



density with the mercury cathode. Overvoltage or current density had little effect within the practicable region studied but temperature had a marked effect. At 27°, 16% current efficiency was obtained on a mercury cathode, while at 6° this dropped to 2.4%, which was about the equivalent of a fresh lead surface at 27°. This drop may have been due partly to a decrease in concentration of strychnine by precipitation at the low temperature. At 66° the current efficiency was surprisingly low, probably due to a change in surface conditions which interfered with the reduction.

The major reduction products were separated and analyzed. The ratio of strychnidine to tetrahydrostrychnine increased with an increase in temperature of reaction and with the length of reaction time. Total yields with the lead cathode were always much lower than reported in previous work. In contrast, about 70 to 80% reduction was obtained in ten to twelve hours with a mercury electrode under comparable reduction conditions and almost complete reduction was obtained in sixteen to twenty hours.

#### Methods

**Apparatus and Method of Reduction.**—In most of the work with the mercury cathode, 50 to 75 ml. of the catholyte was used in a tall cylinder. The mercury cathode had an area of 17.3 sq. cm. For comparative experiments metallic plates were cut to the exact diameter of the cell and set in paraffin in place of the mercury or sodium amalgam cathodes. A platinum anode of approximately the same surface area as the cathode completed the cell. An anode cup of alundum, 2.6 cm. in diameter, was held 2 to 3 mm. above the cathode surface; thus loss of catholyte was minimized and surface oxidation by spattering anolyte avoided. A 0.3 *M* solution of strychnine in 60% (by weight) sulfuric acid was used for most of the reductions. Sulfuric acid of the same concentration was present in the anode cup. Current was supplied through a variable potentiometer from a bank of 6 to 8 lead storage batteries.

**Analysis of Reduction Mixture.**—Small samples were removed at intervals during the reduction and diluted with oxidant-free concentrated sulfuric acid so that they contained between 0.01 and 0.3 mg. of reduced product per milliliter. To each was added an equal volume of standard nitrate solution ( $7.5 \times 10^{-5}$  molar in nitrate and 0.7 molar in hydrochloric acid) and allowed to stand for four to five hours in the dark. The specific absorption coefficient for the 5300 Å. band was determined with a Zeiss-Pulfrich photometer equipped with a 0 to 15-mm. variable depth comparison cell. The instrument had been calibrated with known concentrations of "reduced product" as well as with purified strychnidine. Since the reaction was nearly linear only up to about 15% reduced product, the relative current efficiencies were determined from the reaction curves between 5 and 15% reduction. This procedure

was shown to involve an average error of about 5% largely due to micro sampling difficulties and non-homogeneity of the reaction mixture.

**Separation of Reduction Products.**—The catholyte was immediately diluted with 0.01% sulfurous acid to a sulfuric acid concentration of 28.5% by weight and cooled to 6°. Unconverted strychnine was thus precipitated as the acid sulfate,  $C_{21}H_{22}O_2N_2 \cdot H_2SO_4 \cdot 2H_2O$ .<sup>8</sup>

The strongly acid filtrate was neutralized with ammonium hydroxide and cooled with ice until an amorphous precipitate of free alkaloid was obtained. The use of ammonium hydroxide rather than the customary alkalis facilitated the extraction of the water-soluble alkaloids. The free alkaloid precipitate contained mostly strychnidine and tetrahydrostrychnine with some strychnine and dihydro derivatives. Double extraction with water at 50 to 60° removed most of the soluble tetrahydrostrychnine and dihydro derivatives. The residue, containing the strychnidine, was recrystallized once from alcohol to remove the small amount of strychnine and complete the purification.

The tetrahydrostrychnine was the most difficult alkaloid to obtain pure. The major portion of the tetrahydrostrychnine was precipitated from the concentrated aqueous extracts by the addition of a large excess of ammonium hydroxide. Treatment of this filtrate with chloroform extracted an additional amount of tetrahydrostrychnine. The crude tetrahydrostrychnine was then extracted with a small amount of boiling absolute alcohol and on cooling most of the strychnine and strychnidine crystallized and were removed. Evaporation of the chloroform and alcohol extractions yielded the tetrahydrostrychnine. Several recrystallizations from ethyl acetate were necessary for even an approximate purification. Small amounts of other reduction products were difficult to remove and a brown amorphous substance, relatively soluble in alcohol, was always associated with this fraction. Usually the crude tetrahydrostrychnine was precipitated as tetrahydrostrychnine dipicrate for a rapid approximate analysis.

