[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

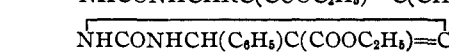
Researches on Pyrimidines. CXXXIII. Some Reactions and Derivatives of 2-Keto-4-phenyl-5-carbethoxy-6-methyl-1,2,3,4-tetrahydropyrimidine

BY KARL FOLKERS[1] AND T. B. JOHNSON

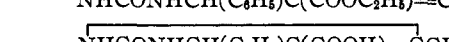
The condensation of urea, an aldehyde, and a β-keto ester to yield a tetrahydropyrimidine of the general formula I, in which R was various alkyl, aryl and alkylaryl groups, was recently reëxamined and many new members of the series described.[2] This investigation has been continued and the present study was made because it seemed that these compounds might possess pharmacological interest. The reactions and derivatives of 2-keto-4-phenyl-5-carbethoxy-6-methyl-1,2,3,4-tetrahydropyrimidine, II, have been studied, and the results of our research are summarized in this paper. This pyrimidine was selected for study because it was readily available in large quantities, although any member of the series could be used, if the basis of selection were a pharmacological one. Some of the reactions and derivatives of this 4-phenyltetrahydropyrimidine, II, as studied by other investigators, and as made in this Laboratory, are discussed under the individual headings.

Hydrolysis.—When Biginelli[3] first made the tetrahydropyrimidine, II, he found that it was somewhat stable toward hydrolytic solutions. All his attempts to saponify the carbethoxy group to obtain the carboxylic acid, III, failed. The only products isolated from his various acidic and basic hydrolytic treatments were the result of ring cleavage.

(I)



(II)



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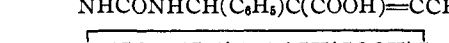

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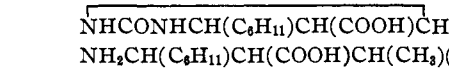


(V)

As would be expected, the reduction of the 5,6-pyrimidine double bond would stabilize the nucleus, and the ester could be saponified to the acid. This has been found to be true, for three grams of 2-keto-4-cyclohexyl-5-carbethoxy-6-methylhexahydropyrimidine, was quantitatively saponified to the acid, IV, by refluxing for five hours in an alcoholic sodium hydroxide solution. The further hydrolysis of this acid, IV, to β,β'-diamino-β-methyl-β'-cyclohexylisobutyric acid, V, will be investigated later.

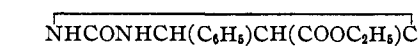
Hydrogenation.—Biginelli's only other experiment with the 4-phenyltetrahydropyrimidine, II, was a reduction with sodium amalgam, which

(1) E. R. Squibb and Sons Organic Chemistry Research Fellow (1932–1933).

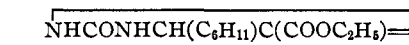
(2) Folkers, Harwood and Johnson, THIS JOURNAL, **54**, 3751 (1932).

(3) Biginelli, *Ber.*, **24**, 1317 (1891); *Gazz. chim. ital.*, **23**, 360 (1893).

gave, supposedly, the 4-phenylhexahydropyrimidine, VI. Recently[4] it was suggested that Biginelli's reduction product was probably a tetrahydro- rather than a hexahydropyrimidine, and it was demonstrated that only the benzenoid nucleus of the 4-phenyltetrahydropyrimidine, II, could be hydrogenated with a platinum catalyst to give the 4-cyclohexyltetrahydropyrimidine, VII. It was further shown that if 4-methyl-6-phenylpyrimidine, VIII, which differed from pyrimidine II only in the position of the double bond, were hydrogenated with a platinum catalyst both the benzenoid nucleus and the 5,6-pyrimidine double bond were reduced to give the pyrimidine IX.



