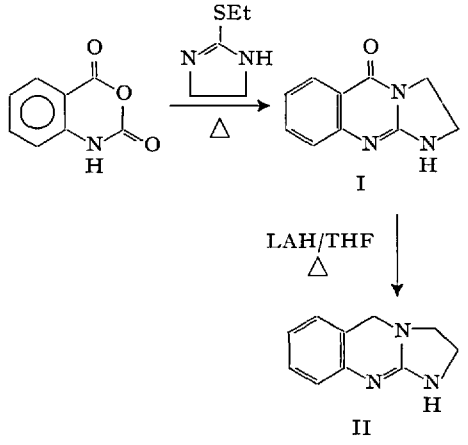
## A Novel Antihypertensive Agent: 1,2,3,5-Tetrahydroimidazo[2,1-b]quinazoline

In the course of a broad investigation of 'amidines'[1] as potential antihypertensive agents, the title compound (II) was synthesized by the lithium aluminum hydride reduction of lactam I[2]. The hydrochloride of II has mp 251–253°C; analysis for $C_{10}H_{11}N_3 \cdot HCl$: Calcd: C, 57.28; H, 5.77; found: C, 56.89; H, 6.00; $\lambda_{max}^{EtOH(KOH)}$ 278 nm ($\log \varepsilon = 4.09$).




This compound is a potent antihypertensive agent which is orally effective in rats, dogs, cats, and rabbits. It lowered the blood pressure significantly in the metacorticoid hypertensive rat[3] (5 mg/kg p.o.), in the unanesthetized neurogenic hypertensive dog[4] (2.5 mg/kg p.o.), and in the normotensive dog (2.5 mg/kg p.o.) without precipitating reflex tachycardia at these doses. The duration of action was sustained up to 48 h. No tolerance developed in a chronic study of 3 weeks duration. Preliminary studies of its mode of hypotensive action seem to exclude a central mechanism. Its peripheral action appears complex, although α-adrenergic blockade has been established as one of the components. Catecholamine depletion was demonstrated by a moderate reduction of norepinephrine level in the rat's heart. Mechanisms involving direct vascular dilation or ganglion blockade were excluded. The possible occurrence of orthostatic hypotension associated with the α-blockade activity of this agent was not observed in the rabbit tilt test[5]; this is in contrast to the result of a parallel study with phenoxybenzamine. The $LD_{50}$ (p.o.) for II (HCl) for rats was found to be 900 mg/kg.

Full reports of the chemistry and pharmacology of this new agent and analogs will be presented in the near future.

*Zusammenfassung.* 1, 2, 3, 5-Tetrahydroimidazo(2,1-b)-chinazolin wurde als neuer Typ eines bei Tieren gut wirksamen Hypotensivums erkannt. Bei α-blockierender Komponente wurde keine orthostatische Hypotonie festgestellt.

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## The Synthesis of Toxicarol Isoflavone

Toxicarol isoflavone, $C_{23}H_{22}O_7$, was isolated from the root of *Derris malaccensis* along with rotenoids (rotenone, toxicarol (I) etc.) by Harper[1]. Its structure was identified as 2″, 2″-dimethylpyrano(6″, 5″:7,8)-5-hydroxy-2′, 4′, 5′-trimethoxyisoflavone (II) on the basis of NMR spectral evidence[2]. II is very likely to be related biogenetically to I. The present paper will describe the synthesis of II confirming the proposed structure.