Dihydro derivatives were obtained in recoverable quantities only from the sodium amalgam reductions. These were separated along with the crude tetrahydrostrychnine from the water extracts. The high solubility of the dihydro derivatives in alcohol permitted their separation from the tetrahydrostrychnine. By successive recrystallizations from ethyl acetate and methanol, nearly pure dihydrostrychnidine was isolated.

## Results and Discussion

**Relative Current Efficiencies.**—The essential data of a number of the reductions on mercury, sodium amalgam and lead cathodes are shown in Table I. The average current was calculated from the ammeter readings taken at each sampling of the reduction mixture. The average reduction was taken from the reaction curve in which current had been plotted against quantity of reduced product. Typical curves are shown in Fig. 1.

(8) Benj. M. G. Zwicker and R. J. Robinson, *THIS JOURNAL*, **63**, 3538 (1941).

TABLE I  
COMPARATIVE INITIAL ELECTROLYTIC REDUCTION RATES

No.	Cathode	Temp., °C.	Current density amp./sq. cm.	Average current (equiv./min.) (10 <sup>3</sup> )	Average reduction (equiv./min.) (10 <sup>3</sup> )	% Current efficiency Relative	Over-all
XIX	Hg	6	0.044	47.6	1.1	2.4	0.5
XX	Hg	14	.043	46.0	4.0	8.7	2.2
XXI	Hg	25	.020	21.1	3.3	15.8	2.3
XXII	Hg	25	.044	47.2	7.3	15.5	2.3
XXIII	Hg	66	.044	47.9	3.4	7.0	1.1
XXIV	Na-Hg	34	.040	49.7	10.9	21.9	2.3
XXVI	Na-Hg	42	.046	46.0	15.6	33.9	2.2
XXVII	Pb	29	.040	42.0	1.1	2.6	0.3

The effect of temperature on the initial reaction rate is apparent from the values observed on mercury cathodes. The efficiencies reported for the sodium amalgam must be considered less accurate than the others, since dihydro derivatives were formed at the same time. The highest over-all efficiency obtained on a lead cathode was 0.34% with 50% reduction in seventy hours, which was considerably less than reported by Clemo, Perkin and Robinson. The over-all efficiency for the mercury electrode was several times higher.

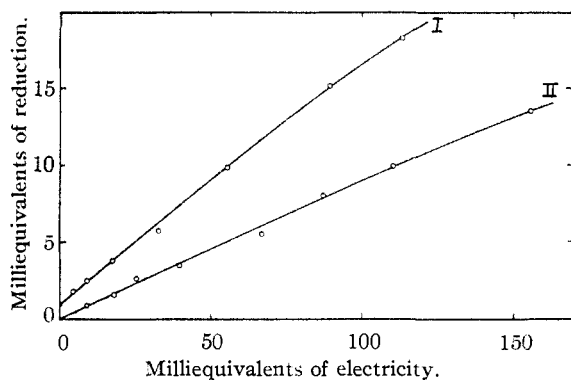


Fig. 1.—Representative rates of electrolytic reduction on mercury cathodes: I, 25°; II, 14°.

**Reduction Products.**—The analyses of several catholytes are summarized in Table II. While the data are only approximate, they are quite useful for making comparisons. In reductions XVIII, XIX and XX the catholyte was heated to 50 to 60° before dilution to increase the yield of strychnidine. However, oxidation occurred even in the presence of sulfurous acid. Reductions III and IV were made in an apparatus of the type used by previous authors. In the sodium amalgam reductions, the dihydro derivatives, mostly isolated as dihydrostrychnidine, constituted one-quarter to one-third of the total reduced strychnine.

