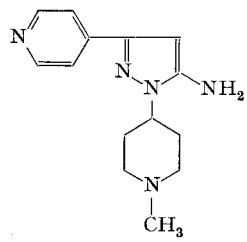
Isonicotinoyl-acetonitril kondensiert und dieses mit N-Methyl-piperidylhydrazin-dihydrochlorid umsetzt.



Das Mono-Hydrochlorid von CIBA 31 531-Ba schmilzt bei 254–256 °C. Es ist gut wasserlöslich. Das pH einer 5%igen Lösung beträgt 6,8.

Die Beeinflussung von systemischem, coronarem und pulmonalem Gefässwiderstand wurde an Katzen in Allobarbital-Urethannarkose (35 mg/kg i.p. und 35 mg/kg s.c. Dial ® Ciba) mit offenem Thorax und fixiertem Minutenvolumen bestimmt. (Modifikation[3] der Methode von RODBARD et al.[4].)

In dieser Versuchsanordnung wurde die Wirkung von CIBA 31 531-Ba (30 mg) mit der von Papaverin HCl (10 mg), Nitroglycerin (1,0 mg) und Isoproterenol-Sulfat (0,03 mg) verglichen. Die Dosen waren so gewählt, dass vergleichbare Senkungen des systematischen Gefässwiderstandes resultierten. Die Substanzen wurden in Absolutmengen in ein mit heparinisiertem Blut von Spender-Katzen gefülltes, venöses Blutreservoir gegeben. Alle Präparate verminderten den Coronarwiderstand stärker und den pulmonalen Gefässwiderstand weniger stark als den systemischen Widerstand. Obwohl die Ausgangswerte des Drucks und Widerstandes in der A. pulmonalis in der vorliegenden Versuchsanordnung hoch waren (39–53 mm Hg entsprechend einem Widerstand von 14600–18100 dyn. sec. cm^{-5}), war er nur schwer beeinflussbar.

Präparat	SW	PW	CW	n
CIBA 31 531-Ba	-47 ± 3	-16 ± 2	-65 ± 3	(10)
Papaverin	-41 ± 3	-9 ± 1	-72 ± 4	(6)
Nitroglycerin	-37 ± 2	-5 ± 1	-57 ± 3	(15)
Isoproterenol	-52 ± 4	-16 ± 4	-83 ± 3	(5)

Angegeben sind die prozentualen Änderungen von systemischem Gefässwiderstand (SW), pulmonalem Widerstand (PW) und Coronarwiderstand (CW) am Wirkungsmaximum. Alle Werte sind $\bar{X} \pm s_{\bar{x}}$; n = Anzahl der Versuche.

Bei vergleichbarer Erniedrigung des systematischen Gefässwiderstandes wurde nur durch CIBA 31 531-Ba und Isoproterenol der pulmonale Gefässwiderstand gesenkt. Während aber Isoproterenol die Herzfrequenz gleichzeitig um $39 \pm 6\%$ und den myocardialen O_2-Verbrauch um $80 \pm 24\%$ erhöhte, verminderte CIBA 31 531-Ba die Herzfrequenz um $5 \pm 1\%$ und den Sauerstoffverbrauch um $21 \pm 4\%$.

CIBA 31 531-Ba scheint direkt an der glatten Muskulatur der Gefässe anzugreifen, da es die Vasokonstriktion, die durch verschiedene Substanzen ausgelöst wurde, in annähernd gleichen Dosen abschwächte. 10 mg/kg i.v. antagonisierten an Katzen die Wirkungen äquipressorischer Dosen von Adrenalin, Noradrenalin oder Angiotensin-II-Amid zu 69 ± 15, 70 ± 15 bzw. $48 \pm 7\%$ ($n = 3$). Auch an den Gefässen der isoliert durchströmten Hinterextremität des Kaninchens[5] wurde die durch Histamin (1 γ/ml), Noradrenalin (0,05 γ/ml) oder Angiotensin-II-Amid (0,01 γ/ml) verursachte Gefässkonstriktion durch CIBA 31 531-Ba γ/ml in annähernd gleichem Ausmass gehemmt. (Histamin zu 39%, Noradrenalin und Angiotensin-II-Amid zu 28%.) Ausführliche Publikationen über tierexperimentelle und klinische Untersuchungen mit CIBA 31 531-Ba erscheinen demnächst.

Summary. 4-[5-Amino-3-(4-pyridyl)-1pyrazolyl]-1-methyl-piperidine (CIBA 31 531-Ba) was found to have a relatively pronounced vasodilator effect on the pulmonary circulation in the open chest, right heart-bypass cat with fixed cardiac output. This compound most probably has a direct effect on the vascular smooth muscle.

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Pharmazeutische Abteilung, biologische und chemische Forschungslaboratorien der CIBA Aktiengesellschaft, Basel (Schweiz), 25. Januar 1966.

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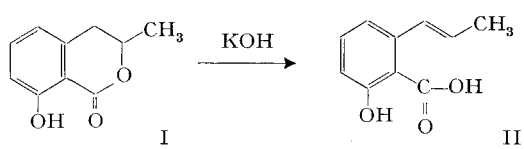
Isolation of the Optical Antipode of Mellein from an Unidentified Fungus

An unidentified fungus, grown in either standing or submerged culture, produced a solvent-extractable metabolite (I) that gave a blue color with ferric chloride.



