Controlled Potential Coulometric Analysis of Amine-Oxides of Pharmaceutical Interest

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Abstract □ Controlled potential coulometry was shown to be a valuable technique for the quantitative determination of certain amine-oxides. From 98 to 100% of chlordiazepoxide and the *N*-oxides of atropine, brucine, 3-bromopyridine, scopolamine, and strychnine was recovered.

Keyphrases □ Amine-oxides—quantitative analysis by controlled potential coulometry □ Electrolyses, controlled potential—quantitative analysis of amine-oxides □ Coulometry, controlled potential—quantitative analysis of amine-oxides

The polarographic reduction of a considerable number of amine-oxides has been reported, including chlordiazepoxide (1, 2), diazepam (3), adenine-*N*-oxide (4, 5), phenazine-*N*-oxide (6), and amine-oxides having a pyridine or quinoline nucleus (7–9). Foffani and Fornasari (10) reported the appearance of a single wave during the reduction of pyridine-*N*-oxide, this being produced by the cationic form. Later these workers (11) reported that the amine-oxide is reduced more readily when conjugation of its bond with the ring is lessened. Emerson and Rees (9) confirmed that diminished conjunction results in a lowered reduction potential.

Although these polarographic studies indicate the feasibility of controlled potential reduction of *N*-oxides, quantitative studies have not been reported.

Table I—Percentage Recovery of Atropine-*N*-oxide by Controlled Potential Coulometric Analysis under Varying Conditions

Sample, mg.	pH	Potential, v.	Recovery, %
19.3[a]	0.40	−0.9	99.0
19.3	0.40	−0.9	96.4
19.3	0.40	−0.9	97.7
38.6	0.40	−0.9	97.0
38.6	0.40	−0.9	97.0
19.3	0.88	−0.9	99.4
19.3	0.88	−0.9	95.8
19.3	0.88	−0.9	99.6
38.6	0.88	−0.9	96.5
38.6	0.88	−0.9	99.9
38.6	0.88	−0.9	93.5
38.6	0.88	−0.9	99.3
19.3	1.57	−1.0	100.7
19.3	1.57	−1.0	97.9
19.3	1.57	−1.0	99.3
38.6	1.57	−1.0	100.0
19.3	2.71	−0.9	93.7
19.3	2.71	−0.9	91.9
19.3	2.71	−1.0	95.7
19.3	2.71	−1.0	95.8
19.3	2.71	−1.0	95.8
38.6	2.71	−1.0	100.0
38.6	2.71	−1.0	97.0
19.3	4.63	−1.0	96.9
19.3	4.63	−1.0	94.7
19.3	4.63	−1.0	96.1

[a] Equivalent to 5.00×10^{-5} *M* atropine-*N*-oxide.

Table II—Percentage Recovery of Amine-Oxides by Controlled Potential Coulometric Analysis

Compound	Potential, v.	pH	Recovery, %[b]
Atropine-*N*-oxide	−1.00	1.57	99.3 ± 1.4
Brucine-*N*-oxide	−1.05	4.63	100.0 ± 2.5
3-Bromopyridine-*N*-oxide	−0.80	0.88	98.5 ± 0.4
Chlordiazepoxide[a]	−0.30	0.40	99.5 ± 0.3
Scopolamine-*N*-oxide	−0.75	4.63	98.0 ± 3.0
Strychnine-*N*-oxide	−0.90	0.88	98.0 ± 0.7

[a] Supplied by Hoffmann-La Roche, Inc. [b] Sample concentration 5×10^{-5} *M*.

EXPERIMENTAL

Equipment—Controlled potential electrolyses were performed using an electronic controlled potential coulometric titrator, model Q-2005, ORNL (12). A Non-Linear Systems digital voltmeter, model 484 A, displayed the readout voltages. Reductions were accomplished in a 125-ml. cell having a 30-ml. mercury pool as the working electrode (cathode). The surface area of the pool was 16 cm.^{2} at rest. Compartments for the saturated calomel reference electrode and the platinum wire nonworking electrode (anode) were isolated from the cathode chamber by glass frits and potassium nitrate-agar plugs. Nitrogen was bubbled through the solution during runs. A four-bladed impeller driven by a Sargent synchronous rotator served to agitate the surface of the mercury pool.

Solvents—Solvents utilized in the study were sulfuric acid–potassium sulfate systems of pH 0.40, 0.88, 1.57, and 2.71, and an acetic acid–sodium acetate system of pH 4.63. A solute concentration of 5×10^{-5} *M* was selected for the work.

Assay Procedure—The solvent was degassed with nitrogen, and the titrator was switched on until a steady current resulted. The titrator was then switched off, and a weighed sample was added to the cell and dissolved. The titrator and the timer were switched on simultaneously and allowed to run until there was no further decrease in the current. The readout voltage and time were recorded, and the readout due to the reduction of polarized water molecules was determined from the background. This was subtracted from the total readout; the equivalents of sample were then calculated by use of a previously determined instrumental calibration factor.

