in 50 ml. of ethanol). Trituration of the resultant gummy, red mass with ethanol and with acetone produced a tan solid (18.0 g.) which melted 75–94°. It was crystallized twice from absolute ethanol to give light tan platelets (17.0 g., 51% yield), m.p. 82–89°. The salt retained moisture and solvent of crystallization very firmly, and these could be removed only at 100° *in vacuo*, accompanied with some decomposition.

Anal. Calcd. for $C_{18}H_{27}N_3O.H_3PO_4$: N, 10.52; H_3PO_4, 24.54. Found:[12] N, 10.68; H_3PO_4, 24.58.

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[12] Corrected for 3.50% loss at 100°, *in vacuo*. Of this total, 1.04% was moisture, as determined by the Karl Fischer method.

7-Chloro-4-(4-dibutylaminobutylamino)-3-methylquinoline

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4-Aminoquinolines are well known for a considerable range of used as chemotherapeutic agents. Representatives of the group have antibacterial,[2] antimalarial,[3] and antitrypanosomal[4] activities, and also worth against extra-intestinal forms of amebiasis.[5–7] 7-Chloro-4-(4-dibutylaminobutylamino)-3-methylaminoline triphosphate has now been shown[8] to be effective against both intestinal and extra-intestinal forms of *Endameba muris*, the protozoan responsible for amebiasis in the hamster. The preparation of the drug was achieved by reaction of 4,7-dichloro-3-methylquinoline with 4-dibutylaminobutylamine, followed by conversion of the resultant base to the phosphate.

EXPERIMENTAL[9]

The reaction of 4,7-dichloro-3-methylquinoline[10,11] (21.2 g., 0.1 mole) with 4-dibutylaminobutylamine[12] (44 g., 0.22 mole) was run in phenol (60 g.) at 160–165° in the presence of a trace of potassium iodide. After 13 hr., the viscous mixture was cooled and quenched in an excess of cold aqueous sodium hydroxide, and the bases taken into methylene chloride. The mixture was extracted with a 2*N* hydrochloric acid, the bases then liberated, extracted with methylene chloride, dried, and fractionated. A 70% yield (25.6 g.) of the desired base was obtained as a viscous, golden oil; b.p. 190–193° (0.08 mm.); n_D^{25} 1.5741.

Anal. Calcd. for $C_{22}H_{34}ClN_3$: C, 70.28; H, 9.11; N, 11.18. Found: C, 69.98; H, 8.74; N, 11.18.

The base (25.5 g.) was dissolved in 150 ml. of propanol-2, chilled to 5°, and treated with a cold solution of 85% phosphoric acid (25.4 g.) in ethanol (100 ml.). A creamy-white phosphate resulted in crystalline form after scratching the vessel, and the solid was collected, washed (ether) and dried superficially. It was suspended in 500 ml. of boiling ethanol, boiling water added to effect solution, and then treated with charcoal. The pure 7-chloro-4-(4-dibutylaminobutylamino)-3-methylquinoline triphosphate (20.5 g., m.p. 186–186.6°) was obtained by two further crystallizations of the slightly impure salt (32.0 g.).

Anal. Calcd. for $C_{22}H_{34}ClN_3.3H_3PO_4$: N, 6.27; H_3PO_4, 43.90. Found: N, 6.17; H_3PO_4, 44.20.

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[1] Present address, Johnson & Johnson Research Center, New Brunswick, N. J.

[2] W. C. Austin, M. D. Potter, and E. P. Taylor, *J. Chem. Soc.*, 1489 (1958).

[3] F. Y. Wiselogle (ed.), *Survey of Antimalarial Drugs, 1941–1945.* Edward Brothers, Ann Arbor, Mich., 1946. Vol. II, pt. 2, pp. 1146, 1149.

[4] E. A. Steck in R. E. Kirk and D. F. Othmer (eds.). *Encyclopedia of Chemical Technology,* Interscience Publishers, Inc., New York, N. Y., 1955, Vol. **14**, p. 330.

[5] N. J. Conan, Jr., *Am. J. Trop. Med.*, **28**, 107 (1948); **31**, 18 (1951).

[6] M. T. Hoekenga and Q. Gonzalo-M., *Am. J. Trop. Med.*, **30**, 625 (1950).

[7] N. J. Conan, Jr., J. A. Head, and A. E. Brewer, *Trans. Roy. Soc. Trop. Med. Hyg.*, **43**, 659 (1950).

[8] The chemotherapeutic testing of the quinoline derivative was done under the direction of Dr. D. A. Berberian at this Institute.

