TABLE I.—EFFECT OF ASPARTATE SALTS ON RESPIRATORY $C^{14}O_2$ PRODUCTION

Treatment	No. of Animals	Respired CO_2[a] 30 min.	60 min.	90 min.
Rested controls	5	2.18 ± 0.44	2.36 ± 0.62	1.75 ± 0.40
Swum controls	15	0.36 ± 0.15	0.62 ± 0.11	0.62 ± 0.25
K Asp. 30 mg./Kg.[b]	8	0.58 ± 0.32	0.96 ± 0.54	0.71 ± 0.25
P[c]		0.025	<0.025, >0.01	0.20
Mg Asp. 30 mg./Kg.	6	0.47 ± 0.32	0.66 ± 0.36	0.58 ± 0.22
P		0.15	0.35	...
K Asp. 15 mg./Kg. + Mg Asp. 15 mg./Kg.[d]	9	0.65 ± 0.40	0.91 ± 0.40	0.87 ± 0.18
P		0.05	<0.025, >0.01	<0.025, >0.01

[a] Means and standard deviations in $\mu c. \times 10^{-3}$ registered at the times indicated after injection of C^{14}-glucose. [b] Aspartate salts were given orally. [c] Significance of mean increase compared with swum controls by one-tailed *t*-test. [d] Spartase, Wyeth.

from the tank (discarding those which did not swim at least 15 minutes) 0.4 ml. of a solution containing 1.7 $\mu c.$ per ml. of uniformly labeled C^{14}-glucose in 2% nonradioactive glucose was injected into the external saphenous vein and the rat was placed in a closed glass chamber swept by 140 ml. of air per minute. The C^{14} content of the respired carbon dioxide was measured by passing the effluent air through the 250-ml. ionization chamber of a Nuclear-Chicago "Dynacon" electrometer connected to a 1 ma. linear recorder.

Representative data from the respired $C^{14}O_2$ curves for the controls and animals receiving individual and mixed aspartate salts are tabulated in Table I. The mean values for the control animals and those receiving the mixed salt are illustrated in Fig. 1, which demonstrates the essential factors observed in these experiments: (*a*) the length of the induction period before appreciable $C^{14}O_2$ is excreted (considerably prolonged in fatigued animals as compared with rested controls); (*b*) the considerably lower maximal rate of $C^{14}O_2$ evolution in the fatigued animals and the longer time taken to reach the maximal rate; (*c*) the differences in total $C^{14}O_2$ output as indicated by the areas under the curves; (*d*) the elevation of the curves of the treated animals above those of the fatigued controls.

Studies on the method are being continued in view of the fairly high degree of individual variation encountered, and glucose-1-C^{14} and glucose-6-C^{14} are being tried in the hope that one of these will result in a more specific response and also help to elucidate the mechanism.

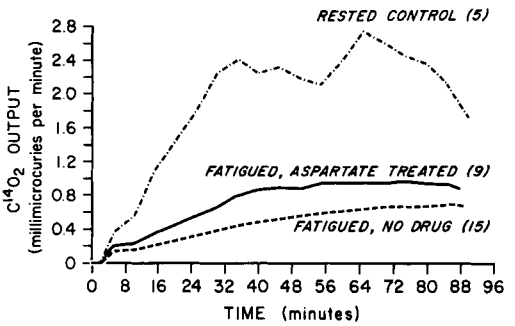

Fig. 1—Respiratory $C^{14}O_2$ output following C^{14}-glucose injection.

(1) Shaw, D. L., Chesney, M. A., Tullis, I. F., and Agersborg, H., *Am. J. Med. Sci.*, in press.
(2) Taylor, B. B., *Western Med.*, **2**, 535(1961).
(3) Kruse, C. A., *Northwest Med.*, **60**, 597(1961).
(4) Rosen, H., Blumenthal, A., and Agersborg, H. P. K., THIS JOURNAL, **51**, 592(1962).

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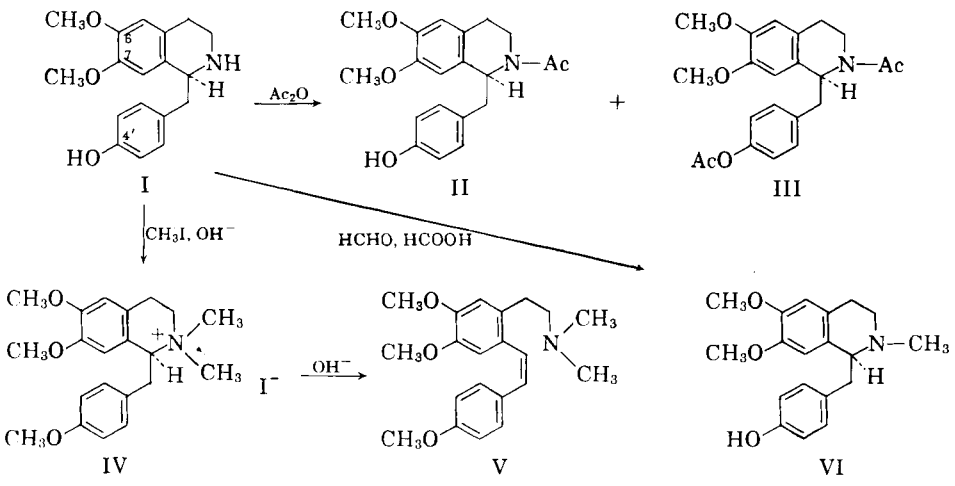
l-N-Norarmepavine

Sir:

Recent reports have described the isolation from Asiatic lotus, *Nelumbo nucifera* Gaertn. (*Nymphaeaceae*), of the alkaloids nuciferine (1, 2, 4), roemerine (2, 4), nornuciferine (2–4), and *dl*-armepavine (5). We report herewith the isolation from American lotus, *Nelumbo lutea* (Willd.) Pers. (*Nymphaeaceae*)[1] of the alkaloids nuciferine (0.046%), *dl*-armepavine (0.0046%), and an apparently new alkaloid (0.047%), to which we assign structure I and the name *l*-N-norarmepavine.