(VI)



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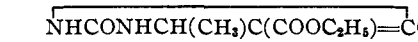

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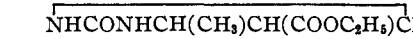
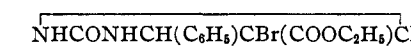


(IX)

If the 5,6-double bond of the pyrimidine II could be reduced in addition to the benzenoid nucleus, then the product should be identical with that obtained from pyrimidine VIII. It has now been found that the hydrogenation of both the 5,6-double bond and the benzenoid nucleus of pyrimidine II can be accomplished[5] with a nickel catalyst at 175° and under 200–250 atmospheres hydrogen pressure. The product was identical with that obtained by the reduction of pyrimidine VIII with a platinum catalyst and the yield was practically quantitative. Professor Adkins and Mr. Wojcik also hydrogenated for us the 4-phenyltetrahydropyrimidine, II, with their copper–barium–chromium oxide catalyst at 200–250°. Such experimental conditions may be expected to give reduction of oxygen linkages. Basic compounds were produced, and these substances are now under investigation in this Laboratory as a part of an extensive program covering the hydrogenation of various pyrimidines, purines, and related substances of cyclic ureide structure under elevated temperatures and pressures.

Bromination.—The reaction of the 4-phenylpyrimidine, II, with two atoms of bromine to give the 5,6-dibromo derivative, X



(X)

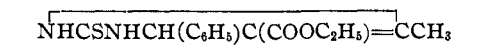
was first described by Hinkel and Hey.[6] Their product melted at 182–183°. The procedure for this bromine addition has been improved by the authors to yield 84.4% of the colorless dibromo derivative.

(4) Folkers and Johnson, THIS JOURNAL, **55**, 1140 (1933).

(5) The authors are indebted to Professor Homer Adkins and Mr. Bruno Wojcik for carrying out this hydrogenation in their laboratory at the University of Wisconsin. Details of the experiment will be published by them elsewhere.

(6) Hinkel and Hey, *Rec. trav. chim.*, **48**, 1283 (1929).

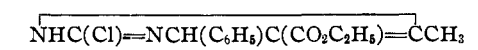
2-Thiotetrahydropyrimidines.—The condensation of thiourea, benzaldehyde and ethyl acetoacetate to give the 2-thio-4-phenyltetrahydropyrimidine derivative, XI, was also first carried out by Hinkel, Hey and Samuel.[7] They reported the formation of two products, which they



(XI)

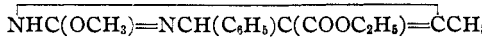
believed to be isomers, one melting at 205° and the other at 203°. However, no convincing evidence was presented to show that these compounds were not the same. Purity of reagents and products in this condensation is an important factor, and, as shown in our first paper,[2] the condensation between pure reagents is only appreciable when catalyzed by acid. Complete directions are given in the experimental part for the preparation of this thio derivative, which was obtained as colorless crystals melting at 207–208° (corr.). We observed no evidence of isomerization.

Alkylation of Tetrahydropyrimidines.—We have found that the 2-keto-4-phenylpyrimidine derivative, II, reacts readily with phosphorus oxychloride with evolution of hydrochloric acid, but the general technique of isolating chloropyrimidines failed to yield the expected 2-chloro derivative, XII. This substance proved to be unusually reactive for a

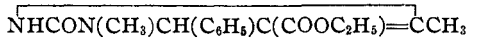


(XII)

chloropyrimidine and was easily hydrolyzed to the original keto compound. When a benzene solution of this chloropyrimidine reacted with sodium methoxide in absolute methanol, a product was obtained which, by analysis, was shown to be a methyl derivative. Its behavior toward acid did not indicate an imido ether structure. After long digestion in alcoholic hydrochloric acid solution, there was no apparent change in the compound. It would seem from this behavior that a methoxy derivative, XIII, if formed, had rearranged to a N-methyl derivative as represented by formula XIV. The stability and resistance to hydrolysis



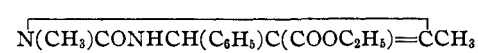
(XIII)



(XIV)

of such N-methylpyrimidines is well known.

According to the formulation of the condensation reaction which gave the pyrimidine, II, it would be expected that a mono-N-substituted urea should react to give a mono-N-substituted pyrimidine. It was found that methylurea, benzaldehyde and ethyl acetoacetate react to give a N-methylpyrimidine, XV, which is not identical with the methyl deriva-



(XV)

tive XIV, obtained by treating the 2-chloro compound, XII, with sodium

(7) Hinkel, Hey and Samuel, *Rec. trav. chim.*, **48**, 1285 (1929).

methoxide. Formulas XIV and XV have been provisionally assigned, therefore, to these respective N-methylpyrimidines.