[9] Analyses were run in these laboratories, and under guidance of Mr. M. E. Auerbach and Mr. K. D. Fleischer. Melting points given are corrected values, whereas boiling points are uncorrected.

[10] E. A. Steck, L. L. Hallock, and A. J. Holland, *J. Am. Chem. Soc.*, **68**, 380 (1946).

[11] H. Andersag, *Chem. Ber.*, **81**, 506 (1948).

[12] S. Archer and C. M. Suter, *J. Am. Chem. Soc.*, **74**, 4305 (1952).

Preparation of Aliphatic Ketones from Lithium Alkyls and Dimethylamides

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The condensation of lithium alkenyls, alkyls, and aryls with dimethylamides to give aldehydes and methyl ketones as a preparative method has been studied by Evans and co-workers.[1,2] In the ketone series, Evans[2] prepared several methyl ketones in practical yields by reacting lithium alkyls with *N,N*-dimethylacetamide. The present paper describes an extended application of this reaction to the synthesis of other aliphatic low molecular weight ketones. This extension includes the use of longer chain *N,N*-dimethylamides and the comparison of yields by interchanging the alkyl chains associated with the carboxamide and lithium groups. For example, ethylisopentyl ketone was formed in 75% yield from the condensation of isopentyllithium and *N,N*-dimethylpropionamide and in 78% yield from ethyllithium and *N,N*,4-trimethylvaleramide. Incidental to this work, this method of ketone synthesis was compared with those involving the well known nitrile-Grignard, and acid halide–

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[1] E. A. Braude and E. A. Evans, *J. Chem. Soc.*, 3334 (1955).

[2] E. A. Evans, *J. Chem. Soc.*, 4691 (1956); *Chem. and Ind. (London)*, 1596 (1957).

TABLE I

PREPARATION OF KETONES FROM LITHIUM ALKYLS

Alkyl Halide	Amide[a]	Ethyl Ketone	Yield, %	B.P., °C. (mm.)	n_D	Analyses, %				2,4-Dinitrophenylhydrazone, M.P., °C. (Uncorr.)
						Calcd.		Found		
						C	H	C	H	
Isopentyl bromide	*N*,*N*-Dimethylpropionamide	6-Methyl-3-heptanone[b]	75	65–66 (25)	1.4118^{26}	74.94	12.58	75.06	12.63	73–75[c]
Ethyl bromide	*N*,*N*,4-Trimethylvaleramide[d]	6-Methyl-3-heptanone[b]	78	71 (28)						72–73[c]
Ethyl bromide	*N*,*N*,2-Trimethylvaleramide[e]	4-Methyl-3-heptanone	80	70–76 (38)	1.4109^{25}	74.94	12.58	74.77	12.68	[f]
Ethyl bromide	*N*,*N*,2-Trimethylpropionamide[g]	2-Methyl-3-pentanone	56[h]	114–115[i] (760)						111–112
Ethyl bromide	*N*,*N*-Dimethylcyclohexanecarboxamide[j]	Ethylcyclohexyl ketone	70	73–77[k] (8)	1.4508^{28}	77.09	11.50	77.09	11.80	150–151

[a] Prepared by the slow addition of an ethereal solution of 1 molar equivalent of the required acid chloride to an ethereal solution containing 2.2 molar equivalents of dimethylamine at 0°. [b] G. Ponzio and A. de Gaspari, *Chem. Zentr.*, 189 (1899I), and H. Thoms and H. Kahre, *Chem. Zentr.*, 547 (1925II), reported the synthesis of this ketone by other methods. The first workers reported a b.p. of 163–163.5°/734.2 mm. The latter reported a b.p. of 160–163°/760 mm., n_D 1.42087, and a semicarbazone melting at 131–132°. A semicarbazone, m.p. 132–133°, was also reported by L. Bouveault and R. Locquin, *Bull. soc. chim. France*, **31**, 1153 (1904). [c] Despite the fact that the ketone obtained by either of the methods given in the table was shown to be homogeneous by vapor phase chromatography, we were unable to duplicate the m.p.'s of the semicarbazones reported by the aforementioned workers. In our hands the semicarbazones gave indefinite and erratic m.p.'s, although they gave satisfactory elemental analyses. The 2,4-dinitrophenylhydrazone proved to be a more reliable and easily purified derivative giving constant m.p.'s regardless of the method of preparation used. Calcd. for $C_{14}H_{20}N_4O_4$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.44; H, 6.70; N, 18.35. [d] B.p. 94–95°/10 mm.; n_D^{25} 1.4444. [e] B.p. 88–90°/10 mm.; n_D^{25} 1.4405. [f] No crystalline carbonyl derivative could be obtained. This confirmed the experience of J. Dubois and R. Luft, *Bull. soc. chim. France*, 1153 (1954), who prepared this ketone by another method. Their physical constants were: b.p. 53–54°/10 mm., n_D^{25} 1.4137, MR 39.05. Calcd. MR: 39.16. Found: 39.16. Vapor phase chromatography revealed a small impurity closely associated with the product. [g] B.p. 29°/13 mm.; n_D^{30} 1.4341. H. Rapoport and R. Bonner, *J. Am. Chem. Soc.* **72**, 2783 (1950) reported a b.p. of 178–179°, and n_D^{25} 1.4388. [h] This yield was obtained in the one run which was made. [i] G. Wagner, *J. prakt. Chem.*, **44**, 257 (1891), reported b.p. 113.8–114°/745 mm. [j] B.p. 118–121°/12 mm., n_D^{24} 1.4765. M. Mousseron, R. Jacquier, M. Mousseron-Canet, and R. Zagdoun, *Bull. soc. chim. France*, 1042 (1952), reported b.p. 135–140°/20 mm. [k] W. Scharvin, *Ber.*, **30**, 2864 (1897), reported b.p. 195°.

