Reduction Experiments.—A mixture of 10 ml. of water, 1.0 g. of sodium hydrosulfite, and 0.5 g. of codeinone was refluxed ten minutes, cooled, made alkaline with ammonia, and extracted with ether. From the dried solvent 0.1–0.2 g. of white residue was recovered. Though not all of the alkaloid was removed from the aqueous phase, an acidified portion gave a negative Mayer test. Perhaps the alkaloid is converted by this treatment in part to compounds similar to the codine oxide sulfonic acids. The ether-soluble residue was only partially soluble in ethyl acetate. Furthermore, the soluble material gradually underwent a change as indicated by its increasing insolubility in this solvent. Its melting point was 140–165°. Although it has been reported that under such conditions codeinone is reduced quantitatively to codeine[12,13] none of the latter was found to result from the above treatment.

A mixture of 0.50 g. of codeinone, 1.43 g. of 42% aqueous hydrazine and 10 ml. of absolute alcohol was heated at 70°. The mixture soon became yellow. After fifteen minutes, it was diluted with water and cooled. The yellow amorphous product which separated furnished no crystalline material from aqueous alcohol and was insoluble in ether.

Acid Transformation Product.—A solution of 7.5 g. of codeinone in 750 ml. of *N* hydrochloric acid was set aside for thirty days, made neutral with solid potassium carbonate, and extracted twice with 150-ml. volumes of chloroform to remove unreacted codeinone. The aqueous phase was made strongly alkaline with carbonate and extracted several times more with chloroform. Recovered from the chloroform, the base (about 3 g.) was crystallized three times from ethyl acetate: irregular plates, m. p. 200° $[\alpha]^{20}D$ −135° (*c*, 0.92, alcohol). The base is soluble in alcohols and water as well as in chloroform and hot ethyl acetate; insoluble in ligroin. Inasmuch as it gives a red color with diazosulfanilic acid, it is presumably phenolic.

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.7; H, 6.73; N, 4.44. Found: C, 68.7, 68.6; H, 6.72, 6.84, N, 4.50.

With hydroxylamine hydrochloride it gave a salt, m. p. 262° (*in vacuo*), which on basification furnished what is presumed to be the free oxime, m. p. 274°. The analytical data for this derivative appear anomalous and are, therefore, reserved.

The dihydro derivative is obtained in good yield by hydrogenation of the new product in alcohol using Adams catalyst. Three crystallizations from ethyl acetate afforded pure material: stout hexagons and prisms, m. p. 207°; $[\alpha]^{20}D$ −115° (*c*, 0.8, alcohol). With diazosulfanilic acid it furnished a red dye, presumably a phenol.

Anal. Calcd. for $C_{18}H_{23}NO_4$: C, 68.2; H, 7.32. Found: C, 68.3; H, 7.32.

Chromate of Neopine.—When a warm solution containing stoichiometric quantities of neopine hydrobromide and potassium chromate was cooled, neopine hydrobromide precipitated. The chromate obtained from a concentrated solution of the hydrochloride and potassium chromate was obtained in relatively small amount and was contaminated by darker products from the spontaneous degradation of this salt.

Chromate of Dihydrocodeine.—Dilute (1 *N*) hydrobromic acid was added to the base until the solution was only slightly basic to methyl red. Then a slight excess of solid potassium chromate was dissolved in this solution; yellow, transparent rhombohedra of the chromate separated on standing. These effloresce in air to opaque, chrome yellow prisms.

Anal. Calcd. for $(C_{18}H_{24}O_3N)_2CrO_4$: C, 60.1; H, 6.72; N, 3.89; Cr_2O_3, 10.5. Found: C, 59.0; H, 6.45; N, 3.76; Cr_2O_3, 10.42.

Chromate of Quinine.—This salt was prepared by mixing a dilute solution of quinine hydrochloride with aqueous potassium chromate.

Anal. Calcd. for $(C_{20}H_{25}N_2O_2)_2CrO_4 \cdot 2H_2O$: C, 59.8; H, 6.78; N, 6.98; Cr_2O_3, 9.92. Found: C, 60.0; H, 6.99; N, 6.71; Cr_2O_3, 9.03.

Addition of chromic acid in dilute acetic acid to the chromate suspended in water caused it gradually to collect in an orange sticky mass which impeded stirring. The reaction was not studied further.