Details of the following reduction are typical: 9.49 g. of Merck U. S. P. XI strychnine sulfate (7.40 g. of strychnine) was dissolved in 30 ml. of distilled water and 45 g.

TABLE II  
ELECTROLYTIC REDUCTION PRODUCTS OF STRYCHNINE

No.	Cathode	Temp., °C.	Current density, amp./sq. cm.	Time, hours	% Strychnine reduced	Strychnidine, Tetrahydrostrychnine
III	Pb	30	0.020	50	52	1.9
IV	Pb	25	.021	47	37	2.0
XXVII	Pb	29	.040	55	24	4.1
XV	Hg	8	.049	49	24	0.5
XIX	Hg	7	.044	46	24	1.4
XX	Hg	14	.043	31	86	3.8
XVIII	Hg	15	.165	32	97	2.9
XVII	Hg	25	.044	20	98	1.3
XXII	Hg	25	.044	35	100	1.5
XXI	Hg	25	.020	32	49	6.5
XVI	Hg	27	.047	14	94	1.4
XXIII	Hg	66	.044	20	34	5.7

of sulfuric acid, sp. gr. 1.84. The solution was cooled and the temperature controlled to within a degree of 25° during reduction. The current was maintained at 0.75–0.76 ampere (0.043–0.044 amp./sq. cm.) by a terminal potential of 4.9 volts and a cathode/catholyte potential of 2.9 volts.

The exposed cylinder walls soon became reddish from air oxidation of the spray. A clear crystalline precipitate persisted until near the completion of the reduction. The diminution of the Otto<sup>9</sup> fading purple test for strychnine in 60% sulfuric acid became apparent after eleven to twelve hours, and after sixteen hours only a faint test was observed. In more concentrated acid, however, the transient purple was still visible, even after thirty-five hours of reduction.

**Separation of the Reduced Products.**—After thirty-five hours the catholyte was siphoned into 83 ml. of 0.01% sulfurous acid. No strychnine acid sulfate separated. The acid was neutralized with concentrated ammonium hydroxide after 100 to 200 g. of ice had been added. Excess ammonia was removed by heating at 40 to 50° for half an hour. The granular precipitate was filtered and extracted twice with 100-ml. portions of water at 40 to 50° to remove the tetrahydrostrychnine.

The crude strychnidine remaining weighed 4.48 g. when vacuum dried over sulfuric acid at 20°. It dissolved in 100 ml. of boiling 95% ethanol and, when cooled to 6°, 3.92 g. of microscopic needles separated, m. p. 253–254° *in vacuo*. These, upon recrystallization from 50 ml. of thiophene-free benzene, yielded long, clear, tetragonal crystals, m. p. 256.5° *in vacuo*.

(9) F. Otto, *Ann.*, **60**, 273 (1846).

The aqueous extracts and filtrate were evaporated under vacuum at 60° to a volume of 100 ml. A buff precipitate of impure tetrahydrostrychnine, weighing 2.83 g., was obtained by the addition of a large excess of ammonium hydroxide. The ammoniacal filtrate yielded 0.195 g. of dipicrate of tetrahydrostrychnine which exploded at 222° *in vacuo*.

The impure tetrahydrostrychnine was dissolved in the alcoholic mother liquor from the strychnidine crystallization, evaporated to 40 ml. and cooled to 6°. Impure strychnidine, m. p. 245–247°, weighing 0.38 g. separated. The alcoholic solution was entirely evaporated and 3.00 g. of impure tetrahydrostrychnine was obtained as a brown amorphous mass, melting slowly between 180–187° *in vacuo* to a reddish brown sirup. Precipitation by an excess of potassium iodide from 0.1 *N* sulfuric acid solution gave 4.72 g. of dried hydriodide. Chloroform extraction of the strongly ammoniacal paste followed by alternate crystallizations from ethanol and ethyl acetate gave 2.15 g. of nearly colorless tetrahydrostrychnine, m. p. 200–202° *in vacuo*. A brown amorphous mass of undetermined composition accumulated in the soluble fractions; 0.2 g. of strychnidine was removed from the more insoluble fractions.