Johnson and Clapp,[8] who studied the alkylation products of oxypyrimidines, stated that "It is interesting to note that the 3-methylpyrimidines melted higher, in every series examined, than the isomeric 1-methylpyrimidines." Granting comparison of our present series of pyrimidines, the melting points of compounds of XIV and XV substantiate the assigned formulas.[9]

Johnson and Clapp also observed that many pyrimidines give a red colored solution when treated with diazobenzenesulfonic acid in the presence of alkali. If there is substitution of alkyl in the 3-position (Fischer's orientation), no red color is formed.[10] Apparently, this test for distinguishing the 3-position substitution is not applicable to the present series, for under conditions which gave colored solutions with uracil, and 6-phenyluracil, there was no development of color with the pyrimidines II, XIV and XV.

Evans[11] has shown that, as was also true for certain hydantoins, N-1 and N-3 substitution of certain uracil compounds could be differentiated by their ultraviolet absorption spectra. The absorption spectra of phenyluracils having a substituent in the N-1 position was found to be different from those phenyluracils which were unsubstituted or had a substituent in the N-3 position.

Through the courtesy of Professor Emma P. Carr and Miss Idjen Ho and Miss Joyce Wadmond at Mount Holyoke College, the ultraviolet absorption spectra of the N-methylpyrimidines have been determined. These measurements will be published later, but it may now be said that the absorption curve for the N-methylpyrimidine XIV, derived from chloropyrimidine is almost identical with that of 4-phenylpyrimidine, II, whereas the absorption curve of the N-methylpyrimidine derived from methylurea shows definite differences. The differences between the two curves are less marked than in the case of the hydantoin and uracil derivatives, but the results are analogous and indicate support for formulas XIV and XV. It is not definite proof, however, for comparison of this series of pyrimidines with the uracils may not be justified.

Syntheses of the N-methylpyrimidines, XIV and XV, was desirable for constitutional proof. A solution by the intermediate condensation of methyl urea and ethylacetoacetate was not feasible in view of previous negative results in this Laboratory. The condensation of methyl isocyanate[12] with ethyl β-aminocrotonate[13] to give ethyl β-(N-methylcar-

(8) Johnson and Clapp, *J. Biol. Chem.*, **5**, 53 (1908–1909).

(9) The new orientation has been used for naming compounds XIV and XV, whereas Johnson and Clapp used the pyrimidine orientation of Emil Fischer.

(10) Johnson and Clapp, *J. Biol. Chem.*, **5**, 163 (1908–1909).

(11) Evans, THIS JOURNAL, **54**, 641 (1932).

(12) Slotta and Lorenz, *Ber.*, **58**, 1322 (1925); Slotta and Tschesche, *ibid.*, **60**, 298 (1927).

(13) Michaelis, *Ann.*, **366**, 337 (1908).

bamido)-crotonate, XVI, and subsequent reaction with benzaldehyde would be expected to yield the 3-methylpyrimidine compound XIV.

$$CH_3NHCONHC(CH_3){=}CHCOOC_2H_5 \quad \text{(XVI)}$$

$$CH_3\underset{\underset{NH}{\|}}{C}CH(COOC_2H_5)CONHCH_3 \quad \text{(XVII)}$$

$$\text{(XVIII)}\ NH_2CON(CH_3)C(CH_3){=}CHCOOC_2H_5$$

It was found, however, that methyl isocyanate reacted with ethyl β-aminocrotonate to give ethyl α-(N-methylcarbamyl)-β-iminobutyrate, XVII.[14] Behrend and Hesse have shown that methyl isothiocyanate reacts with ethyl β-aminocrotonate similarly. Phenyl isocyanate reacted with ethyl β-aminocrotonate[15] to give both ethyl α-(N-phenylcarbamyl)-β-iminobutyrate and ethyl β-(N-phenylcarbamido)-crotonate.

Similarly, the condensation of isocyanic acid with ethyl β-methylaminocrotonate[16] might be expected to yield the ethyl β-(methylcarbamido)-crotonate, XVIII, and a subsequent reaction with benzaldehyde to give the 1-methylpyrimidine, XV. However, potassium cyanate cannot be made to react with the hydrochloride of ethyl β-methylaminocrotonate in aqueous solution for this amine salt decomposes into methylammonium chloride and ethyl acetoacetate just as the hydrochloride of ethyl β-aminocrotonate is decomposed by water into ammonium chloride and ethyl acetoacetate.[17] Likewise, in acetic acid solution, wherein hydrolysis is retarded, the corresponding carbamido-crotonic esters could not be detected after treating either ethyl β-methylaminocrotonate, or ethyl β-aminocrotonate with potassium cyanate. If the amine ester were present as ethyl β-methyliminobutyrate, reaction with isocyanic acid would, of course, not be expected.