Grignard condensations and was found to be greatly superior in yield and ease of purification of the products. For example, ethylisopentyl ketone was formed in only 20–38% yield from either the condensation of 4-methylvaleronitrile with ethylmagnesium bromide or the condensation of propionitrile with isopentylmagnesium bromide.[3] It was found, however, that the scope of the reaction was limited to primary lithium alkyls, as attempts to prepare 4-methyl-3-heptanone and ethylcyclohexyl ketone from *N*,*N*-dimethylpropionamide, lithium, and 2-bromopentane and cyclohexyl bromide, respectively, gave only negligible amounts of ketonic products.[4] These two ketones were, however, prepared smoothly and in good yields from *N*,*N*,2-trimethylvaleramide and *N*,*N*-dimethylcyclohexylcarboxamide and ethyllithium.

Table I summarizes the results obtained in the preparation of some known representative ethyl ketones.

EXPERIMENTAL[5,6]

The following is a general procedure by which the ketones listed in Table I were prepared.

The lithium alkyls were prepared by the procedure of Gilman and co-workers.[7]

A suspension of 1.6 gram-atoms of lithium ribbon, cut into small pieces, in 800 ml. of anhydrous ether was prepared in a flask fitted with reflux condenser, nitrogen inlet tube, thermometer, and addition funnel. The suspension was cooled to −10°, and, while the system was being swept with nitrogen, a solution of 0.83 mole of the required alkyl bromide in 200 ml. of anhydrous ether was added over a period of 2 hr. The mixture was stirred for 1 hr. longer at −10°. Then the temperature was lowered to −20° and a solution of 0.8 mole of the required *N*,*N*-dimethylamide in 200 ml. of anhydrous ether was added dropwise over a period of 1.5 hr. The temperature was then allowed to rise gradually to 25° over a period of 3 hr. with continued stirring under nitrogen atmosphere. At the end of this time, the solution was cooled to −10° and 500 ml. of a cold, saturated ammonium chloride solution was slowly added. The mixture was stirred for 30 min., and the ether layer was separated, washed with 1*N* hydrochloric acid and with water and dried.

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(3) For a discussion of the reactions of nitriles having α-hydrogens with Grignard reagents see C. R. Hauser and W. J. Humphlett, *J. Org. Chem.*, **15**, 359 (1950).

(4) Evans, ref. 2, noted a similar limitation with other examples.

(5) All melting points and boiling points are uncorrected.

(6) The authors are indebted to Mr. Louis Brancone and staff for the microanalyses.

(7) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949).

Evaporation of the solvent at reduced pressure left a colorless liquid residue which was distilled through a 10-in. Vigreux column.

