Table 1 *Mean values of pK_a for the two pesticides, N-hydroxy phthalimide (I) and 4-carboxy N-phenyl phthalimide (II) in water-organic solvent mixtures.*

Organic solvent	Org. solv. %	Dielectric constant	pK_a I	pK_a II
	4.1	79.8	6.31	8.15
	8.2	78.12	6.46	8.28
Methanol	16.2	74.96	6.57	8.41
	25.1	71.47	6.71	8.49
	34.7	67.41	6.82	8.56
	3.9	77.5	6.27	8.24
	7.8	76.6	6.48	8.38
Ethanol	15.9	74.7	6.62	8.44
	24.6	72.7	6.69	8.60
	33.6	68.8	6.78	8.67
	5.6	80.22	6.86	8.00
Ethylene	11.0	79.47	6.79	7.93
glycol	21.7	77.92	6.64	7.90
	32.2	76.12	6.40	7.86
	42.5	73.91	6.33	7.67
	6.3	81.06	6.87	7.83
	12.3	80.06	6.79	7.75
Glycerol	24.0	78.80	6.72	7.59
	35.2	77.23	6.63	7.50
	45.80	75.51	6.47	7.43
Aqueous medium		74.42	6.91	8.86

presence of organic solvent increases the ionization of these compounds. The rate by which the ionic forms are produced is influenced by both the nature and the amount of the organic solvent added. The elimination of the proton is enhanced as the amount of glycol or glycerol increases whereas an increase in methanol or ethanol content decreases the ionization process. This behaviour may be explained[7] on the basis that glycol and glycerol acting as proton acceptors, and facilitating the dissociation of the proton from the hydroxyl group in (I) and from the carboxylic group in (II).

The decrease in ionization in the presence of ethanol or methanol can be attributed to the blocking of π-electrons of the C = O group in the two compounds through intermolecular hydrogen bonding which renders excitation of π-electrons more difficult, thus resulting in higher pK_a values. The displacement of the absorption bands to shorter wavelengths by increasing methanol or ethanol concentrations at constant pH, can be attributed to the decrease in concentration of the ionized form as a result of association with the molecules of these solvents.

The variation of pK_a with dielectric constant (D) in solvent mixtures is given by the relation[8]

$$pK_a = pK_0 + \frac{0.43\ Ne^2}{RT} \cdot \frac{Z_1 Z_2}{r_1 + r_2}\left(\frac{1}{D}\right)$$

where pK_a = acid dissociation constant in solvent mixtures, pK_0 is the dissociation constant in pure water, Z_1, Z_2 are the charges carried out by the ions in equilibrium, and r_1, r_2 are the radii of the ions involved in equilibrium.

The plots of pK_a as a function of $1/D$ however, do not strictly show linear relationships. This indicates that the changes in pK_a with the solvent proportion, though mainly governed by dielectric constant, yet solvolysis and solvent basicities play an important role.

9 April 1985; Revised 25 July 1985

1. Arcoria, A., Lumbroso, H. and Passerini, A., *Bull. Soc. Chim. France*, 1959, p. 754.
2. Monske, R. H., *Org. Synthesis*, 1952, XII.
3. Britton, H. T. S., *Hydrogen ions*. Chapmann and Hall, London, II edn., Vol. 1, 1952.
4. Vogel, A. I., *Practical organic chemistry*, Longmans, London, 1956.
5. Issa, I. M., Issa, R. M., Idriss, K. A. and Hammam, A. M., *Indian J. Chem.*, 1976, **14B**, 117.
6. Issa, R. M., Hammam, A. M. and Etaiw, S. H., *Z. Phys. Chem.*, 1972, **251**, 177.
7. Issa, I. M., Issa, R. M., Idriss, K. A. and Hammam, A. M., *Indian J. Chem.*, 1975, **13**, 136.
8. Charlot, G. and Tremillon, B., *Chemical reactions in solvents and melts*, Pergamon Press, London, 1969, p. 55.