2-Aminotetrahydropyrimidines.—After considerable experimentation, the 2-imino-4-phenylpyrimidine derivative, XIX, was obtained by the reaction of the 2-chloro derivative with dry ammonia. It was never

$$\overline{NHC(NH)NHCH(C_6H_5)C(COOC_2H_5){=}C}CH_3 \quad \text{(XIX)}$$

obtained, however, analytically pure, and it exhibits an unusually high degree of unstability by hydrolyzing readily to the original 2-keto derivative and ammonia. Fisher and Johnson,[18] in their discussion of the chemistry of convicine, state that "there is no evidence that a 2-imino group is split off from pyrimidines by dilute acids as ammonia." The 2-imino group of our new pyrimidine XIX was immediately hydrolyzed by heating to boiling its solution in dilute hydrochloric acid. It even slowly hydrolyzed at 25° when dissolved in dilute hydrochloric acid and

(14) Behrend and Hesse, *ibid.*, **329**, 346 (1903).

(15) Behrend and Meyer, *Ber.*, **33**, 621 (1900); Behrend, Meyer and Buchholz, *Ann.*, **314**, 209 (1901).

(16) Knoevenagel and Reinecke, *Ber.*, **32**, footnote on 420 (1899).

(17) Collie, *J. Chem. Soc.*, **71**, 303 (1897).

(18) Fisher and Johnson, THIS JOURNAL, **54**, 2040 (1932).

it was also hydrolyzed to the 2-keto compound when it was dissolved in an alcoholic solution of picric acid.

Experimental Part

2-Keto-4-phenyl-5,6-dibromo-5-carbethoxy-6-methylhexahydropyrimidine, X.—A solution of 6.2 g. of bromine in 60 ml. of dry chloroform at 5° was added to 5 g. of the 4-phenylpyrimidine derivative, II, suspended in 30 ml. of dry chloroform, also at 5°. After standing for three and one-half hours at room temperature, the open flask was heated for fifteen minutes on the steam-bath. Enough chloroform was now added under reflux until all solid had redissolved. The cooled chloroform solution was washed with 100 ml. of 10% sodium carbonate solution and then distilled under reduced pressure at 50–60° to a low volume, after which 50 ml. of ethanol was added and the distillation continued until 30–40 ml. of solvent remained. Precipitation sometimes occurred during the distillation. After standing overnight in the refrigerator, filtering and drying, the crude product of m. p. 171–171.5° weighed 7.5 g. After three crystallizations, 6.8 g. or 84.4% of the dibromo derivative was obtained of m. p. 180–181° (corr.). Crystallization loss was kept small by dissolving each yield in 175 ml. of ethanol under the reflux, then distilling 80 ml. of the solvent, and, finally, adding slowly 100 ml. of water to the boiling solution, which was again placed under the reflux. Each solution was placed in the refrigerator overnight for complete crystallization.

2-Thio-4-phenyl-5-carbethoxy-6-methyl-1,2,3,4-tetrahydropyrimidine, XI.—A mixture of 3.8 g. of thiourea, 9.7 g. of ethyl acetoacetate, 5.3 g. of benzaldehyde, 20 ml. of absolute ethanol and four drops (5 ml. pipet) of concentrated hydrochloric acid was refluxed for two hours. The solution was seeded and allowed to stand for twenty-four hours for crystallization, after which the product was filtered and washed with 25 ml. of 50% alcohol; yield, 6.3 g. After one recrystallization from alcohol, the product melted at 207–208° (corr.) and was not raised by further crystallization; yield, 5.8 g., or 42.0%.

