hydrogenated at atmospheric pressure in the presence of palladium-charcoal catalyst to yield I, m.p. 120–121°.

Anal. Calculated for $C_{27}H_{30}N_2$: C, 84.77; H, 7.91; N, 7.32. Found: C, 84.69; H, 8.33; N, 7.14.

The UV-spectrum showed maxima at 256 nm (ε 3710), 262 (3990) and 269 (2920), while minima occurred at 236 nm (ε 1450) and 267 (2860). The assignment of the axial conformation to the pyrrolidino group was based on nmr evidence as well as comparative methylation rate studies[3] on I and its equatorial epimer (obtained by another route). Finally, I was prepared independently by a displacement reaction of pyrrolidine with the *p*-bromobenzenesulfonate ester of the corresponding equatorial alcohol[3]. The water-soluble citrate salt of I, Su-15049A, was also prepared, by reaction with citric acid in 95% ethanol; m.p. 187–189°.

Anal. Calculated for $C_{27}H_{30}N_2 \cdot C_6H_8O_7$: C, 68.97; H, 6.67; N, 4.88. Found: C, 69.10; H, 6.68; N, 5.13.

A report on the preparations and structure-activity relationships of a number of analogs of Su-15049 will be published at a future date.

In rats given 5 ml/100 gm of either 0.2 or 0.9% sodium chloride solution, Su-15049 administered orally enhanced the excretion of sodium in doses of 0.6–50 mg/kg (straight line log-dose-response curve; slope, (36.6)) up to amounts approximately 8 times that of controls. Urine volume increased but by lesser relative amounts. Potassium excretion might be slightly increased (× 2), unaffected or decreased depending on the method of testing. The activity of the drug was largely abolished by adrenalectomy[4].

In 13 normal unanesthetized dogs, given 100 ml of 0.9% NaCl, Su-15049 at an oral dose of 5.0 mg/kg increased urine volume over a 6 h period by 63%, sodium excretion by 116% and chloride by 75%. A dose of 1.67 mg/kg was only slightly less active while 0.5 mg/kg was inactive. Potassium excretion was not significantly altered by any dose[5].

Zusammenfassung. Die Synthese von 1-(Pyrrolidino)-3,5-diphenyl-4-(α-pyridyl)-cyclohexan, Su-15049, und dessen wasserlöslichen Citrats werden beschrieben. Diese Verbindungen besitzen starke diuretische und natriuretische Eigenschaften; sie sind aber nicht kaliuretisch wirksam.

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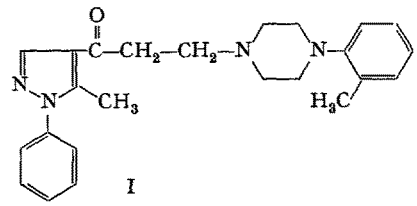
Research Department, CIBA Pharmaceutical Company, Summit (New Jersey 07901, USA) 6 March 1967.

[4] The nature of this adrenal dependence is being separately studied and reported by Dr. R. GAUNT and associates.

[5] Dr. E. J. CAFRUNY, University of Minnesota (personal communication) has found that in dogs Su-15049A does not appreciably affect the glomerular filtration rate or paraminohippurate clearance. Stop-flow studies indicated that its marked enhancement of Na^+ and Cl^- excretion was exerted primarily in the proximal portion of the renal tubules. It may, however, affect distal ion exchange mechanisms in such a way as to result in the observed net lack of enhanced K^+ excretion.

1-(5-Methyl-1-phenyl-4-pyrazolyl)-3-[4-(o-tolyl)-piperazinyl]-1-propanone[1], a New Synthetic Antihypertensive Agent

CIBA 1002-Go, which is 1-(5-methyl-1-phenyl-4-pyrazolyl)-3-[4-(o-tolyl)-piperazinyl]-1-propanone hydrochloride (I), has been studied to ascertain its antihypertensive properties in experimental animals:



I

Go. 1002 has been found to have potent hypotensive properties in animals. It produced a prolonged fall of blood pressure of 25–30 mm of mercury when given intravenously or intra-intestinally at doses of 0.5–1 mg/kg in pentobarbitone anaesthetized cats and dogs. Go. 1002 produced reversal of adrenaline pressor effect and inhibited carotid occlusion pressor response and antagonized the pressor response elicited by high doses of amphetamine and tyramine in anaesthetized normotensive dogs and cats. A potentiation of vasodepressor effects of isoprenaline was observed after the administration of Go. 1002 in anaesthetized dogs.

Go. 1002 lowered the blood pressure of renal hypertensive rats to normotensive levels within 24 h when given at doses of 5–10 mg/kg twice a day for 10 days. This compound did not show any ganglionic blocking activity or marked interference with the transmission of impulses in the cervical sympathetic chain. This has been shown by recording action potentials from cervical sympathetic postganglionic fibres as well as by recording contractions of the nictitating membrane of the cat.

