48% hydrobromic acid, and 30 ml of glacial acetic acid was sealed in a Carius tube and heated for 3 hr at 200°. The product was worked up in the usual way and purified by chromatography on alumina with petroleum ether (bp 30–60°). The yield of **11** was 1.3 g (34%), mp 152–152.5°. The product had an ultraviolet spectrum typical of an anthracene.

Anal. Calcd for $C_{25}H_{18}$: C, 94.32; H, 5.69. Found: C, 94.46; H, 5.59.

Elbs Reaction Procedure.—A mixture of 3 g of 2-benzylphenyl 1-naphthyl ketone and 1 g of powdered zinc was heated for 3 hr at 415–430° in an atmosphere of nitrogen. The product was worked up in the usual way and purified by chromatography on alumina with petroleum ether. The product was 0.9 g (32%) of 7-phenylbenz[*a*]anthracene, mp 182–183°. No other products were isolated.

Cyclodehydration Procedure Using Alumina.—A mixture of 1.5 g of 2-benzylphenyl 1-naphthyl ketone and 15 g of alumina was heated at 250° for 2.5 hr at a pressure of 1 mm. After cooling, the alumina was poured onto a chromatography column packed with alumina and the product was eluted with petroleum ether. Only 7-phenylbenz[*a*]anthracene was obtained: 0.2 g (14%), mp 182–183°.

Cyclodehydration Procedure Using Liquid Hydrogen Fluoride.—The ketone, 1.5 g of 2-benzylphenyl 2-naphthyl ketone, was placed in a 125-ml polyethylene bottle and the bottle was half-filled with liquid hydrogen fluoride. During the addition, the mixture was stirred with a magnetic stirring bar. After the addition, the solution was allowed to stand without stirring until the hydrogen fluoride had evaporated. The oil was dissolved in benzene and washed with water. The oil that was left after removal of the benzene crystallized on addition of ethanol. Recrystallization of this material from ethanol gave 0.2 g (14%) of 9-(2-naphthyl)anthracene, mp 199.5–200°. Concentration of the mother liquor gave 1.2 g of starting material.

Alkylation of Unsymmetrical β-Diketones through Isomeric Disodio Salts in Liquid Ammonia. Structural Effects on Ease of Dianion Formation[1]

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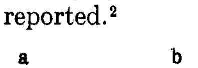
Received August 17, 1965

A study was made of structural effects on the relative ease of secondary ionization at methyl, methylene, and methinyl sites of unsymmetrical β-diketones by sodium amide in liquid ammonia to form disodio salts. The relative ease of ionization at the secondary sites was phenylacetyl > acetyl > propionyl > isobutyryl. This was determined by alkylation of disodio salts of unsymmetrical diketones and analysis of the reaction mixtures for the isomeric alkylation products. Moreover, in an intermolecular comparison of secondary ionizations the relative ease of ionization at the methyl and γ-methylene sites of acetylacetone and dipropionylmethane, respectively, was found to be acetyl > propionyl, but in this intermolecular comparison the difference was not so great as that observed in the intramolecular one. These results show that many unsymmetrical β-diketones can be alkylated through only one of the two possible disodio salts to form a single product essentially uncontaminated by the isomeric one.

Alkylations at the terminal methyl group (a-position) of unsymmetrical β-diketone **1** with benzyl chloride has previously been effected by means of 2 molecular equiv of potassium amide in liquid ammonia, which converted **1** to dipotassio salt **1''**.[2,3] No alkylation at the b-position of **1** was observed.[2] Similarly, exclusive benzylation at the terminal methyl group of 2-acetylcyclohexanone and 2-acetylcyclopentanone was reported.[2]



$\overset{a}{C}H_3COCH_2CO\overset{b}{C}H_2CH_2C_6H_5$

1

$KCH_2CO\overset{K}{C}HCOCH_2CH_2C_6H_5$

1''