Summary

1. It has been found that a suspension of codeine chromate is oxidized by chromium trioxide to codeinone, and from this observation a reliable method for preparing this ketone has been developed. Unfortunately this process for obtaining a ketone from a basic alcohol is not generally applicable.

2. Attempts to convert codeine to codeinone by dehydrogenation were unsuccessful.

3. Certain of the physical and chemical properties of codeine are described.

4. It was discovered that in hydrochloric acid solution codeinone is transformed into a new base, $C_{18}H_{21}NO_4$.

BETHESDA 14, MD. RECEIVED JANUARY 28, 1950

[CONTRIBUTION FROM THE NATIONAL INSTITUTES OF HEALTH]

The Preparation and Degradation of 6-Methylcodeine[1]

BY STEPHEN P. FINDLAY AND LYNDON F. SMALL

In continuance of the search for compounds having improved analgesic characteristics, the preparation and properties of 6-methylcodeine have been investigated. Although ketones derived from the morphine alkaloids (*e. g.*, codeinone[2] and dihydrocodeinone[3]) do not react readily with Grignard reagents in the customary manner, Small and Rapoport demonstrated recently that dihydrocodeinone and dihydromorphinone do react with organolithium reagents to furnish the anticipated tertiary alcohols.[4] However, from codeinone (A) and methyllithium they were unsuccessful in isolating pure 6-methylcodeine (B), a failure which was ascribed to the quality of the ketone.

The method for preparing codeinone having been improved,[5] it has been found that methyllithium acts upon codeinone to furnish the ex-

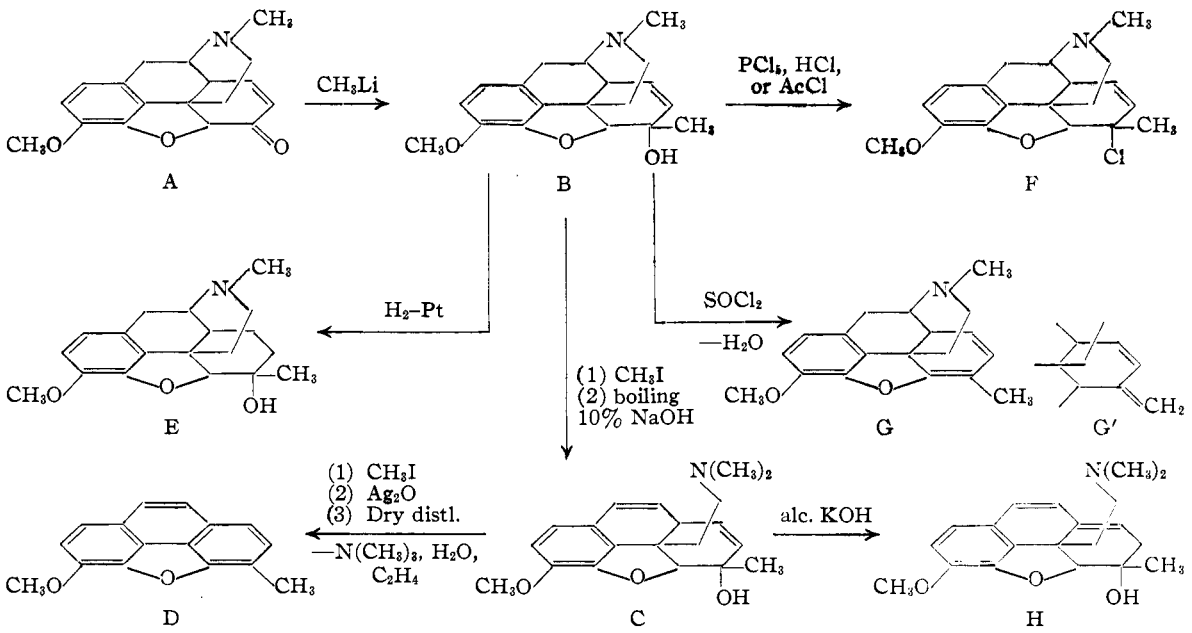
(1) This investigation was aided by award of a United States Public Health Service Postdoctorate Fellowship to S. P. F.