SYNTHESIS OF 1-[N-SUBSTITUTED ARYL, N-(4′-DIMETHYLAMINO-3-NITRO-BENZYL)AMINO]-2-[4″(IMIDAZOLIN-2-YL AMINO) BENZOYL]-ETHANE HYDROIODIDES AS ANTIHYPERTENSIVE AGENTS

AMARIKA SINGH and V. S. MISRA
Department of Chemistry, Lucknow University, Lucknow 226 007, India.

1-([N-SUBSTITUTED aryl, N-(4′-dimethylamino-3′-nitrobenzyl) amino]-2-[4″-(imidazolin-2-yl amino) benzoyl]-ethane hydroiodides (VI) have been synthesised by the Mannich reaction of N-substituted

aryl-3-nitro-4-N,N-dimethylaminebenzylamine (V) with p-amino imidazoline acetophenone hydroiodide (VII). The structures of these compounds have been confirmed by elemental analysis, IR and PMR spectra. All the compounds were evaluated for their cardiovascular activity. Compound no. 4 was found to possess appreciable antihypertensive activity and low toxicity.

Imidazoline derivatives are associated with pronounced CVS activity[1,2]. Recent studies on this moiety furnished an efficient antihypertensive agent like 'clonidine'[3,4]. The structural requirement for most of the antihypertensive agents is- N-C-CH-as in hydralazine and clonidine. A dichlorophenyl moiety also effects the cardiovascular system[3]. In view of these observations it was thought desirable to prepare a few compounds of type (V) and screen them for their cardiovascular activity.

The tests were carried out on cats which were anaesthetised with α-chlorolose (30 mg/kg i.v.) and blood pressure was recorded from left common carotid artery by means of a mercury manometer on smoked Kymograph paper. Pressure responses were evoked by either occluding both the carotid artery for a period of 10–30 sec or by injecting 10 μ/kg of noradrenaline intravenously. ALD_{50} evaluation of all compounds was carried out on albino mice of either sex weighing in between 15–25 g. The title compounds were administered by i.p. route at different dose levels in each separate group of animals. After 24 hr the percentage mortality in each group was observed from data obtained and ALD_{50} calculated by method of Smith[5].

The melting points were determined in open capillaries in conc. H_2SO_4 melting point bath and are uncorrected. IR spectra in KBr phase were recorded using Perkin-Elmer 157 & 177 spectrophotometers (λ_{max} in cm^{-1}). The PMR spectra were recorded on a Varian $A_{60}D$ instrument using TMS as the internal standard (chemical shift in ppm). The homogeneity of compounds was checked on silica gel-G coated plates. All compounds gave satisfactory elemental analyses.

N-Imidazoline acetophenone hydroiodide or p-aminoimidazolin-acetophenone hydroiodide (VII): A mixture of 2-methylmercapto-2-imidazoline hydroiodide (0.1 mol) and *p*-aminoacetophenone (0.1 mol) was dissolved in dry methanol. The reaction mixture was refluxed for 24 hr. On concentration in vacuum and cooling a solid separated out, which was recrystallised from benzene-pet-ether (60–80), yield 50%, m.p. 167°, IR: 3130 (NH), 1650 (C=N), 3050, 2900 (CH Ar & Ali), 1670 (C=O) etc.

N-Substituted aryl-3-nitro-4-N,N-dimethylamine-benzylamine (V) (table 1): A solution of 4-dimethyl-3-

Table 1. *Characterisation data N-substituted aryl-3-nitro-4-N,N-dimethylamine-benzylamine (V)*

Compound No.	X	X′	M.P. (°C)
1	H	4-NO_2	45
2	2-Cl	3-Cl	40
3	2-Cl	5-Cl	56
5	2-Cl	6-Cl	59
5	H	4-Br	60
6	H	4-CH_3	63
7	H	4-OCH_3	66–67