We have now determined the relative extents of methylation at such a- and b-positions of four other unsymmetrical β-diketones through their disodio salts in liquid ammonia. The disodio salts were chosen rather than the dipotassio salts because, in contrast to the latter, which would probably undergo rapid metal–hydrogen exchange with the monopotassio salts of the alkylation products,[4] the disodio salts should exhibit such exchanges very slowly if at all.[4] Moreover, the disodio β-diketones appeared to be quite soluble in liquid ammonia, whereas dipotassio β-diketones often were not. The general procedure involved addition of the β-diketone to 2 molecular equiv of sodium amide in liquid ammonia, followed by 1 molecular equiv of methyl iodide. Thus, unsymmetrical β-diketone **2** underwent methylation at the a- and b-positions to form **3** and **4** to the extents of 89 and 11%, respectively (Scheme I).[3]

Similarly, unsymmetrical β-diketones **4** and **5** underwent methylation at the a- and b-positions to the relative extents of 99:1, and β-diketone **9** exhibited exclusive methylation at the b-position, the methylene hydrogen of which is activated by the phenyl group (Schemes II–IV). **9** also underwent exclusive alkylation at the b-position with the larger halides, *n*-butyl bromide and benzyl chloride. It is to be noted that two of the unsymmetrical β-diketones studied, **4** and **5**, were produced as one of the two possible alkylation products of **2** and **4**, respectively.

The relative amounts of the isomeric methylation products of unsymmetrical β-diketones **2** and **4**, and the *n*-butylation product of **9** were determined by vpc comparisons with authentic samples. The relative amounts of methylation products from **5** could not be determined by vpc since conditions were not found where the isomers could be separated. However, the product composition was determined by vpc of the neutral fraction of an alkaline hydrolysate. Only traces of pinacolone which would arise from b-isomer **8** could be observed; the major product was 3-methyl-2-butanone derived from a-isomer **7**. The validity of this method of analysis was demonstrated by the fact

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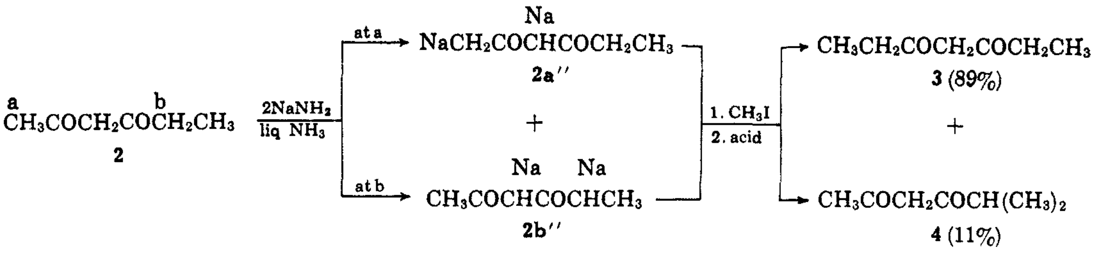
[1] Supported by the National Science Foundation.

[2] T. M. Harris and C. R. Hauser, *J. Am. Chem. Soc.*, **81**, 1160 (1959).

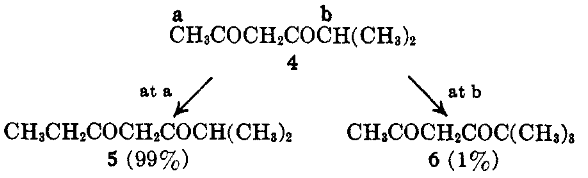
[3] For convenience, mono- and dialkali salts are designated by prime (') and double prime (''), respectively, and only carbanion resonance forms are indicated even though other resonance forms may contribute more to the structures of the anions.

[4] With potassio salts but not with sodio salts proton transfers occur readily between diketone monoanions and dianions: see K. G. Hampton, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 61 (1965). In addition, the possibility exists particularly with potassio salts for direct or solvent-mediated intramolecular proton transfer within the dianions; for example, interconversion of **2a''** and **2b''** (Scheme I) might occur.

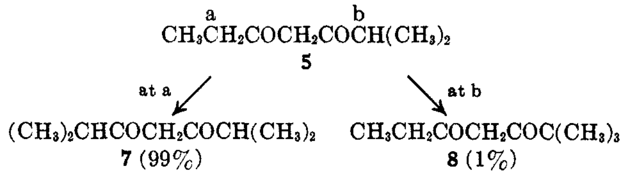
SCHEME I



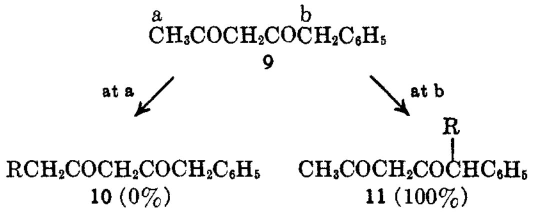
SCHEME II



SCHEME III



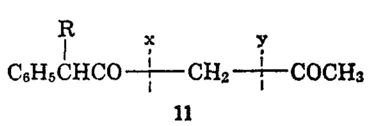
SCHEME IV



R = CH_3, n-C_4H_9, or $CH_2C_6H_5$

that hydrolysis of an authentic sample of **8** afforded principally pinacolone in the neutral fraction.

