorbed after both oral and intramuscular administration in rats and rabbits, producing higher blood levels than those of quinidine and procainamide administered at equal doses. In rats and rabbits, the compound is eliminated in the non-metabolized state to the extent of 50–60% during the first 24 h after treatment and 15–20% in the following 24 h.

Riassunto. Il DA 1686, corrispondente al 1,5-dimorfolino-3-(1-naftil) pentano, è un derivato della naftalina ad attività antiaritmica come risulta dalle prove in vitro (orecchiette isolate di cavia) e in vivo (cani, conigli, cavie e ratti). Il composto è ben assorbito dopo somministrazione orale e viene escreto nelle urine non metabolizzato.

C. BIANCHI, T. BRUZZESE, S. CASADIO, G. COPPI, G. PALA, G. P. SANNA and C. TURBA

Research Laboratories of the Istituto De Angeli S.p.A., Milano (Italy), 11th November 1966.

Novobiocin and the Binding of Magnesium Ions

It has been shown by WEINBERG[1] and BROCK[2] that Mg^{++} ions overcome the antibacterial activity of novobiocin against Gram-negative, but not Gram-positive, bacteria. In addition, evidence has been presented[2] to demonstrate that the antibiotic and cation form a complex, although more recent studies[3] may suggest otherwise. This problem has also been under study in our laboratories.

Novobiocin monosodium was a gift from Merck, Sharpe and Dohme Ltd., Hoddesdon (Herts, England). Magnesium chloride, $MgCl_2 \cdot 6H_2O$, and sodium chloride were of 'Analar' grade. The water used was obtained from an ion-exchange column, and had a specific conductance of 10^{-6} ohm^{-1} cm^{-1}. The spectra of novobiocin alone and in the presence of magnesium chloride were recorded over the range 200–450 nm in a Unicam SP 800 spectrophotometer, using 1 cm cells (Table I). It can be seen from the results that there is no evidence for the formation of a complex between novobiocin and Mg^{++}.

BROCK[2] carried out difference spectra with strong ($10^{-2}M$) solutions of novobiocin sodium and magnesium chloride, and obtained a peak at 360 nm; he therefore concluded that a complex was formed at high concentrations. Our findings with difference spectra (Table II), which are quite different in shape from the ordinary spectrum of novobiocin, suggest that the peak obtained by BROCK[2] was only an apparent, and not a true one. The results presented in Table II show that when solutions of novobiocin sodium of different concentrations are placed in the sample and reference cells, the peak obtained for the difference spectrum is displaced to longer wavelengths; the greater the concentrations, the greater is the shift. This shift is an apparent one, because when the spectrum of an $8 \cdot 10^{-4}M$ solution of novobiocin sodium (which is higher than the concentrations used in some of the difference spectra) was recorded against water, using 1 mm cells, the λ_{max} was still at 308 nm. Thus, the peaks obtained by difference spectra are false, since the spectrophotometer is insensitive to absorbtion differences between the sample and reference solutions when both are absorbing very strongly. In the experiments carried out by BROCK[2], a mixture of $10^{-2}M$ novobiocin sodium and $10^{-2}M$ magnesium chloride was placed in the sample cell and a $10^{-2}M$ solution of novobiocin sodium in the

[1] E. D. WEINBERG, Bact. Rev. *21*, 46 (1957).
[2] T. D. BROCK, Science, *136*, 316 (1962).
[3] P. J. NIEBERGALL, D. A. HUSSAR, W. A. CRESSMAN, E. T. SUGITA and J. T. DOLUISIO, J. Pharm. Pharmac. *18*, 729 (1966).

Table I. Absorption spectra of novobiocin sodium in presence and absence of magnesium chloride

Sample solution		Reference solution	λ^1_{max}	Absorbance at λ^1_{max}	λ^2_{max}	Absorbance at λ^2_{max}
Concentration of						
Novobiocin sodium	$MgCl_2$					
$8 \cdot 10^{-4}M$	absent	water	308	1.60	240	1.81
$8 \cdot 10^{-4}M$	$8 \cdot 10^{-4}M$	$8 \cdot 10^{-4}M$ $MgCl_2$	308	1.59	240	1.78
$8 \cdot 10^{-4}M$	$8 \cdot 10^{-2}M$	$8 \cdot 10^{-2}M$ $MgCl_2$	308	1.61	240	1.80

1 cm cells were used in all experiments.