(2) Small and Lutz, "Chemistry of the Opium Alkaloids," United States Government Printing Office, Washington, D. C., 1932, p. 248.

(3) Lutz and Small, THIS JOURNAL, **57**, 2651 (1935).

(4) Small and Rapoport, *J. Org. Chem.*, **12**, 284 (1947).

(5) Findlay and Small, THIS JOURNAL, **72**, 3247 (1950).



pected product in nearly quantitative yield. The absence of the other possible diastereoisomer in the reaction product is reminiscent of the behavior of dihydrocodeinone under the same conditions. The failure of 6-methylcodeine to yield an oxime, and its facile conversion by catalytic hydrogenation to 6-methyldihydrocodeine (E), obtainable directly from dihydrocodeinone, are sufficient justification for the structure assigned (B).

In its chemical behavior 6-methylcodeine is largely analogous to codeine.[6] Hofmann degradation of its methiodide furnished 6-methyl-α-methylmorphimethine (C), a homolog of α-methylmorphimethine. Dry distillation of the methohydroxide of this base yielded 6-methylmethylmorphenol (D), which is the 6-methyl derivative of the compound obtained by the corresponding degradation of α-methylmorphimethine methohydroxide.[6] The presence of the aromatic ring system in the nitrogen-free product (D) was demonstrated by its conversion to a red molecular compound with picric acid.[7] As in the codeine series, 6-methyl-α-methylmorphimethine (C) is transformed by boiling alcoholic potassium hydroxide to the β-isomer (H), and this isomerization is accompanied by a similar spectacular change in optical rotary power[6,8] (Table I).

TABLE I

-Methylmorphimethine	$[\alpha]^{20}D$ in alcohol
α	−212°
β	+438° (+414°)
6-Methyl-α	−220°
6-Methyl-β	+357°

(6) Ref. 2, 268 ff.

(7) *Cf.* Pfeiffer, "Organische Molekülverbindungen," Stuttgart, 1922, 218 ff.

(8) Small, *J. Org. Chem.*, **12**, 361 (1947).

Because the alcoholic group is both allylic and tertiary, endeavors to replace it with chlorine did not proceed smoothly. However, small yields of 6-methylchlorocodide (F) were obtained by the agency of phosphorus pentachloride, concentrated hydrochloric acid, and acetyl chloride in glacial acetic acid. A high value for chlorine in a preliminary analysis of the product obtained by use of phosphorus pentachloride permitted the inference that, as in the case of 6-methyldihydrocodeine, some nuclear halogenation had occurred.

The action of thionyl chloride resulted in a compound which could not be purified to constant melting point either by fractional crystallization or by chromatography. Recrystallization of the intermediate fractions of a chromatographic analysis furnished material which was apparently inhomogeneous. It contained no detectable halogen and had the composition of a dehydration product of 6-methylcodeine and may be a mixture of G and G′.

In mice 6-methylcodeine has an analgesic activity twice that of codeine, but its toxicity is three times as great.

Experimental[9]

Methyllithium.—This reagent was prepared essentially according to the procedure of Perrine and Rapoport.[10]

6-Methylcodeine.—A mixture of 100 ml. of molar ethereal methyllithium and 500 ml. of absolute ether contained in a three-necked, one-liter round-bottomed flask equipped with a seal stirrer, condenser, and drying tube was cooled to −8°, and 14.7 g. of codeinone was added with stirring from an addition tube. After another hour of stirring cold, the mixture was decomposed with ice-water, the ether phase separated, the aqueous phase extracted once with ether, and the combined ether solutions dried and distilled. The pale brown, gummy residue thus obtained

(9) All melting points herein recorded are corrected.

(10) Perrine and Rapoport, *Ind. Eng. Chem., Anal. Ed.*, **20**, 635 (1948).

crystallized almost at once: 15.7 g. of crude product. A portion was crystallized twice from ligroin (65–70°) and sublimed for analysis: m. p. 114.5–116.5°, $[\alpha]D^{20}$ −163° (*c*, 1.1, alcohol).

Anal. Calcd. for $C_{19}H_{23}NO_3$: C, 72.8; H, 7.40. Found: C, 72.6; H, 7.50.