In the methylation of β-diketone **9**, the product was shown by vpc not to contain any of the a-isomer **10** (R = CH_3), but the b-isomer **11** (R = CH_3) could not be separated from the starting compound **9** by this process. However, the crude mixture was indicated to consist mainly of the b-isomer by alkaline hydrolysis to afford α-methylated phenylacetone and only a small amount of phenylacetone. No 2-butanone, which would have resulted from hydrolysis of the a-isomer **10** was observed.[5] Similarly, the benzylation product of β-diketone **9** was indicated to contain the b-isomer **11** (R = $CH_2C_6H_5$) and not the a-isomer.[5]

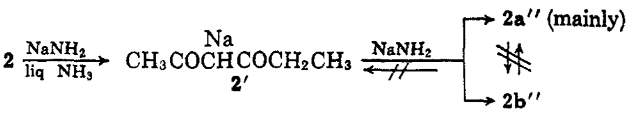

$$\overset{R}{C_6H_5CHCO}\overset{x}{\vdots}CH_2\overset{y}{\vdots}COCH_3$$

11

It can be seen from Schemes I–IV that the order of methylation observed was phenylacetyl > acetyl > propionyl > isobutyryl. At least with unsymmetrical β-diketone **9**, variation of the alkyl halide did not affect the result (Scheme IV). The degree of specificity was high in all cases. These results are of obvious synthetic value, since they show that unsymmetrical β-diketones containing any of these four terminal groups or closely related groups will undergo alkylation through their disodio salts in such a selective fashion that one product will be formed almost to the exclusion of the other. Moreover, the rules of selectivity for alkylation probably are valid also for acylation, carbonation, and other types of condensation reactions.

It is likely that the alkylation products arise in about the same ratio that ionization had occurred. For example, β-diketone **2** was initially converted to its monosodio salt **2′**, which then underwent a secondary ionization at the methyl or methylene position to form disodio salts **2a″** or **2b″**, respectively (Scheme V).[3] These disodio salts probably were not in equilibrium with one another or with the monosodio salt **2′** and, to the extent that alkylation of both dianions was complete and no side reactions had occurred, product ratios accurately reflected the ratio of dianions **2a″** and **2b″** that had been present.

SCHEME V



Evidence that isomeric dianions, such as **2a″** and **2b″**, are not in equilibrium with one another can be deduced from studies of the relative reactivities[6] of various types of disodio salts of diketones. It has been found that propionyl-type disodio salts like **2b″** are more reactive than acetyl type like **2a″**. Thus, if substantial amounts of **2b″** had been in a rapid equilibrium with **2a″**, the formation of **4**, not **3**, would have predominated. Moreover, the ratio of the a- and b-isomers of the methylation product of β-diketone **2** did not change appreciably when the halide was added 3 or 30 min after addition of the β-diketone to the reagent (see Experimental Section). This indicates that slow equilibration could not have caused the ratios we observed to be significantly different from the initial ionization ratios.

The fact that the diketones did not undergo quantitative alkylation (see Experimental Section) decreases to some extent the reliability of the conclusions that can be drawn concerning the relative reactivity of various structural types. However, it seems probable that the principal factors contributing to these yields were ones which would affect equally the formation of each of the dianions. Prominent among these is the