**Conversion of Tetrahydrostrychnine to Strychnidine.**—Two grams of crude tetrahydrostrychnine was treated with ten times its weight of phosphorus oxychloride in a stream of carbon dioxide. After refluxing for forty-five minutes at 60–70° under partial vacuum, the excess reagent was removed by vacuum distillation in the presence of carbon dioxide. The residual brown sirup was carefully diluted with 30 ml. of 0.01% sulfurous acid. Ten ml. of a 20% potassium iodide solution was added and the mixture cooled to 5°. The microcrystalline precipitate was dissolved in hot water, made strongly ammoniacal and extracted with chloroform. The extracts were dried and the brown mass was crystallized from benzene to give 1.72 g. of crude strychnidine, m. p. 248–250° *in vacuo*. Slow recrystallization from benzene gave pure strychnidine, m. p. 256–257° *in vacuo*.

**Properties of Reduction Products.**—At 25° 2.37 g. of strychnidine was soluble in 100 g. of 95% ethanol, 4.53 g. in 100 g. of benzene and 1.45 g. in 100 g. of ethyl acetate. The methoxy dihydrostrychnidine, prepared from alkaline alcoholic hydrolysis of the strychnidine methosulfate, is the most characteristic derivative.<sup>10</sup> No trace of violet coloration formed in 94% sulfuric acid on addition of a trace of chromic acid but a stable crimson color appeared immediately on dilution to 80%.

Strychnidine after five recrystallizations from benzene gave long, clear tetragonal prisms, m. p. 256.7° *in vacuo*, to

(10) A. E. Oxford, Wm. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, 2389–2410 (1927).

a colorless sirup; 0.1002 g. of this gave 0.1501 g. of methiodide from benzene with methyl iodide; calcd. 0.1498 g.; 34.25 mg. gave 17.44 mg. of AgI; calcd. 27.45% I, obs. 27.53% I.

Tetrahydrostrychnine was purified by several recrystallizations from ethyl acetate and ethyl alcohol after precipitation as the hydriodide from dilute acid solution. It slowly lost one molecule of alcohol or ethyl acetate of crystallization at 110° but not in vacuum at room temperature. The acetyl derivative, prepared with acetyl chloride or acetic anhydride, was easily identified as a brown varnish soluble in ether, giving a purple Otto strychnine reaction. Considerable strychnidine was formed during the reaction.

1.6352 g. of vacuum-dried tetrahydrostrychnine crystallized from ethyl alcohol lost 0.1421 g. at 110°. For one alcohol of crystallization, calcd. 8.83%; obs. 8.69%. The residue, m. p. 202–204° *in vacuo*, recrystallized from ethyl acetate, gave 1.7549 g. of monoclinic needles which lost 0.2601 g. at 110°; for one ethyl acetate, calcd. 15.03%; obs. 14.83%. 0.0994 g. of pure base gave 0.1489 g. of vacuum dried methiodide from anhydrous methyl alcohol and excess methyl iodide; calcd. 0.1411 g. for C<sub>21</sub>H<sub>26</sub>O<sub>2</sub>N<sub>2</sub>·CH<sub>3</sub>I. At 100° the salt slowly lost weight. 36.63 mg. gave 18.30 mg. silver iodide; calcd. 26.62% I, obs. 27.03% I.

Dihydrostrychnidine, m. p. 214–215° *in vacuo*, crystallized as colorless to yellowish leaflets and plates from anhydrous methanol.

### Summary

Solid metallic cathodes were found to be quite inefficient in the electrolytic reduction of strychnine.

In 60% sulfuric acid, a mercury cathode gave strychnidine and tetrahydrostrychnine in excellent yields. The ratio of the two could be varied by varying the temperature and length of reduction.

Sodium amalgam cathodes gave 20 to 30% dihydrostrychnidine and an even greater rate of reduction than mercury.

The separation of strychnine as an acid sulfate in 28.5% sulfuric acid solution was found to be critical.

A procedure for separation of the reduction products was recommended, based on solubility relationships.

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