This base resembles 6-methyldihydrocodeine in being extremely soluble in most organic solvents. It did not give an oxime or a positive diazosulfanilic acid test. In the presence of Adams catalyst it consumed one mole of hydrogen to furnish 6-methyldihydrocodeine; m. p. 109.5–111.5°; methiodide; m. p. 240°; $[\alpha]^{20}D$ −140° (*c*, 0.89, alcohol); reported[4] 116°, 251–252°, and −139°, respectively).

The **salicylate** was precipitated by addition of dry ether to an absolute alcoholic solution of the base and salicylic acid which had not, on long standing, deposited any crystals. The salt was crystallized twice from ethyl acetate; stout prisms, m. p. 167–169°.

Anal. Calcd. for $C_{26}H_{29}NO_6$: C, 69.2; H, 6.47. Found: C, 69.2; H, 6.78.

The **perchlorate** was prepared in and purified from absolute alcohol; stout, ill-defined crystals, m. p. 139–144°.

Anal. Calcd. for $C_{19}H_{24}ClNO_7 + C_2H_5OH$: C, 54.8; H, 6.57. Found: C, 54.9; H, 6.59.

The **methiodide** was easily prepared in and purified from methanol: m. p. 232–233°.

Anal. Calcd. for $C_{20}H_{26}INO_3$: C, 52.8; H, 5.76. Found: C, 52.6; H, 5.72.

6-Methyl-α-methylmorphimethine.—6-Methylcodeine methiodide (5.2 g.) was boiled ten minutes in 20 ml. of 10% aqueous sodium hydroxide. The oil which formed almost immediately crystallized on cooling. After taking up all the basic material in ether, the solvent was removed: 3.4 g. (91%) of pink crystals. The base was crystallized once from ligroin and once from ethyl acetate; tiny prisms, m. p. 106.5–107.5°, $[\alpha]^{20}D$ −222° (*c*, 1.2, alcohol).

Anal. Calcd. for $C_{20}H_{25}NO_3$: C, 73.4; H, 7.71. Found: C, 73.2; H, 7.81.

The **methiodide** was prepared in methanol and crystallized from methanol–ethyl acetate. The pale yellow, apparently amorphous product softened at 135° and melted 203.5–205.5° (dec.). A satisfactory analysis for the salt was not obtained.

6-Methylmethylmorphenol.—Freshly precipitated and carefully washed silver oxide (prepared from 3.70 g. of silver nitrate and 0.87 g. of sodium hydroxide) was transferred to a hot solution containing 3.4 g. of 6-methyl-α-methylmorphimethine methiodide in 35 ml. of water, with the aid of an equal volume of water. After shaking 5 hours the mixture was centrifuged free of silver compounds and the orange, supernatant solution concentrated *in vacuo* at 40° to a brown, tough glass. This, dissolved in a little methanol, was transferred to a sublimation apparatus and, after removal of the solvent, was sublimed at 100° (1 mm.). The sublimate was crystallized twice from methanol from which it separated in fine prisms: m. p. 89–90°.

Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.4; H, 5.13. Found: C, 81.5; H, 5.37.

The **picrate** was prepared in and purified from methanol: small, deep red prisms, m. p. 138.5–139.5°.

Anal. Calcd. for $C_{22}H_{15}N_3O_9$: C, 56.8; H, 3.25. Found: C, 57.1; H, 3.37.

Isomerization of 6-Methyl-α-methylmorphimethine to the β-Isomer.—A mixture of 1 g. of crude 6-methyl-α-methylmorphimethine, 1 g. of potassium hydroxide, and 10 g. of 60% alcohol was refluxed two hours. The dark brown residue, obtained by removal of the solvents *in vacuo*, was treated with ether and water and the ether extracts dried and distilled. A quantitative yield of transparent oil was obtained, which furnished crystals slowly from ligroin. Like the α-isomer this compound is easily soluble in most organic solvents. It was sublimed for analysis; ill-defined crystals, m. p. 95.5–97°; mixed m. p. with the α-isomer, 81–90°; $[\alpha]^{20}D$ +357° (*c*, 1.1, alcohol).

The **methiodide** was prepared in benzene and purified from methanol; small prisms and platelets, m. p. 283–284°.

Anal. Calcd. for $C_{21}H_{28}INO_3$: C, 53.7; H, 6.02. Found: C, 53.5; H, 6.12.