2-Keto-1,6-dimethyl-4-phenyl-5-carbethoxy-1,2,3,4-tetrahydropyrimidine, XV.—A solution of 3.3 g. of methylurea, 4.8 g. of benzaldehyde, 8.7 g. of ethyl acetoacetate, 20 ml. of absolute ethanol, and four drops of concentrated hydrochloric acid was refluxed for two hours. Scratching induced crystallization and after twenty hours at 25° the crystals were filtered, washed with 20 ml. of 50% alcohol, and dried. The yield of 8.2 g. was dissolved in 100 ml. of hot ethanol and then distilled to a residue of 25 ml. After long standing, 7.3 g. (59.8%) of pyrimidine XV separated. The m. p., 176–178° (corr.), was not raised by further crystallization.

Anal. Calcd. for $C_{15}H_{18}O_2N_2$: C, 65.65; H, 6.62; N, 10.22. Found: C, 65.65; H, 6.48; N, 10.05, 10.06.

2-Chloro-4-phenyl-5-carbethoxy-6-methyl-1,4-dihydropyrimidine, XII.—Fifteen grams of the 2-keto-pyrimidine derivative, II, and 25 ml. of freshly distilled phosphorus oxychloride were heated for one hour on the steam-bath, and then allowed to stand overnight. The excess phosphorus oxychloride was removed by distillation at 25–30 mm. and a bath temperature of 95°. The residue of 25.2 g. was dissolved in 350 ml. of dry benzene. This benzene solution contains the 2-chloro derivative along with residual phosphorus compounds. In reaction of this 2-chloro derivative with sodium methoxide, the phosphorus compounds were removed, but in its reaction with ammonia, they were not removed.

Reaction of Methyl Isocyanate and Ethyl β-Aminocrotonate.—Five grams of methyl isocyanate and 11.3 g. of ethyl β-aminobutyrate were mixed at 5° and allowed to stand in a tightly stoppered flask at 25° for four days. The crystals, after trituration with ether, filtering and drying, weighed 7.1 g. (43.5%). After one crystallization from dilute alcohol, they melted at 123.5–125.5° (corr.). A second crystallization did not alter the

melting point. The crystals were ethyl α-(N-methylcarbamyl)-β-iminobutyrate. Behrend and Hesse[14] gave 124–126° as the melting point for this compound as derived by desulfurization of the corresponding thiocarbamyl derivative.

3,6-Dimethyl-2-keto-4-phenyl-5-carbethoxy-1,2,3,4-tetrahydropyrimidine, XIV.—The benzene solution of the 2-chloro derivative obtained from 15 g. of the 2-keto-pyrimidine was cooled to 5° and washed with the following solutions (cooled to 5°): (A) 150 ml. of 5% sodium carbonate solution plus 100 ml. of a saturated sodium chloride solution; (B) 75 ml. of the sodium carbonate solution plus 50 ml. of the sodium chloride solution; (C) 100 ml. of the sodium chloride solution. The benzene layer and any residual emulsion was then filtered through a Buchner funnel to remove a small amount of the precipitated 2-keto-pyrimidine. The benzene layer was then removed from the filtrate and distilled to about half of its original volume at 85 mm. and a final maximum bath temperature of 35–40°. To this was added 50 ml. of absolute methanol (dried twice over lime and once over magnesium methoxide) in which 1.3 g. of sodium had been dissolved. After forty-five hours of standing at room temperature, the solvents were removed under diminished pressure in a bath of not over 85°. Then 100 ml. of water and 100 ml. of ether were added to the residue. More 2-keto-pyrimidine separated and was removed by filtering both layers through a Buchner funnel with slight suction, and, after drying, weighed 4.7 g. It melted at 199–201°. The ether was evaporated to leave a thick gum. This gum separated from dilute alcohol as an oil which would not crystallize. However, if the gum were repeatedly taken up in a few ml. of methanol which was allowed to evaporate at room temperature, it solidified entirely after two days; crude yield, 7.2 g. After three crystallizations from ethanol and water, the yield was 4.3 g., m. p. 159–160° (corr.).

Anal. Calcd. for $C_{15}H_{18}O_3N_2$: C, 65.65; H, 6.62; N, 10.22. Found: C, 65.35; H, 6.52; N, 10.49, 10.31.

This methyl derivative, after refluxing for four hours in 15 ml. of ethanol and 5 ml. of concentrated hydrochloric acid, and isolation, melted at 155–158° (corr.). This stability indicated that the methyl was attached to nitrogen, having rearranged from its original position on oxygen during the preparation.

