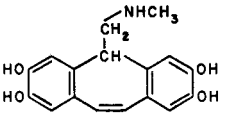
JORI, A., PRESTINI, P. E. & PUGLIATTI, C. (1969). *J. Pharm. Pharmac.*, **21**, 387–390.
KAKIHANA, R., NOBLE, E. P. & BUTTE, J. C. (1968). *Nature, Lond.*, **218**, 360–361.
KHAZAN, N., SULMAN, F. G. & WINNIK, H. Z. (1961). *Proc. Soc. exp. Biol. Med.*, **106**, 579–581.
KITAY, J. I., HOLUB, D. A. & JAILER, J. W. (1959). *Endocrinology*, **65**, 548–554.
MAICKEL, R. P., WESTERMANN, E. O. & BRODIE, B. B. (1961). *J. Pharmac. exp. Ther.*, **134**, 167–175.
MÄKELÄ, S., NÄÄTÄNEN, E. & RINNE, U. K. (1959). *Acta Endocr.*, **32**, 1–7.
ORRENIUS, S. & ERNSTER, L. (1967). *Life Sci.*, **4**, 1473–1482.
RADZIALOWSKI, F. M. & BOUSQUET, W. F. (1968). *J. Pharmac. exp. Ther.*, **163**, 229–238.
SHALLEK, W. & ZABRANSKY, F. (1966). *Archs int. Pharmacodyn. Thér.*, **161**, 126–131.
SUPERSTINE, E. & SULLMAN, F. G. (1966). *Ibid.*, **160**, 133–146.
WELLS, H., BRIGGS, F. N. & MUNSON, P. L. (1956). *Endocrinology*, **59**, 571–579.

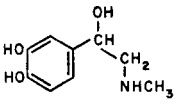
An improved method for the preparation of adnamine

We have recently been interested in the preparation of some *N*-alkyl substituted homologues of noradnamine (5-aminomethyl-2,3,7,8-tetrahydroxydibenzo[*a*,*e*]cycloheptatriene) for pharmacological testing. The *N*-methyl derivative, adnamine (I), was originally obtained by Kawazu (1958) by boiling a solution of adrenaline (II) in 10% hydrochloric acid for 3·5 h. Recently Roberts & Broadley (1967) reported that the main crystalline product usually obtained in this manner was not adnamine (I) but was identical to the product isolated previously by Funk & Freedman (1923) and Öppinger & Vetter (1942) and described as diadrenaline ether (III). Roberts & Broadley (1967) further reported that reasonable yields of adnamine (I) could consistently be obtained with stronger acids and longer reaction times than those employed by Kawazu. The production of adnamine (I) by this latter procedure, is, however, often accompanied by the copious formation of tarry by-products which complicates the isolation and purification of the product.

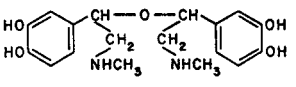
Recent work in these laboratories has shown that the product previously described as diadrenaline ether (III) does not have structure III but is, in fact, 6-(3′,4′-dihydroxy-α-methylaminomethylbenzyl)adrenaline (IV). The trivial name adrepine was proposed for this substance (Forrest, Kašpárek & others, 1969). Preliminary paper chromatographic evidence suggested that IV was an intermediate in the conversion



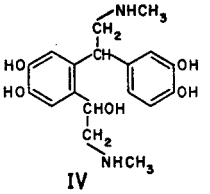
I



II



III



IV

of II into I. This conversion could be brought about by heating IV above its melting point or in solution in 10% hydrochloric acid. It has now been shown that good yields of pure adnamine can be consistently obtained by this latter procedure. The reaction parameters have been systematically varied and those giving the optimum yields of adnamine are described below.

Adrepine hydrochloride was prepared by the method used by Öppinger & Vetter (1942) to obtain "diadrenaline ether". A sample (500 mg) was dissolved in 10% hydrochloric acid [conc. HCl (2·85 ml) + water (7·15 ml)] and the solution heated, under reflux, on an oil bath at 95–100°. A colourless crystalline product began to crystallize out of the solution after about 2 h. After being maintained at this temperature for 5 h the reaction mixture was cooled and allowed to stand at 4° overnight and adnamine hydrochloride was obtained as a colourless crystalline solid. The product, obtained by filtration, was chromatographically homogeneous (n-butanol, saturated with 3N HCl) but was further purified by recrystallization from water or 70% ethanol. In this manner pure adnamine hydrochloride was obtained as colourless needles, m.p. 262–264°. λ_{max}^{EtOH}, nm (ϵ_{max}^{EtOH}): 215 (32,000); 235 (31,000); 312 (16,000). Found: C, 60·9; H, 5·4; N, 4·2; Cl, 10·65%, calc. for $C_{17}H_{18}O_4NCl$: C, 60·8; H, 5·4; N, 4·2; Cl, 10·6%. These values were obtained with a sample dried *in vacuo* at 120° for 1 h. Kawazu (1958) has reported that adnamine hydrochloride crystallizes from aqueous solution as a hemi-hydrate (m.p. 264–265°).

Adnamine exhibits an intense blue fluorescence in ultraviolet light. Solutions in dilute hydrochloric acid have excitation and fluorescence maxima at 310 and 395 nm respectively.

Atlantic Regional Laboratory,
National Research Council of Canada,
Halifax, Nova Scotia, Canada.

JANET E. FORREST
D. J. ROBERTS*
R. A. HEACOCK

June 27, 1969

* NRCC Visiting Scientist (1967). Permanent address: Department of Pharmacology, School of Pharmacy, Portsmouth College of Technology, Portsmouth, Hants, England.

REFERENCES

FORREST, J. E., KAŠPÁREK, S., HEACOCK, R. A. & FORREST, T. P. (1969). *Canad. J. Chem.*, **47**, 2118–2121.

FUNK, C. & FREEDMAN, L. (1923). *J. Am. chem. Soc.*, **45**, 1792–1795.

KAWAZU, M. (1958). *J. pharm. Soc. Japan*, **78**, 399–402.

ÖPPINGER, H. & VETTER, H. (1942). *Mednl. Chem.*, **4**, 343–367.

ROBERTS, D. J. & BROADLEY, K. J. (1967). *J. Chromat.*, **27**, 407–412.