6-Methylchlorocodide: (a) **Using Phosphorus Pentachloride.**—A solution of 2 g. of 6-methylcodeine in 6 ml. of absolute chloroform was added with stirring during one hour to 2.0 g. of phosphorus pentachloride dissolved in 6 ml. of the same solvent. The mixture was protected from moisture and maintained at 0° during the addition. After two hours at room temperature it was poured on ice, made alkaline to Congo Red with aqueous potassium hydroxide and alkaline to litmus with sodium carbonate. The mixture was shaken with chloroform and the extracts washed, dried, and concentrated *in vacuo* to a yellowish gum which solidified upon addition of ligroin. By digestion with ligroin (65–71°) the product was leached from the amorphous and higher melting by-products. The material recovered from ligroin was sublimed at 130–140° (0.3 mm.) and recrystallized several times from ligroin. An analysis at this point was sufficiently high in chlorine to warrant the conclusion that some nuclear chlorination (presumably at the 1-position[4]) had occurred. Recrystallized twice more the product melted at 162.5–163.5°.

Anal. Calcd. for $C_{19}H_{22}ClNO_2$: C, 68.7; H, 6.71; Cl, 10.7. Found: C, 68.9; H, 6.73; Cl, 10.7.

(b) **Using Concentrated Hydrochloric Acid.**—To 4 ml. of hydrochloric acid (37%) 0.5 g. of powdered 6-methylcodeine was added in small portions. After eighty minutes the pink solution was added to excess, ice-cold 3 *N* ammonium hydroxide and extracted with ether. The residue from the washed, dried, and concentrated extract was taken up in ethyl acetate and precipitated with ligroin. By alternate sublimations and crystallizations from ligroin, pure 6-methylchlorocodide was isolated in small yield; m. p. 163.5–164° (no depression of m. p. after mixture with the product from the phosphorus pentachloride reaction).

(c) **Using Acetyl Chloride.**—A mixture of 0.5 g. of 6-methylcodeine, 1.7 ml. of glacial acetic acid, and 1.0 ml. of acetyl chloride stood two days at room temperature and then was concentrated *in vacuo* to dryness. The residue was treated with aqueous sodium bicarbonate and extracted with ether. The brown crystalline residue from the ethereal solution, purified as in the case of the hydrochloric acid product, furnished a small quantity of 6-methylchlorocodide, m. p. 162–163.5°.

6-Methylcodeine and Thionyl Chloride.—A solution of 0.7 ml. of thionyl chloride and 10 ml. of chloroform was added with stirring at 0° and over a period of twenty minutes to 2.5 g. of base in 15 ml. of the same solvent. After another twenty minutes at 0° the ice-bath was removed. An hour later the mixture was poured onto ice, made alkaline with ammonia, and extracted with chloroform. The extract was washed, dried, and concentrated to 2.4 g. of yellowish residue which was digested with ligroin (65–70°) to give 1.3 g. of ligroin-soluble material; m. p. ~ 150°.

Inasmuch as this seemed to be a mixture, 1 g. in 25 ml. of benzene was chromatographed on 40 g. of alumina (Alcoa, Grade F-20, mesh 80–200) using the flow method. The eluents employed did not afford a sharp separation but the middle fractions (fifteen altogether) aggregating 0.40 g. had melting points about 186–189° and were combined. Sublimed and crystallized twice from ethyl acetate they furnished ill-defined crystals which melted higher, at 192–193.5°. In hot alcohol containing a little nitric acid they did not react with silver nitrate, nor did they give a positive halogen reaction in the sodium fusion test.

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.3; H, 7.18; N, 4.74. Found: C, 77.0; H, 7.19; N, 4.82.

The peculiar character of this reaction product can be

appreciated from the behavior of an end fraction representing 18% of the starting material and melting at 194.5–195.5°. By rechromatographing on alumina, seven successive fractions were obtained having the following melting points: 196.5–201°, 193–209°, 199–218°, 200.5–222°, 200–219°, 200–221.5°, 206–224°.

Acknowledgment.—We are indebted to Mr. William C. Alford and his assistants for the microanalyses herein reported; also to Dr. Nathan B. Eddy under whose direction the pharmacological properties of 6-methylcodeine were determined.

Summary

The preparation of 6-methylcodeine by the action of methyllithium on codeinone and also its chemical properties and degradation are described.