Table 2 *Physical data and cardiovascular activity of title compounds*

Compd.+	X	X′	M.P.°C	Effect on blood pressure and heart rate 15 minutes %BP	%IR	Effect on CO/NA response	ALD_{50} mg/kg i.p.
1.	H	4-NO_2	80	6.6	2.1	No effect	500
2.	2-Cl	3-Cl	95	27.8	3.2	"	1000
3.	2-Cl	5-Cl	103	30.6	12.8	"	1000
4.	2-Cl	6-Cl	109	32.2	13.6	"	1000
5.	H	4-Br	112	16.2	6.8	No blocked NA slightly inhibited	500
6.	H	4-CH_3	116	22.8	12.2	No effect	1000
7.	H	4-OCH_3	122	14.2	6.2	"	1000

+ Dose 5 mg/kg i.v.
%change as compared to control in blood pressure and heart rate.
decrease in B.P. and heart rate.

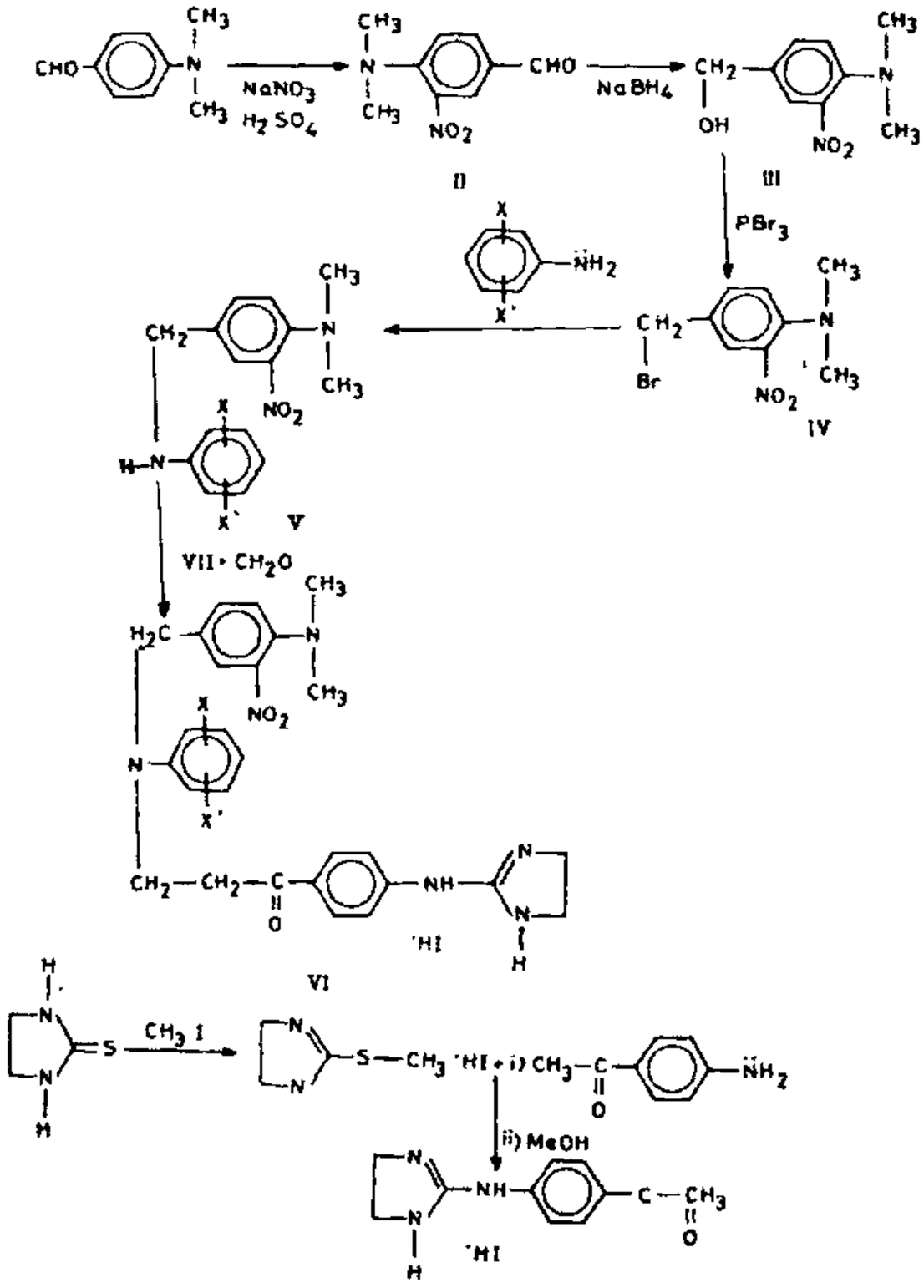
nitrobenzyl bromide (0.1 mol) in dry ether was added, under stirring to an appropriate substituted aniline (0.01 mol). The reaction mixture was stirred for about 9 hr, the ether layer was washed with cold water, and the separated solid was recrystallised from ethanol. IR:3120(NH), 1530, 1340 (NO_2) for all the compounds. The compounds were obtained in about 45–50 % yield.

