that at ionic strengths 0.2 and 0.4 the measurements have not been extended to sufficiently low protein concentrations to exclude a further downward curvature to lower sedimentation constants, such a possibility is minimized by the behavior at 0.1 ionic strength. Although the latter data cannot be precisely extrapolated, they do show a trend toward a common intercept with the data obtained at the higher ionic strengths. It must be concluded, therefore, that in the presence of phosphate buffer *p*H 2.6, the extrapolated sedimentation constant of bovine insulin is in agreement with a molecular weight of 12,000.

Acknowledgment.—We are indebted to Mr. Roger M. Wade for the performance of sedimentation measurements.

DEPARTMENT OF BIOCHEMISTRY
UNIVERSITY OF WASHINGTON
SEATTLE 5, WASHINGTON

The Relative Catalytic Activity of Nickel Produced by the Reduction of Nickel(II) Bromide with Liquid Ammonia Solutions of Different Alkali Metals[1]

BY GEORGE W. WATT AND PEGGY I. MAYFIELD

RECEIVED NOVEMBER 1, 1952

Burgess and co-workers have reported marked differences in both the chemical and catalytic activity of silver and nickel precipitated by the reduction of salts with solutions of metals in liquid ammonia at its normal boiling temperature. Thus, the reduction of certain silver salts with solutions of potassium yielded silver far more active than that which resulted when sodium was employed.[2] Similar differences were observed in studies involving the reduction of silver salts with solutions of calcium[3] and in the reduction of nickel salts with sodium, potassium and calcium.[4] No explanation of these differences was proposed by Burgess, *et al.*, and since similar observations have been made in our laboratories it seemed worthwhile to carry out somewhat more definitive experiments.

In view of the presently accepted interpretation of the physical nature of solutions of metals in liquid ammonia,[5] it seems unlikely that differences in the properties of these reduction products are attributable to any inherent differences in the nature of the metal solutions. Rather it is more likely that both the chemical and catalytic activities of the reduction products are determined by rate factors and solubility relationships.

Although both the rates of solution of the alkali and alkaline earth metals in ammonia and the rates of the ensuing reactions with nickel(II) bromide are too rapid for accurate measurements, our experiments show qualitatively that both of these rates increase from lithium to cesium. Furthermore, the solubilities of the by-products (alkali bromides and amides) increase in the same direction. Thus, one obtains from the corresponding reactions, elemental nickel that is different in only one important respect, namely, surface area. This is shown by the fact that for the products obtained using lithium, sodium, potassium, rubidium and cesium as the reducing metals, catalytic activity per unit surface area is substantially constant. The relative insolubility of the by-products obtained using calcium obviated a rigorous comparison including this metal.

Burgess and Eastes[4] have attributed the pyrophoric character of the elemental nickel so-produced to the presence of adsorbed hydrogen. While all of the products prepared in our studies were pyrophoric in a degree that increased from lithium to cesium, the corresponding quantities of adsorbed hydrogen per unit weight of metal showed no consistent trend.

Experimental

Materials.—Hexamminenickel(II) bromide was prepared as described by Watt.[6] All other materials were commercial reagent grade chemicals.

Reduction Reactions.—The equipment and procedures employed were in all respects the same as those described previously[7] except that lithium was maintained in an atmosphere of nitrogen prior to addition to the solution and suspension of nickel(II) bromide, and that rubidium and cesium were added in fragile glass ampoules that were subsequently crushed.

When samples of hexamminenickel(II) bromide of the order of 2.5 g. in 15–20 ml. of liquid ammonia at −33.5° were treated with alkali metals (*ca.* 10% in excess of that required for complete removal of bromide ion), both the rates of solution of the alkali metals and the rates of the ensuing reactions with the bromide were quite evidently dependent upon the alkali metal employed. *Approximate* total times that elapsed between the addition of the alkali metal and the disappearance of the blue color characteristic of solutions of these metals in ammonia were as follows: Li, 5 min.; Na, 20 sec.; K, 10 sec.; Rb, < 10 sec.; Cs, << 10 sec. Following completion of the reactions, the ammonia-insoluble products were washed with liquid ammonia, with ethanol, and thereafter handled out of contact with the atmosphere and under strictly anhydrous conditions.