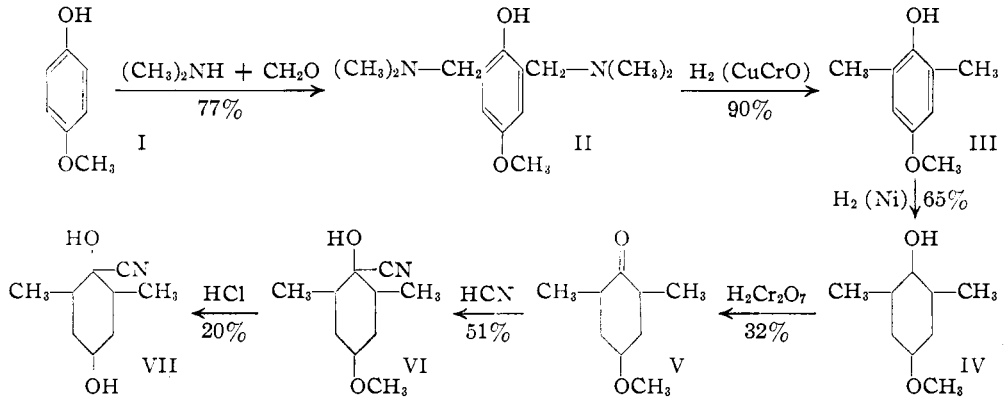
BETHESDA 14, MD. RECEIVED JANUARY 28, 1950

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF MARYLAND]

Preparation and Reactions of 2,6-Dimethyl-4-methoxycyclohexanone

BY WILKINS REEVE AND ALEXANDER SADLE

The preparation and reactions of 2,6-dimethyl-4-methoxycyclohexanone cyanohydrin (VI) have been studied with the object of using this material as an intermediate in the synthesis of substituted cyclohexadienes.



Hydroquinone monomethyl ether (I) has been reported to react with dimethylamine and formaldehyde to form a mono-Mannich base.[1]

We have found that under more drastic conditions a di-Mannich base (II) may also be obtained in good yields. The condensation proceeds exclusively at the two and the six positions. The di-Mannich base undergoes hydrogenolysis to 2,6-dimethyl-4-methoxyphenol (III) in good yield. This represents a new and more practical synthesis of this material. The physical properties of this product agree with those reported in the literature.[2] The presence of the two methyl groups in the positions ortho to the phenolic group can be demonstrated by attempting to couple the material with diazotized *p*-toluidine; no colored product can be obtained. Furthermore, the methoxy group can be hydrolyzed with concentrated hydrogen bromide to give 2,6-dimethylhydroquinone. This latter compound has previously been made by methods which established its structure beyond all doubt.[3,4]

Hydrogenation of the 2,6-dimethyl-4-methoxyphenol yielded the previously unreported 2,6-dimethyl-4-methoxycyclohexanol (IV). This was oxidized to 2,6-dimethyl-4-methoxycyclohexanone (V). The oxidation proceeded in an anomalous manner in that after part of the alcohol had been oxidized, the reaction seemed to stop. There was no evidence of further reaction on the addition of more alcohol, even though the chromic acid was present in threefold excess.

Although attempts to prepare the cyanohydrin of 2,6-dimethylcyclohexanone have been reported[5] unsuccessful, 2,6-dimethyl-4-methoxycyclohexanone (V) rapidly adds hydrogen cyanide in an ethanol solution containing a little potassium cyanide.

The cyanohydrin groups of 2,6-dimethyl-4-methoxycyclohexanone cyanohydrin are resistant to attack by acids. After refluxing for two hours with concentrated hydrochloric acid, the only material which could be isolated was the 2,6-dimethyl-4-hydroxycyclohexanone cyanohydrin (VII) in a 6% yield. Heating with alcoholic hydrogen chloride for two hours at 100° also yielded the 2,6-dimethyl-

(1) Decombe, *Compt. rend.*, **197**, 258 (1933).
(2) Bamberger, *Ber.*, **36**, 2040 (1903).
(3) Noelting and Bauman, *ibid.*, **18**, 1151 (1885).
(4) Jones and Kenner, *J. Chem. Soc.*, 1842 (1931).
(5) Noyes, *Am. Chem. J.*, **20**, 789 (1898).