I

I was isolated, and its chemical and physical properties were essentially the same as those for mellein, (−)-3-methyl-3,4-dihydro-8-hydroxyisocoumarin, a metabolite produced by several fungi[1–3]. The only distinguishing property is the optical rotation which is numerically the same for I and mellein but opposite in sign. Therefore, it seems likely the two compounds are optical antipodes.

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For the isolation of I, the unidentified fungus was fermented in a modified Czapek-Dox medium[4] under conditions of aeration and agitation at 24 °C for 12 days. The product was extracted from the culture filtrate at pH 2.5 (300 l) into chloroform. The extract was washed with dilute sodium bicarbonate, concentrated to a residue and chromatographed on silica gel (Grace, chromatographic grade) with hexane-chloroform (3:1). Eluate fractions containing material giving a blue color with ferric chloride were combined and evaporated to dryness. The residue was crystallized from hexane-ethyl ether (4:1) to yield 5.7 g of I. Anal. C, 67.45; H, 5.85. Calcd. for $C_{10}H_{10}O_3$ (mellein): C, 67.43; H, 5.61, m.p. 51.5–52 °C; $[\alpha]_D^{25}$ + 88 (c, 1.03 in methanol), $[\alpha]_D^{25}$ + 102 (c, 1.07 in chloroform). λ_{max} (log ε) = 212 (4.30); 245 (3.86); 312 (3.62) nm in methanol. Alkali shifted the maximum at 312 nm to 344 nm, which was reversed with acid. The IR-spectrum of I was the same in all essential respects with that reported for synthetic (±)-mellein[5].

The nuclear magnetic resonance spectrum of I ($CDCl_3$, 60 MC/sec, in PPM from tetramethylsilane as internal standard) showed a total of 10 protons. These could be assigned to O–CH–C*H*$_3$ (δ = 1.53, doublet); CH-C*H*$_2$-phenyl (δ = 2.97, doublet); O–C*H*–CH$_3$ (δ = 4.75, quartet); three ortho-substituted aromatic protons (δ = 6.73, doublet; δ = 6.87, doublet; and δ = 7.45, triplet), and one phenolic proton (δ = 11.05, singlet)[6]. This interpretation is consistent with structure I for the metabolite.

Potassium hydroxide fusion at 185 °C for 45 min[7] converted I to the acid II. The product was recovered from an acidified, aqueous solution of the alkali melt by ethyl ether extraction and crystallization from hexane-ethyl ether (2:1). Yield, 60%. Anal. C, 67.54; H, 5.52. Calcd. for $C_{10}H_{10}O_3$: C, 67.43; H, 5.61, m.p. 165 °C with sublimation; λ_{max} (log ε) = 254 (4.08); 318 (3.64) nm in methanol. The IR absorption spectrum of II showed broad absorption in the region of 2500 cm^{-1} and strong peaks at 1630 and 1130 cm^{-1} expected of a chelated carboxylic acid[8]. In the spectrum of I the carbonyl absorption was at 1660 cm^{-1} and there was a strong peak at 1160 cm^{-1} attributed to an ester linkage[8], which were not present in the spectrum of II. These data indicate that II is 6-trans-propenyl-salicylic acid, the alkali-fusion product of mellein[9,11].

Zusammenfassung. Ein Stoffwechselprodukt eines nicht klassifizierten Pilzes wurde als (+)-3-methyl-3,4-dihydro-8-oxyisocumarin, der optischen Antipode von Mellein, identifiziert.

E. L. PATTERSON, W. W. ANDRES, and N. BOHONOS

Biochemical Research Section, Lederle Laboratories Division, American Cyanamid Company, Pearl River (New York, USA), December 6, 1965.

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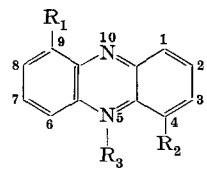
[11] Acknowledgments: We thank the Organic Chemical Research Section of these laboratories for the microchemical and spectral analyses.

In vivo Oxidative Coupling of Anilines and Phenolic Anilines[1]

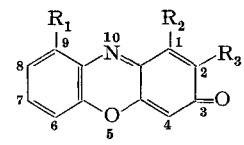
The principle of oxidative coupling in nature has received wide attention in recent years. According to a hypothesis by BARTON[2] various classes of natural products, such as alkaloids, plant pigments and microbial metabolites, contain numerous representatives which may be thought to arise biogenetically by oxidative coupling of phenolic precursors. Recent feeding experiments with labeled precursors, e.g. by BATTERSBY[3], proved the validity of the phenolic oxidative coupling principle in the biosynthesis of certain alkaloids.

Inasmuch as phenolic oxidative coupling is believed to proceed via radical pairing, the possibility that also anilines or phenolic anilines are subject to in vivo coupling seems obvious. The previously demonstrated in vitro feasibility of such coupling, either by electron transfer agents[4] or in air under catalysis of enzymes isolated from higher animals[5], suggests a similar pattern in nature. However, no in vivo coupling has heretofore been observed.

Inspection of presently known natural products shows that examples on which this hypothesis may be tested are restricted to compounds with the phenazine (I) and 3(3H)-phenoxazinone (II) skeleton.



I



II

Besides the type II ommochromes, phenazines and 3(3H)-phenoxazinones have been found exclusively as pigmented metabolites of microorganisms. Considered as a group there is a noticeable recurrence of either an acyl or hydroxyl group in positions 1, 4, 6, or 9 of I and an acyl group in positions 1 and 9 and a nitrogen function in

[1] This work was supported by Grant GB-2290 of the National Science Foundation.
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