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The Question of Active Cobalt in the Decomposition of Grignard Reagents in the Presence of Cobaltous Halides

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Kharasch, Lewis, and Reynolds[1] have proposed the following reaction scheme to account for the products formed when phenylmagnesium bromide is allowed to react with an alkyl halide in the presence of a cobaltous halide.

$$C_6H_5MgBr + CoX_2 \longrightarrow C_6H_5CoX + MgBrX$$

$$2C_6H_5CoX \longrightarrow C_6H_5C_6H_5 + 2\cdot CoX$$

$$RX + \cdot CoX \longrightarrow R\cdot + CoX_2$$

Wilds and McCormack[2] have pointed out several weaknesses of the above scheme, such as the fact that organocobalt compounds of this type have not been prepared before, nor is there any evidence for the existence of the cobalt subhalide radical. Furthermore, they found that the reactivity of the mixture was only somewhat diminished if the Grignard reagent and the cobaltous halide were brought together several hours before the introduction of the alkyl halide; a fact which argues against the presence of a thermally unstable intermediate. As an alternative path they have proposed finely divided, active cobalt as the reactive intermediate.

$$2RMgX + CoX_2 \longrightarrow 2MgX_2 + CoR_2$$

$$CoR_2 \longrightarrow Co + 2R\cdot$$

$$Co + 2R'X \longrightarrow CoX_2 + 2R'\cdot$$

Walling[3] has stated a preference for this latter proposal and has cited as additional evidence the work of Chu and Friel[4] who found that the sodium-naphthalene radical ion in tetrahydrofuran solution instantly reduced cobaltous chloride to metallic cobalt in a highly reactive colloidal form which reacted with air and reduced cupric chloride to the cuprous state.

In order to test the hypothesis of active cobalt as the reactive intermediate in the reactions of Grignard reagents with alkyl halides in the presence of cobaltous halides, a tetrahydrofuran solution of active cobalt was prepared by the method of Chu and Friel. Treatment of this solution with ethyl bromide failed to produce any gaseous reaction products. A further test of this hypothesis was conducted by adding a suspension of cobaltous chloride and ethyl bromide in tetrahydrofuran to a solution of the sodium-naphthalene radical ion. Again no gaseous products were produded.

In order to rule out the possibility that the solvent or the naphthalene was entering into the above reactions a solution of phenylmagnesium bromide in tetrahydrofuran was prepared. A portion of naphthalene was also added to this solution. Addition of ethyl bromide and cobaltous bromide in tetrahydrofuran now produced an immediate evolution of gas which amounted to 48% of the theoretical amount. Analysis of this gas showed that it was 28% ethane and 72% ethylene. These findings are in good agreement with the observations of Kharasch, Lewis, and Reynolds[1] who reported a similar yield for the reaction of phenylmagnesium bromide, ethyl bromide, and cobaltous chloride in ethyl ether.

While the above results do not allow one to draw any further conclusions regarding the mechanism proposed by Kharasch *et al.*, it seems reasonable that the postulation of reactive colloidal cobalt may now be abandoned. It is not likely that the state of the cobalt produced by the Grignard reagent is sufficiently different from that produced by the reaction with the sodium-naphthalene radical ion to account for the complete inactivity toward ethyl bromide in the latter case.

EXPERIMENTAL

All reactions were carried out in a 500 ml., two necked flask equipped with a dropping funnel and a condenser. The apparatus was flushed with nitrogen before each reaction. Stirring was provided by a magnetic stirrer. All gases were collected over a saturated brine solution. Gas analysis was carried out by chromatography over a charcoal filled column at 32° with helium as the eluting gas.

Reaction of ethyl bromide with active cobalt. A solution of the sodium-naphthalene radical ion was prepared by reacting 2.4 g. of finely dispersed sodium with 14 g. of naphthalene in 150 ml. of anhydrous tetrahydrofuran. To the dark green solution was added a mixture of 6.5 g. of anhydrous cobaltous chloride and 7.85 g. of ethyl bromide in 100 ml. of tetrahydrofuran. The reaction immediately turned to dark black, and heat was evolved. However, no gas was given off.

In another experiment the cobaltous chloride was added to the solution of the radical ion before the addition of the ethyl bromide in the tetrahydrofuran. Again the solution turned dark black, and no gas was evolved.

Reaction of phenylmagnesium bromide, ethyl bromide, and cobaltous bromide. A solution of phenylmagnesium bromide in tetrahydrofuran was prepared from 7.85 g. (0.05 mole) of bromobenzene, 1.30 g. of magnesium, and 50 ml. of tetrahydrofuran. The mixture was heated for 0.5 hr. after the initial vigorous reaction had subsided. The mixture was

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(1) M. S. Kharasch, D. W. Lewis, and W. B. Reynolds, *J. Am. Chem. Soc.*, **65**, 495 (1943).

(2) A. L. Wilds and W. B. McCormack, *J. Org. Chem.*, 14, 45 (1949).

(3) Cheves Walling, *Free Radicals in Solution*, John Wiley and Sons, New York, 1957, p. 589.

(4) T. L. Chu and J. V. Friel, *J. Am. Chem. Soc.*, **77**, 5838 (1957).