By a modified Hoesch reaction, 2,2-dimethyl-5-hydroxy-7-methoxychroman[3] was condensed with 2,4,5-trimethoxy-phenylacetonitrile[4] in the presence of anhydrous aluminum chloride to give the corresponding desoxybenzoins (III, mp 177–178°, NMR[5] 14.17$_s$ (Phenol [intramolecular hydrogen bonding]) and IV, mp 152–154°, NMR 6.8$_{bs}$ (Phenol[other phenol]). Treatment of III with ethyl formate in the presence of sodium gave the dihydropyranoisoflavone (V, mp 188–189.5°, IR 1663, 1641 cm$^{-1}$ (Nujol), UV $\lambda_{max}^{EtOH}$ nm (log ε); 259(4.50), 295(4.17), NMR 1.87$_t$(J = 7 Hz), 2.80$_t$ (J = 7 Hz) (–$CH_2$–$CH_2$–), 7.86$_s$ ($C_2$–H). Found: C, 67.51; H, 5.86. $C_{24}H_{26}O_7$ requires: C, 67.59; H, 6.15%). V was dehydrogenated with DDQ to give toxicarol isoflavone methyl ether (VI, mp 179–181°, IR 1665, 1641 cm$^{-1}$ (Nujol); UV $\lambda_{max}^{EtOH}$ nm (log ε); 264 (4.58), 293$_{sh}$(4.08), NMR 1.48$_s$ (6H) ($(CH_3)_2C <$), 3.72$_s$, 3.83$_s$, 3.90$_s$(6H) ($CH_3O$), 5.57$_d$ (J = 10 Hz) ($C_{3''}$-H), 6.31$_s$ ($C_6$-H), 6.59$_s$ ($C_{3'}$-H), 6.74$_d$(J = 10 Hz) ($C_{4''}$-H), 6.97$_s$ ($C_{6'}$-H), 7.80$_s$ ($C_2$-H). Found: C, 66.71; H, 5.89. $C_{24}H_{24}O_7 \cdot 1/2H_2O$ requires: C, 66.50; H, 5.81%) (lit.[1] mp 178°). The partial demethylation of VI with anhydrous aluminum chloride in acetonitrile gave the desired isoflavone (II, mp 220–220.5°, IR 1656 cm$^{-1}$, UV $\lambda_{max}^{EtOH}$ nm (log ε); 269(4.62), NMR 1.47$_s$(6H) ($(CH_3)_2C <$), 3.79$_s$, 3.86$_s$, 3.92$_s$ ($CH_3O$), 5.58$_d$ (J = 10 Hz) ($C_{3''}$-H), 6.29$_s$ ($C_6$-H), 6.65$_s$ ($C_{3'}$-H), 6.72$_d$ (J = 10) ($C_{4''}$-H), 6.92$_s$ ($C_{6'}$-H), 7.92$_s$ ($C_2$-H), 12.92$_s$ (OH). Found: C, 67.50; H, 5.42. $C_{23}H_{22}O_7$ requires: C, 67.31; H, 5.41%) (lit.[1] mp 219°), which was easily converted into

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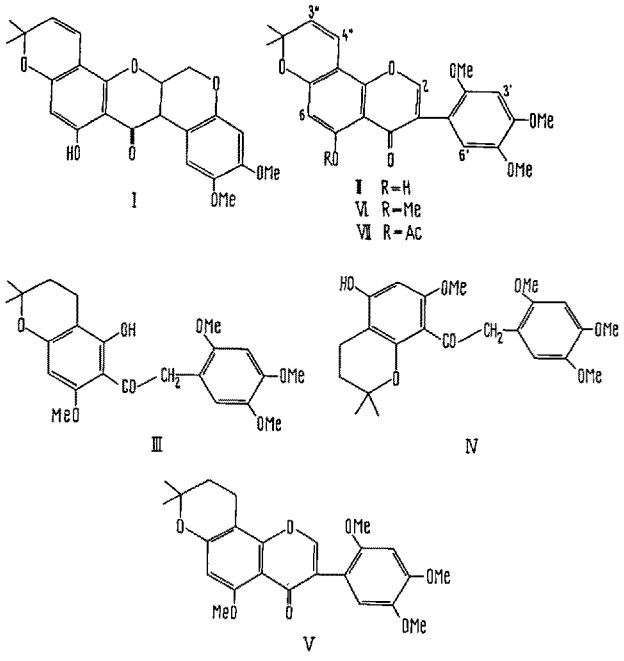
[5] The NMR-spectra were measured with a Hitachi R-20 (60 MHz) spectrometer, using tetramethylsilane as the internal standard (δ-value in $CDCl_3$; *s*, singlet; *bs*, broad singlet; *d*, doublet; *t*, triplet).