Go. 1002 caused significant depletion of catecholamines from the heart and the brain of rats at doses of 2.5 mg/kg and 10 mg/kg respectively. It also interferred with the uptake of noradrenaline by the rat heart.

Pressor responses elicited by direct electrical stimulation of hypothalamic and medullary vasomotor centres in the cat were markedly depressed by Go. 1002 given intra-arterially in the lingual artery in doses of 0.25 to 0.5 mg/kg.

This compound produced marked peripheral vasodilation possibly by acting on adrenergic β-receptors and also by sensitizing these receptors to adrenaline.

A convenient method of preparation of Go. 1002 is as follows[2]: Treatment of ethoxymethylene acetylacetone

[1] Hydrochloride = CIBA 1002-Go.

[2] V. P. ARYA, in *CNS Drugs* (Council of Scientific and Industrial Research, New Delhi 1966), p. 35.

with phenylhydrazine gives the known 4-acetyl-5-methyl-1-phenyl pyrazole in good yield. Mannich condensation of the above pyrazole with N-(o-tolyl)-piperazine dihydrochloride and paraformaldehyde in the presence of catalytic amounts of hydrochloric acid affords Go. 1002 as colourless, tasteless leaflets after recrystallization from methanol. It melts with decomposition at 235–237 °C; calculated for $C_{24}H_{28}N_4O.HCl$: C, 67.81, H, 6.88, N, 13.18. Found: C, 68.05, H, 6.89, N, 13.00. Its UV-spectrum shows λ_{max} at 250 nm (log ε 4.34) in ethanolic solution. Its IR-spectrum exhibits a strong band at 1658 cm^{-1} in nujol mull.

Zusammenfassung. 1-(5-Methyl-1-phenyl-4-pyrazolyl)-3-[4-(o-tolyl)-piperazinyl]-1-propanone (I; CIBA 1002-Go), senkt an normotonischen und hypertonischen Tieren den Blutdruck. Die Drucksenkung kann auf eine periphere Vasodilatation und eine Hemmung hypothalamischer oder medullärer Vasomotorenzentren bezogen werden. Ausserdem wirkt CIBA 1002-Go adrenolytisch.

V. P. Arya, R. S. Grewal, J. David and C. L. Kaul

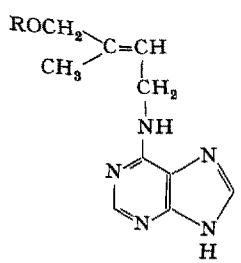
CIBA Research Centre, Goregaon East, Bombay 63, (India), 17th March 1967.

[3] Contribution No. 96 from CIBA Research Centre.

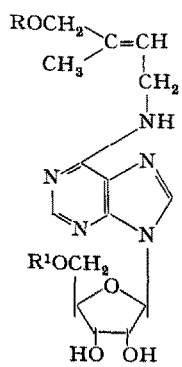
Phosphorylated Derivatives of the Cytokinins, Zeatin and its 9-β-D-ribofuranoside, Naturally Occurring Adenine and Adenosine Derivatives with Plant Cell-Division Promoting Activity

Compounds which induce plant cell division in the presence of indole acetic acid have been named cytokinins[1], and activity of this type is shown in varying degrees by a wide variety of synthetic 6-alkylamino purines related to kinetin (6-furfurylaminopurine), a degradation product of deoxyadenosine[2]. Naturally occurring substances with kinetin-like properties have been detected in a wide variety of excised plant tissues[3–7] and in addition to their cell division promoting activity are implicated in many physiological processes[8–12].

The first naturally occurring cytokinin was isolated from immature sweet corn (*Zea Mays*) kernels and named zeatin[13] (for a review see [14]). Its structure (Ia) was based on a combination of chemical, UV, proton magnetic resonance, mass spectral, and enzymic evidence, and finally confirmed by comparison with synthetic material prepared by our unambiguous route[15].



(Ia) R = H
(Ib) R = $-COCH_3$
(Ic) R = $-SO_2 \cdot C_6H_4 \cdot CH_3$
(Id) R = $-SO_2 \cdot CH_3$



(IIa) R = H, R^1 = H
(IIb) R = H, R^1 = $-PO \cdot (OH)_2$
(IIIa) R = $-P{:}O \cdot (OH)_2$, R^1 = H
(IIIb) R = R^1 = $-P{:}O \cdot (OH)_2$

Most workers report 3 major active cytokinins by bioassay of chromatogram zones in plant extracts, one of which appears generally to be zeatin. The other substances may be the corresponding 9-β-D-ribofuranoside of zeatin (IIa) and its 5'-phosphate (IIb)[16,17]. In one case[16] the structure of the material regarded as the nucleoside (IIa) was fully established by direct comparison with synthetic material[15]. A compound believed to be the nucleotide (IIb) was detected by Miller[17] in maize extracts and a pure crystalline product was isolated from the same source by Letham[18]. The probable structure assigned to the 5'-phosphate was based on its hydrolysis with 5'-nucleotidases to a riboside, presumably 9-β-D-ribofuranosylzeatin (IIa) and the further conversion of this to

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