1[N-Substituted-N-(4'-dimethylamino-3'nitro benzyl)amino]-2-[4''-(imidazolin-2 yl amino) benzoyl]-ethane hydroiodides (VI): Appropriate N-substituted aryl-3-nitro-4-N,N-dimethylamine benzylamine (0.025 mol) in ethanol (20 ml) was mixed with aq. formaldehyde solution (40 %, 1 ml) and compound (VI), (0.025 mol). The reaction mixture was heated for 10 min on a steam bath, left for 24 hr, washed with pet. ether (60–80) and recrystallised from ethanol. The physical data of these compounds are cited in table 2 and the reaction scheme is shown in figure 1. The compounds were obtained in about 50–60 % yield. IR: 3350 (NH, 3050, 2880 (CH), 1660 (C=O), 1530, 1340 (NO_2) for all compounds. PMR: ($CDCl_3$) of compound (2), (chemical shift in ppm), 2.88 (s, 6H, N-$(CH_3)_2$; 6.70–7.50 (m, 10H, Ar-H); 8.02 (s, 1H, NH), 3.48 (s, 4H, CH_2-CH_2) etc.

Thanks are due to Dr R. S. Kapil and Prof. B. N. Dhawan, CDRI for spectral and bioassay of compounds respectively and AS is thankful to UGC (New Delhi) for a fellowship.

24 November 1984; Revised 26 August 1985

1. Deprez, D. F., *Chem. Abstr.*, 1980, **85,** 12, 3965.
2. Hayashi, K., Nunami, K., Sakai, K., Ozaki, Y., Kato, J. and Kinashi, K., *Chem. Pharm. Bull.*, 1983, **10,** 31, 3553.
3. Schmitt, H. and Schmitt, H., *Eur. J. Pharmacol.*, 1969, **6,** 8.
4. Kobinger, W. and Walland, A., *Eur. J. Pharmacol.*, 1967, **2,** 155.
5. Smith, C. C., *J. Pharm. Exptl. Ther.*, 1950, **100,** 408.
6. Rogers, E. F., *Ann. Rep. Med. Chem.*, 1967, **11,** 233.



Scheme 1

A NEW RAPID COLORIMETRIC ESTIMATION OF UREA IN URINE USING ORTHOPHTHALALDEHYDE

C. N. RAMCHAND and
K. I. TRIPURASUNDARI.
Department of Biochemistry, Faculty of Science,
M. S. University of Baroda,
Baroda 390 002, India.
* *Present address: Dept. of Neuropsychiatry & Behavioral Science, School of Medicine, University of South Carolina, Columbia SC 29208, USA*

ORTHOPHTHALALDEHYDE (OPT) is a fluorogenic substance[1] that reacts nonspecifically with a number of biogenic compounds[2, 3], yielding intensely fluorescent condensation products in an alkaline medium in the presence of a reducing agent[7]. OPT was also used to detect peptides in fractions collected during column chromatography.

OPT is found to give a coloured product with diaminopropionic acid which is obtained on hydrolysis of β-N-oxalyl α, β-diaminopropionic acid (ODAP) in the *Lathyrus sativus* seeds.[4].