Properties of the Reduction Products.—By methods previously described,[7] the highly pyrophoric ammonia-insoluble products were analyzed for nickel, nitrogen, bromine and

TABLE I

PROPERTIES OF PRODUCTS FROM THE REDUCTION OF NICKEL (II) BROMIDE WITH ALKALI METALS IN LIQUID AMMONIA

	Ammonia-insoluble product				
Alkali metal	Ni, %	H_2, cc./g.	Surface area, m.^{2}/g.	Reaction rate	Rate/unit area
Li	82.3	17.6	30[a]	1.6	0.05
Na	93.6	7.5	27	3.1	.11
K	92.0	18.7	54	3.8	.07
Rb	90.4	10.4	105	8.8	.08
Cs	83.9	2.1	127	9.1	.07

[a] This value was determined using a sample washed with liquid ammonia but not with ethanol and involves a correction for an initial rapid uptake of ammonia during the surface area determinations. This was attributed to the ammonation of impurities present and the validity of this procedure was confirmed by a surface area estimate obtained from electron photomicrographs of an ethanol-washed product which showed an average particle radius of 88 Å. and led to a computed surface area of 38 m.^{2}/g.

---

(1) This work was supported, in part, by the Office of Naval Research, Contract N6onr-26610.

(2) W. M. Burgess and F. R. Holden, THIS JOURNAL, **59**, 459 (1937).

(3) W. M. Burgess and F. R. Holden, *ibid.*, **59**, 462 (1937).

(4) W. M. Burgess and J. W. Eastes, *ibid.*, **63**, 2674 (1941).

(5) W. C. Johnson and A. W. Meyer, *Chem. Revs.*, **8**, 273 (1931); *cf.* W. L. Jolly, *ibid.*, **50**, 351 (1952).

(6) G. W. Watt, "Inorganic Syntheses," Vol. II, McGraw-Hill Book Co., Inc., New York, N. Y., 1950, p. 194.

(7) G. W. Watt, W. F. Roper and S. G. Parker, THIS JOURNAL, **73**, 5791 (1951).

alkali metal after washing with ammonia, and usually only for nickel following washing with ethanol. In addition to surface area measurements, the quantities of hydrogen associated with the reduction products were determined. Catalytic activity was evaluated in terms of catalysis of the hydrogenation of allyl alcohol. The essential data are given in Table I, in which the catalytic activity of the nickel is expressed as the rate (in millimoles H_2 consumed/min./g. of catalyst) of the catalyzed hydrogenation reaction and the numerical values of which are taken from those portions of the corresponding rate curves over which the rates were substantially linear with time. In all cases this condition prevailed over at least three-fourths of the total reaction time.

Reduction Reactions Employing Calcium.—Similar reduction reactions employing excess calcium occurred at about the same rate as those involving lithium. Owing to the insolubility of calcium amide[8] and calcium bromide,[9] purification of the nickel by washing with liquid ammonia was ineffective. The composition of a typical ammonia-insoluble product was as follows: Ni, 17.4; Br, 44.0; N, 21.4; Ca, 11.7. Although 16% excess calcium was used in this particular case, unreacted hexamminenickel(II) bromide was present. Washing with ethanol was only partially effective as a means of purification and no means was found to purify the products without eliminating the catalytic activity of the elemental nickel present.

---

[8] F. W. Bergstrom, *Ann.*, **515**, 34 (1934).

[9] M. Linhard and M. Stephan, *Z. physik. Chem.*, **167**, 87 (1933).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF TEXAS
AUSTIN 12, TEXAS

The Synthesis of Aryl and Aralkyl Amidines of Pharmacologic Interest[1]

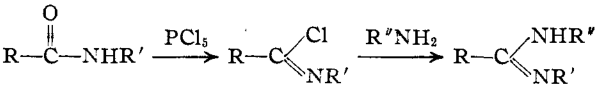
BY GEORGE L. WEBSTER AND JACOB S. RODIA[2]

RECEIVED AUGUST 14, 1952

In a previous paper from this Laboratory[3] it was shown that hydrochlorides of methoxysubstituted benzamidines possessed local anesthetic activity. The fact that all of these compounds produced sloughing of tissue at the site of injection suggested the desirability of preparing a new series of amidines in an effort to eliminate the undesirable toxicity.

Since most local anesthetics require the use of a vasoconstrictor agent to increase the duration of anesthesia, it also appeared of interest to investigate whether the incorporation in the amidine molecule of the β-phenylethylamine skeleton would give rise to a substance having both local anesthetic and vasoconstrictor properties.

