

THE PREPARATION OF 2-ALKYLCYCLOHEXANONES*

By E. RITCHIE† and W. C. TAYLOR†

In an investigation which has now been discontinued, it was necessary to develop a flexible method for the preparation of 2-alkylcyclohexanones. Initially two methods appeared to be attractive: (a) the alkylation of an enamine of cyclohexanone followed by acid hydrolysis¹ and (b) the alkylation of 2-ethoxycarbonylcyclohexanone followed by ketonic hydrolysis; but closer examination of the literature revealed that each had serious disadvantages. Under the best conditions the overall yield from an enamine and a simple alkyl halide is less than 50%² and moreover the use of α,ω -dihaloalkanes gives a mixture of products.³ In the second route, the alkylation of the β -keto ester was frequently difficult, affording low yields even after prolonged refluxing in toluene or xylene of the sodium or potassium derivative with the alkyl halide.^{4,5} In addition, hydrolysis to the ketone was unsatisfactory; under acid conditions hydrolysis was often very slow⁶ and under alkaline conditions hydrolysis to the dicarboxylic acid was usually a major competing reaction.^{7,8}

However, by a few simple modifications the difficulties in the second method were easily overcome and the 2-alkylcyclohexanones prepared in an overall yield of 70–75%. The sodium derivative of 2-ethoxycarbonylcyclohexanone was readily formed by adding sodium hydride to a solution of the ester in benzene–dimethylformamide⁹ and alkylation accomplished in high yield by refluxing the solution with the alkyl halide plus sodium iodide. Since ketonic hydrolysis of the resulting esters appeared to be slow because of their low solubility in aqueous acid, a mixture of acetic and hydrochloric acid (or hydrobromic acid in the case of esters of higher molecular weight) was employed, when the desired reaction was smoothly effected. It appears that these very convenient procedures could be profitably extended to other β -keto esters.

Experimental

Alkylation of 2-Ethoxycarbonylcyclohexanone.—The ester (51 g, 0.3 mole) in dry benzene (100 ml) was added in one lot to a suspension of sodium hydride (8 g, 0.33 mole) in benzene (300 ml) and dimethylformamide (200 ml). After refluxing for about 1 hr almost all of the sodium hydride had dissolved. Anhydrous sodium iodide (45 g, 0.3 mole) was then added, followed by

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† Department of Organic Chemistry, University of Sydney.

¹ Stork, G., Brizzolara, A., Landesman, H., Szmuszkowicz, J., and Terrel, R., *J. Amer. Chem. Soc.*, 1963, **85**, 207.

² Opitz, G., Mildenerger, H., and Suhr, H., *Liebigs Ann.*, 1961, **649**, 47.

³ Opitz, G., and Mildenerger, H., *Liebigs Ann.*, 1961, **650**, 115.

⁴ Hibbit, D. C., and Linstead, R. P., *J. Chem. Soc.*, 1936, 470.

⁵ Cope, A. C., and Synerholm, M. E., *J. Amer. Chem. Soc.* 1950, **72**, 5228.

⁶ Shechter, H., and Kirk, J. C., *J. Amer. Chem. Soc.*, 1951, **73**, 3087.

⁷ Grewe, R., *Ber. dtsh. chem. Ges.* 1943, **76**, 1072.

⁸ Kon, G. A. R., *J. Chem. Soc.*, 1933, 1081.

⁹ Ramirez, F., and Paul, A. P., *J. Org. Chem.*, 1954, **19**, 183.

the alkyl chloride or bromide (0.33 mole). Sodium halide was precipitated almost immediately. The mixture was refluxed overnight, cooled, poured into dilute acid, and shaken with ether. The extract was washed, dried, and distilled. The esters were obtained in yields of 90–95%.

The following alkylation products were prepared: n-butyl, b.p. 142–144° at 14 mm, n-dodecyl, b.p. 192–194° at 1.5 mm; 1,6-hexamethylenebis, b.p. 230–240° at 1 mm; 2-ethoxy-carbonylethyl, b.p. 189–191° at 15 mm; 3-ethoxycarbonylpropyl, b.p. 146–148° at 0.5 mm.

Ketonic Hydrolysis.—The ester (50 g) was refluxed for 24 hr with glacial acetic acid (100 ml) and concentrated hydrochloric or hydrobromic acid (100 ml). The cooled mixture was diluted, saturated with salt, and extracted with ether. The extract was washed several times with saturated brine, dried, and distilled. The yields were about 80%.

The following 2-alkylcyclohexanones were obtained: n-butyl, b.p. 98° at 15 mm, semicarbazone m.p. 150° (lit. m.p. 150°); n-dodecyl, b.p. 157° at 0.7 mm, m.p. about 26°, *semicarbazone*, colourless needles from methanol, m.p. 96–97° (Found: C, 70.4; H, 11.8%. Calc. for $C_{19}H_{37}ON_3$: C, 70.5; H, 11.5%); 1,6-hexamethylenebis, b.p. 150–185° at 1 mm, a colourless oil, about half of which crystallized as colourless prisms, m.p. 68° (lit.³ a liquid, b.p. 145–146° at 0.01 mm) from light petroleum (Found: C, 77.7; H, 10.8%. Calc. for $C_{18}H_{30}O_2$: C, 77.7; H, 10.8%); 2-carboxyethyl, b.p. 150–155° at 1 mm, m.p. 62° (lit. m.p. 62°); 3-carboxypropyl, b.p. 165–167° at 1 mm, m.p. 58–59° (lit. m.p. 59°).