The new alkaloid, m.p. 152–153°, $[\alpha]_D^{25}$ − 23°

[1] Air-dried leaves and stems, collected in Wisconsin in 1959–1961. We thank Professor H. H. Iltis of the University of Wisconsin for confirming the identity of the plant. A voucher specimen is deposited in the University of Wisconsin Herbarium.



(c 1.33, $CHCl_3$), $[\alpha]_{546}^{26}$ − 40° (c 1.03, $CHCl_3$), λ_{max}^{EtOH} 228 mμ (ε 15,400), 282 mμ (ε 5,000), 287 mμ (ε 4,900), was shown to have the formula $C_{16}H_{15}NO(OCH_3)_2$.

Anal.—Calcd. for $C_{18}H_{21}NO_3$: C, 72.21, H, 7.07; N, 4.68; OCH_3, 20.73. Found: C, 72.06; H, 7.02; N, 4.89; OCH_3, 20.15; equiv. weight by titration with perchloric acid, 304.

Acetylation of I with acetic anhydride-pyridine, followed by chromatography on neutral alumina, gave an amorphous O,N-diacetate (III), IR bands at 5.70, 6.18 μ, and a crystalline N-acetate (II), m.p. 237–238°, IR band at 6.20 μ but none in the 5.6–6.0 μ region, soluble in dilute sodium hydroxide.

Anal.—Calcd. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 69.95; H, 6.82; N, 3.92.

The foregoing facts established that I possesses a phenolic hydroxyl group and an acylable amino group.

Exhaustive methylation of I gave the 1-(4′-methoxybenzyl) - 6,7 - dimethoxy - 2 - methyl-1,2,3,4-tetrahydroisoquinoline methiodide (IV), m.p. 127–129° (6–9). Treatment with alkali yielded the methine V, m.p. 86–87°, characterized by direct comparison (mixed m.p., IR) with an authentic sample (10). Methylation of I with formalin and formic acid yielded *d*-armepavine (VI), m.p. 139–140°, $[\alpha]_D^{25}$ + 91° (c 1.19, $CHCl_3$). The infrared spectrum of the methylation product in chloroform was superimposable upon that of a sample of *l*-armepavine, m.p. 140–141°, prepared by sodium-liquid ammonia reduction of cycleanine (11). Mixture of equal quantities of *d*- and *l*-armepavine and crystallization from acetone yielded *dl*-armepavine, m.p. 166–167°. The melting point was undepressed by admixture of the sample isolated from *N. lutea*, and the infrared spectra of the respective samples in chloroform were identical. Hence, the name *l*-N-norarmepavine is proposed for the new phenolic secondary base. A total synthesis of *dl*-1-(4′-hydroxybenzyl) - 6,7 - dimethoxy - 1,2,3,4 - tetrahydroisoquinoline has been reported (12).

Diazomethane methylation of *d*-armepavine (derived from *l*-N-norarmepavine) yielded a nonphenolic base, m.p. 62–63°, $[\alpha]_D^{28}$ + 79° (c 0.84, $CHCl_3$) which was identified as *d*-l-(4′-methoxybenzyl) - 6,7 - dimethoxy - 2 - methyl - 1,2,3,4-tetrahydroisoquinoline by direct comparison with an authentic sample (10). The latter compound has recently been shown to possess the L-configuration at C-1 (13).[2] Consequently, the absolute configuration of L-(*l*)-N-norarmepavine may be represented as in I.

(1) Arthur, H. R., and Cheung, H. T., *J. Chem. Soc.*, **1959**, 2306.
(2) Tomita, M., Watanabe. Y., Tomita, M., and Furukawa, H., *J. Pharm. Soc. Japan*, **81**, 469(1961).
(3) Tomita, M., Watanabe, Y., and Furukawa, H., *ibid.*, **81**, 942(1961).
(4) Tomita, M., Watanabe, Y., and Furukawa, H., *ibid.*, **81**, 1202(1961).
(5) Tomita, M., Watanabe, Y., and Furukawa, H., *ibid.*, **81**, 1644(1961).
(6) Konovalova, R., Yunusov, S., and Orekhov, A., *Ber.*, **68**, 2158, 2277(1935).
(7) Marion, L., Lemay, L., and Portelance, V., *J. Org. Chem.*, **15**, 216(1950).
(8) King, H., *J. Chem. Soc.*, **1940**, 737.
(9) Tomita, M., Fujita, E., and Murai, F., *J. Pharm Soc. Japan*, **71**, 226(1951).
(10) Fujita, E., and Tomimatsu, T., *ibid.*, **79**, 1260(1959).
(11) Fujita, E., and Murai, F., *ibid.*, **71**, 1043(1951).
(12) Yamaguchi, H., and Nakano, K., *ibid.*, **79**, 1106(1959).
(13) Tomita, M., private communication.

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