protons usually resonate at slightly higher fields (δ = 2.8–3.5 ppm) than protons adjacent to oxygen (O-C-H) in acylic and larger-ring cyclic ethers or alcoholic OH functions, for which δ = 3.3–3.7 ppm or 3.5–4.5 ppm respectively, are the characteristic ranges.

In the present studies, the diepoxides (IV) and (VI) were used as model compounds regarding the assignation of epoxide proton lines. In the case of (VI) containing only epoxide protons, the spectrum was confined to the 2.4–2.8 ppm range. The observed vicinal coupling constants belonging to the multiplet structure have comparatively small values characteristic for epoxide structures[6]. Measurements on (IV) led to the same conclusions. The chemical shifts of the epoxide protons were in the 2.5–3.2 ppm range, the O-C-H proton shift belonging to the cyclic ether was 3.7 ppm.

Treatment of DBE (V) with alkali at pH 7.5 yields diepoxy-butane (VI) as an isolable product. In the proton resonance spectra of this reaction mixture the major part of the absorption was really found in the epoxide range (2.7–3.3 ppm). An additional multiplet structure was observed at 3.7 ppm which may indicate that either the conversion of starting molecules was not complete or side reactions were also present. (Chemical assay revealed about 50% yield of epoxide.)

In contrast to findings with the epoxide models, in the spectrum of the reaction product of DMM the protons attached to the carbohydrate skeleton resonated in the 3.4–4.2 ppm range, and no evidence was found to support the presence of an epoxide structure, although the thiosulphate test indicated an 'epoxide'-yield of 70%. The chemical shift of the methyl protons in the reaction product differed from the original value measured in DMM which indicates that the parent molecules were completely transformed in the reaction, but no unequivocal conclusions could be drawn concerning the nature of the reaction product.

Experiments with the cytostatic agents dibromomannitol and dibromodulcitol gave similar results to those obtained with DMM.

From these results it appears that the hydrolysis of dimesylmannitol and dibromohexitols does not yield epoxide products. Although the nature of the products of this in vitro reaction is not cleared up, there are no grounds to suppose that alkylation via an intermediary epoxide plays in vivo an important role in the cytostatic action of these compounds[7].

Zusammenfassung. Die NMR-Spektren der Reaktionsprodukte der alkalischen Hydrolyse des Dimesylmannits bestätigten die bisher angenommene Bildung von Epoxiden nicht.

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2nd January 1967.

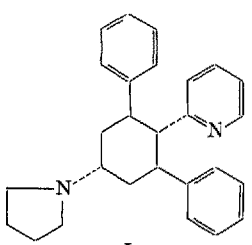
[6] N. S. Bhacca and D. H. Williams, *Application of NMR Spectroscopy in Organic Chemistry* (Holden-Day Inc., San Francisco, London, Amsterdam 1964), p. 99.

[7] The authors are indebted to Miss M. Kajtár for her participation in the NMR measurements.

[8] Present address: Belgrad-rkp. 18. II. 12a, Budapest V (Hungary).

A New Type of Non-Kaliuretic Diuretic Compound

In the course of a structure-study on the alkaloid lobinaline[1] and a synthesis of dehydrolobinaline, a partial dehydrogenation product derived from the alkaloid[2], a considerable excursion into the chemistry of triarylcyclohexanones[3] was required to elucidate the stereochemistry of the degradative and synthetic intermediates involved. Pharmacological screening of these intermediates revealed that 1-(N-pyrrolidino)-3, 5-diphenyl-4-(α-pyridyl)-cyclohexane (I, Su-15049) posseses marked diuretic and natriuretic activity in the rat and dog. The preparation and properties of this compound form the subject of the present report.



I

The initial step in the preparative sequence for Su-15049, which was also directed to a synthesis of the lobinaline ring system[2,3], involved a combination aldol-Michael condensation of 2-phenacylpyridine with benzalacetone to yield 3-hydroxy-3, 5-diphenyl-4-(α-pyridyl)-cyclohexanone. It was subsequently demonstrated[3] by nmr and chemical methods that this substance possesses the all equatorial *trans, trans* conformation of the aryl groups about the central ring. Dehydration of the aldol with phosphoric acid at room temperature yielded *trans*-3, 5-diphenyl-4-(α-pyridyl)-cyclohexen-2-one, which on low pressure hydrogenation with palladium-charcoal catalyst yielded largely *trans, trans*-3, 5-diphenyl-4-(α-pyridyl)-cyclohexanone. For the purpose of attaching a side-chain at position 2 of the ring to effect a synthesis of the lobinaline ring system, the ketone was converted to its pyrrolidine enamine derivative. This enamine was also

[1] M. M. Robison, W. G. Pierson, L. Dorfman, B. F. Lambert and R. A. Lucas, J. org. Chem. *31*, 3206 (1966).

[2] M. M. Robison, B. F. Lambert, L. Dorfman and W. G. Pierson, J. org. Chem. *31*, 3220 (1966).

[3] M. M. Robison, W. G. Pierson, L. Dorfman and B. F. Lambert, J. org. Chem. *31*, 3213 (1966).

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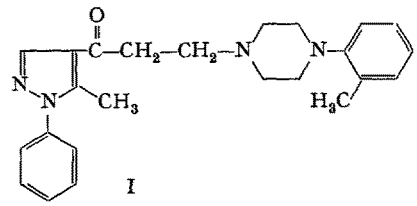
Research Department, CIBA Pharmaceutical Company, Summit (New Jersey 07901, USA) 6 March 1967.

[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.