2-Imino-4-phenyl-5-carbethoxy-6-methyl-1,2,3,4-tetrahydropyrimidine, XIX.—The distillation residue from 15 g. of the keto-pyrimidine II and 25 ml. of phosphorus oxychloride was dissolved in 100 ml. of dry benzene and again distilled under diminished pressure to a thick residue. This was then dissolved in 250 ml. of dry benzene and dry ammonia bubbled through for one-half hour at ice-bath temperature. Allowing the solution to warm to 25°, ammonia was still bubbled through for one hour and the mixture finally allowed to stand overnight. Then 200 ml. of water was added and the mixture well shaken. The precipitate was removed by filtering and was washed with 50 ml. of benzene and 50 ml. of water, respectively.

This insoluble precipitate of 14.1 g. was shown not to contain any free 2-imino derivative by trituration with 225 ml. of 5.3% hydrochloric acid for a half hour at 10–20°. It contained phosphorus and extraction with hot butanol yielded the original 2-keto-pyrimidine derivative. One gram boiled with 200 ml. of water and recrystallized from ethanol and water, decomposed in the capillary at about 293° (uncorr.). It still contained phosphorus.

The benzene layer was cooled to 5°, extracted three times each with 110 ml. of 4.3% hydrochloric acid solution at 5° and the combined extracts made alkaline at 5° with concentrated ammonium hydroxide. A gum precipitated which was dissolved in a few ml. of warm alcohol, cooled, and precipitated by addition of 100 ml. of water. An oil separated which soon solidified. It was filtered and dried in a desiccator. The yield was 3 g. This substance melted at 85–87° and was completely soluble in dilute hydrochloric acid, and, on standing, the 2-keto-pyrimidine formed by hydrolysis was pre-

cipitated. If placed in an Abderhalden dryer at 25° and 23 mm. (or 1 mm.), it continually lost weight and decomposed to a yellow glass-like mass. However, it was kept in a corked bottle for one week under normal conditions without any apparent change. The analysis of this product gave very unsatisfactory results, and the study of its properties will be continued.

Summary

1. In this paper are recorded some experimental results obtained by the further study of Biginelli's 2-keto-4-phenyl-5-carbethoxy-6-methyl-1,2,3,4-tetrahydropyrimidine.

2. The presence of the double bond in the 5,6-positions of the pyrimidine cycle is revealed by the action of bromine giving a characteristic dibromo derivative.

3. 2-Thio-4-phenyl-5-carbethoxy-6-methyl-1,2,3,4-tetrahydropyrimidine has been synthesized according to Hinkel, Hey and Samuel's method. We observed no evidence of the isomerization of this pyrimidine.

4. Alkylation of Biginelli's tetrahydropyrimidine is accomplished by interaction of this pyrimidine with phosphorus oxychloride followed by treatment with an alcoholate. The methyl compound obtained by this technique proved to be isomeric with the methylpyrimidine obtained by condensation of methylurea, benzaldehyde and ethyl acetoacetate. Both compounds are apparently N-methyl derivatives.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Mechanism of the Wurtz–Fittig Reaction. The Direct Preparation of an Organosodium (Potassium) Compound from an RX Compound

BY HENRY GILMAN AND GEORGE F. WRIGHT

Introduction

Present evidence[1] indicates that the Wurtz–Fittig reaction involves free radicals

$$2RX + 2Na \longrightarrow 2R- + 2NaX \quad (I)$$
$$2R- \longrightarrow R-R \quad (II)$$

and the intermediate formation of organo-alkali compounds

$$RX + 2Na \longrightarrow RNa + NaX \quad (III)$$
$$RNa + RX \longrightarrow R-R + NaX \quad (IV)$$

Organometallic compounds are definitely formed from RX compounds and metals like lithium, beryllium, magnesium, zinc, etc. Indirect evidence for the intermediate formation of organosodium and organo-po-

(1) Wooster, "Organo-alkali Compounds," *Chem. Rev.*, **11**, 1 (1932). An excellent recent review of the mechanism of the Wurtz–Fittig reaction is presented on pp. 79–83 and describes studies by Schorigin, Morton, Fuchs, Schlubach, Kirrmann, Goldschmidt, Ziegler, Schlenk, Kraus, Wooster, and Clarke and Bachmann.