RESULTS AND DISCUSSION

The most effective reduction potential for the quantitative recovery of a given compound was a function of the pH, as demonstrated by the experimental results for atropine-*N*-oxide (Table I). Mean values, based on these data, demonstrate this reduction potential–pH relationship even more clearly. With a reduction potential of −0.9 v. (*versus* saturated calomel electrode) at pH's 0.40, 0.88, and 2.71, the percent recoveries are 97.7 ± 1.3, 98.3 ± 1.7, and 93.3 ± 1.4, respectively. With a reduction potential of −1.0 and pH's 1.57, 2.71, and 4.63, recoveries are 99.3 ± 1.4, 95.8 ± 0.05, and 95.9 ± 0.90%, respectively.

Results, under optimum conditions, for those *N*-oxides successfully determined are shown in Table II. Pyridine-*N*-oxide, 2,6-lutidine-*N*-oxide, and quinoline-*N*-oxide gave meaningless recoveries since their amine-oxide reduction waves overlapped the catalytic hydrogen wave.

Samples of less than 5×10^{-5} mole were not used because weighing errors adversely affected the accuracy of the coulometric results. Utilization of samples significantly greater than 5×10^{-5} mole led to unacceptably long coulometric reduction periods.

Vigorous agitation of the mercury pool surface during coulometry was critical. Decreased current efficiency resulted if the vigorous agitation was not maintained.

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Chemistry and Pharmacological Evaluation of 1-Phenyl-2-propanols and 1-Phenyl-2-propanones

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Abstract □ Various ring-methoxylated 1-phenyl-2-propanols and 1-phenyl-2-propanones were synthesized and pharmacologically evaluated. Most compounds had depressantlike activity. The ketones were readily reduced by rabbit liver microsomes. No reductase activity was found in rat and mouse liver preparations. Partition coefficients were determined, and a linear correlation between LRA_{50}'s (loss of righting ability in 50% of the mice) and partition coefficients was observed for six of the compounds investigated.

Keyphrases □ 1-Phenyl-2-propanols, 1-phenyl-2-propanones, derivatives—synthesis, pharmacological evaluation as psychotomimetic agents □ Partition coefficients—1-phenyl-2-propanols, 1-phenyl-2-propanones, derivatives □ Structure–activity relationships—1-phenyl-2-propanols, 1-phenyl-2-propanones, derivatives □ TLC—identification □ GLC—analysis

In the study of psychotomimetic agents, the identity of active chemical species has been the subject of controversy. Harley-Mason *et al.* (1) suggested that the hallucinogenic action of mescaline was caused by a metabolite. Goldstein *et al.* (2) isolated 3,4,5-trimethoxyphenylethanol (I) as a product of mescaline metabolism. When I was injected into rabbits, a mescalinelike effect was observed. They proposed that the corresponding aldehyde, 3,4,5-trimethoxyphenylacetaldehyde (II), was the "active" intermediate.

Since methoxylated amphetamines are psychotomimetics related to, and generally more potent than, mescaline (3), it was decided that the oxygen analogs of methoxylated amphetamines, namely 1-phenyl-2-propanols (III) and 1-phenyl-2-propanones (IV), be synthesized and their pharmacology examined. Recent studies on the metabolism of amphetamine revealed that significant amounts of IV*a* are excreted by rabbits, while small amounts are excreted by man (4).

Initial studies were conducted on 1-(3,4-dimethoxyphenyl)-2-propanol (III*c*), which was found to have an immediate, but short-lived, depressantlike effect on a conditioned avoidance response in the rat (5). Encouraged by this action, a systematic study of the series was begun. The effects of ring methoxylation on potency, metabolism, and partition coefficients are reported here.

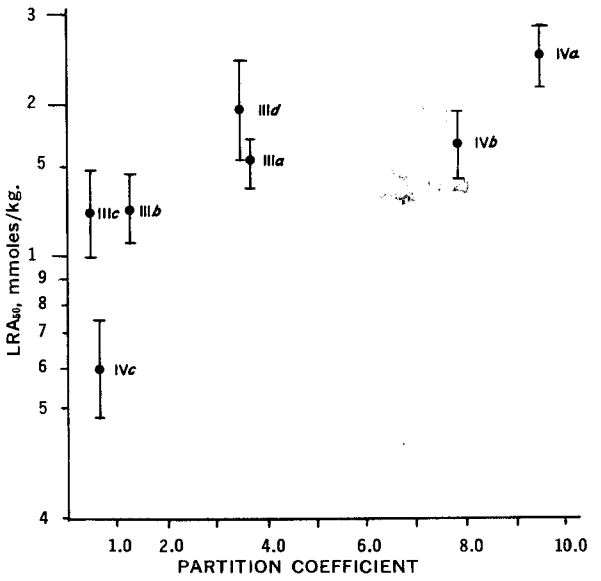

Figure 1—*Plot of* LRA_{50}*'s* versus *partition coefficients. For* n = 6 *(excluding IVc), the correlation coefficient = 0.84.*