an acetate (VII, mp 212–215°, IR 1777, 1658, 1640 $cm^{-1}$, NMR 2.39$_s$ ($CH_3CO$), 7.86$_s$ ($C_2$-H)) (lit.[1] mp 210°). The spectral properties of the synthetic samples II, VI and VII were superimposable upon those recorded earlier [2] for natural toxicarol isoflavone and its derivatives.

*Zusammenfassung.* Die Synthese von Toxicarol Isoflavon (2″, 2″-Dimethylpyrano(6″, 5″: 7, 8)-5-hydroxy-2′, 4′ 5′-trimethoxyisoflavon) aus 2, 2-dimethyl-5-hydroxy-7-methoxychroman wird beschrieben.

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## Different Response of Adenine Nucleotide Synthesis de novo in Kidney and Brain During Aerobic Recovery from Anoxia and Ischemia

Anoxia or ischemia causes in various mammalian tissues a substantial loss of nucleotides due to dephosphorylation and further degradative processes[1,2]. In order to clarify whether the different abilities of organs to recover functionally from anoxia or ischemia are related to their capability to restore normal nucleotide levels, studies of the post-anoxic or post-ischemic synthesis de novo of adenine nucleotides were performed on kidney and brain. These two organs are known to exhibit very pronounced differences with respect to their potency of post-anoxic recovery.

*Material and methods.* In a first series of experiments slices of kidney and brain cortex of rats were incubated anaerobically in Krebs-Ringer-bicarbonate medium containing 0.25 m*M* glycine (preparation of slices, conditions of incubation and composition of the medium see[3]). After 30 min of anaerobic incubation (95% $N_2$–5% $CO_2$) the slices were allowed to recover aerobically (95% $O_2$–5% $CO_2$) for 60 min. During this period the synthesis de novo of adenine nucleotides (ATP, ADP, AMP) was determined by measuring the incorporation of 2-$^{14}$C-glycine (0.7 μCi/ml medium) into the adenine ring of the nucleotides (methodical details see[3]). Slices incubated only aerobically but otherwise treated alike served as controls.

A second series of experiments was performed in vivo on kidney and brain of ether anesthetized rats respirated artificially. Unilateral renal ischemia (30 min) was achieved by ligation of the a. renalis, brain ischemia (20 min) by ligation of all arteries originating from the arcus aortae. 30 min after re-establishment of the circulation, a period sufficient for the elution into the blood of protein and nucleotide degradatives accumulating during ischemia, the animals were exposed for 60 min to i.v. injected 1-$^{14}$C-glycine (25 μCi/100 g body weight), the incorporation of which into adenine nucleotides of kidney and brain was measured. Control values were obtained from sham-operated animals.

In both series of experiments, the tissues were quickly frozen in liquid nitrogen. Preparation of $HClO_4$ extracts, quantitative determination of ATP, ADP and AMP and measurements of the total radioactivity of adenine nucleotides were done according to methods already described[1,3]. Glycine was quantitated using a distillation procedure[4]. The radioactivity of glycine was measured either in an aliquot of the distillate (experiments with 2-$^{14}$C-glycine) or in a portion of the eluate containing the purified glycine after its isolation by column chromatography[5] (experiments with 1-$^{14}$C-glycine).

The rates of biosynthesis de novo of adenine nucleotides were calculated by relating the total radioactivity of adenine nucleotides, which results only from the incorporation of radioactive glycine during the de novo-formation of the purine ring, to the mean specific activity (MSA) of the tissue glycine precursor pool. MSA values were computed in each experiment from the specific activities of the tissue glycine always determined after 60 min of exposure to labelled glycine, and a correction factor obtained from special kinetic studies on the time dependent changes of the specific activities of the tissue glycine (Figures 1 and 2).

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