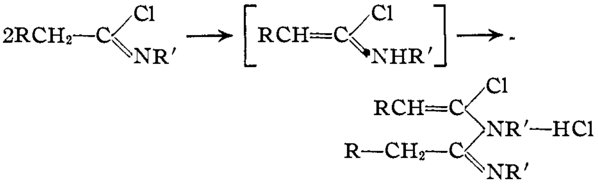
This paper deals with the synthesis of a number of new N,N'-disubstituted amidines. The amidines listed in Table I were prepared by a modification of the method of Hill and Cox[4] in yields ranging from 43 to 81%.



$$R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}NHR' \xrightarrow{PCl_5} R{-}C\genfrac{}{}{0pt}{}{\diagup Cl}{\diagdown\!\!\diagdown NR'} \xrightarrow{R''NH_2} R{-}C\genfrac{}{}{0pt}{}{\diagup NHR''}{\diagdown\!\!\diagdown NR'}$$

In the preparation of the amidines numbered 1, 2, 4, 5 and 6 in Table I, the phosphorus oxychloride formed by the interaction of the acylamino compound and phosphorus pentachloride was removed under reduced pressure prior to the addition of the amine. This procedure was found to be essential to the synthesis of the amidines (1 and 2), since their preparation required the use of an aminophenol with an unprotected phenolic group. In the other cases, this modification was adopted in order to shorten the time during which the β-phenylethylamide would be in contact with the phosphorus halide. It is known[5] that β-phenylethylamides are cyclized by phosphorus halides to the corresponding 3,4-dihydroisoquinoline derivatives.

Since the imidochlorides are very unstable and readily change into chlorovinylamidinium chlorides,[6] probably according to the reaction



it was necessary in the preparation of the disubstituted phenylacetamidines to conduct the conversion of the starting anilide into the imidochloride in the presence of the arylamine. By employing the method of Hill and Cox such a change was prevented and the expected disubstituted phenylacetamidine obtained in good yield.

In the preparation of the vanillamidines it was found that the carbethoxyl group proved to be satisfactory for the protection of the phenolic hydroxyl group. Its subsequent removal was easily accomplished with dilute alkali without affecting the amidine.

Experimental

Carbethoxyvanilloylanilide.—Vanillic acid, m.p. 207°, prepared from vanillin by the method described by Pearl,[7] was carbethoxylated according to the procedure given by Heap and Robinson.[8] A solution of 60 g. of carbethoxyvanillic acid in 150 ml. of thionyl chloride was boiled for 45 minutes or until active evolution of hydrogen chloride ceased. After removal of the excess reagent under reduced pressure, the residue was dissolved in 100 ml. of anhydrous ether, cooled and 45 ml. of aniline in 100 ml. of anhydrous ether was gradually added with stirring. The white solid which consisted of aniline hydrochloride and the desired anilide was successively washed with 100-ml. portions of water, dilute alkali, dilute acid and water. The product was recrystallized from 95% alcohol, filtered by suction and dried; yield 62.0 g., m.p. 132–133°.

Anal. Calcd. for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.44; N, 4.44. Found: C, 64.70; H, 5.42; N, 4.39.

Preparation of the Amidines.—One and one-tenth molecular proportion of phosphorus pentachloride in 50 ml. of sodium-dried benzene was heated on a water-bath under reflux until active evolution of hydrogen chloride ceased. The solution was cooled and 0.03–0.05 mole of the anilide was added. In the preparation of amidines numbered 5 and 6, the imidochloride was formed in the absence of the solvent using one molecular proportion of phosphorus pentachloride. The reaction mixture was then heated for two hours on a water-bath, after which the solvent and the phosphorus oxychloride formed during the reaction were removed

---

[1] An abstract of a thesis submitted by J. S. Rodia to the Graduate College of the University of Illinois in partial fulfillment of the requirements for the Degree of Doctor of Philosophy.

[2] American Foundation for Pharmaceutical Education Fellow, 1951–1952.

[3] M. J. Sintov, *et al.*, THIS JOURNAL, **71**, 3990 (1949).

[4] A. J. Hill and M. V. Cox, *ibid.*, **48**, 3215 (1926)).

[5] R. Adams, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 74.

[6] J. V. Braun, F. Jostes and A. Heymons, *Ann.*, **453**, 113 (1927).

[7] I. Pearl, THIS JOURNAL, **68**, 2180 (1946).

[8] T. Heap and R. Robinson, *J. Chem. Soc.*, 2341 (1926).