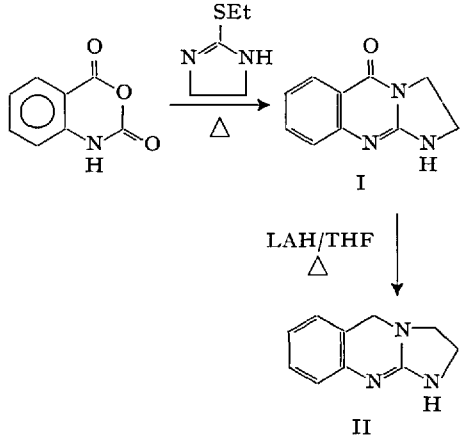
A Novel Antihypertensive Agent: 1,2,3,5-Tetrahydroimidazo[2,1-b]quinazoline

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.) of 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 λ_{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 λ_{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 λ_{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).