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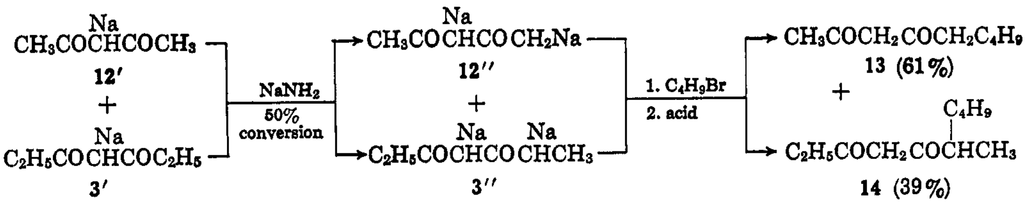
[5] Diketone **11** underwent cleavage primarily at position y to give α-alkylated phenylacetone rather than at x to give acetone, apparently because the carbonyl group at x is sterically hindered. Cleavage at both of the corresponding positions would be expected with **9** and **10** to form phenylacetone and the aliphatic ketone.

[6] Unpublished results of K. G. Hampton, T. M. Harris, and C. R. Hauser. Results are to be published soon.

Scheme VI



fact that either excess or insufficiency of any one of the three reagents, diketone, sodium amide, or alkyl halide, would cause a decrease in the formation of alkylation products. Solvolysis of methyl iodide in ammonia and adventitious moisture may also have been contributing factors. No substances other than the reported alkylation products or recovered starting materials were detected by gas chromatography, ruling out the possibility that some dianions underwent alkylation partially or exclusively on oxygen, while others reacted only at carbon. O-Alkylation products have not been observed in the alkylation of dianions of diketones.[2,4,6]

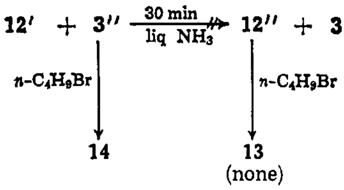
Incidentally, because in the earlier study exclusive formation of the acetyl alkylation product had been observed in the reaction of dipotassio salts, the methylation of **2** by means of potassium amide was also examined. Although the dipotassio salts of **2** were largely precipitated and were possibly in equilibrium with one another, essentially the same ratio (87:13) of **3** and **4** was observed as had been obtained with the disodio salts, which were essentially in solution.[7]

One different comparison of the competitive formation of disodio salts was made in which the competition was between acetyl and propionyl sites in separate diketone molecules. An equal molar mixture of acetylacetone (**12**) and dipropionylmethane (**3**) was treated with 3 equiv of sodium amide in liquid ammonia. The first 2 equiv produced the monosodio salts **12′** and **3′**, respectively, and these competed for the final equivalent of base. Treatment of the resulting mixture of **12″** and **3″** with *n*-butyl bromide afforded a 61:39 mixture of the respective butylation products **13** and **14** (Scheme VI).[8]

The lower ratio of methyl to methylene alkylation products obtained with these diketones than had been obtained with diketone **2** may be largely accounted for by the fact that, as the third equivalent of sodium amide was added to the mixture of monosodio salts, the more reactive salt **12′** (derived from acetylacetone) was depleted faster, thus improving the competitive position of the other monosodio salt **3′**. Consequently, although the acetyl-type disodio salt **12″** still is the principal one formed, the two types of reactive sites appear much more closely matched in this intermolecular competition than in the study of diketone **2** where the two competing sites were embodied in a single molecule.

The success of this intermolecular comparison of secondary ionization sites depended upon the inability of the disodio salt of dipropionylmethane (**3″**) to abstract a proton from the monosodio salt of acetylacetone (**12′**). That this proton transfer does not occur under these conditions was demonstrated by butylation of a mixture of these sodio salts (that had been prepared separately and then mixed together) in liquid ammonia (Scheme VII). The mixture was stirred for 30 min before the alkyl halide was added. Vpc indicated that the only alkylation product was **14** from dipropionylmethane. No proton transfer from acetylacetone had occurred.

Scheme VII



The sodio salt results, particularly the intramolecular comparison using diketone **2** and the intermolecular comparison using diketones **1** and **3**, are of interest in comparison with those recently obtained by House and Trost with 2-heptanone.[9] They observed that the enolate anion resulting from methyl ionization was the principal anion formed under kinetically controlled conditions. However, with conditions that allowed equilibration of anions they obtained mostly the more branched enolate anions, resulting from ionization of the 3-methylene group. While it is not known whether the more or the less stable dianions have been formed in our preparation of the disodio salts, their observation with the monoketone appears to indicate that the dianions are the more basic ones in these cases. Thus, their result lends some support to our conclusion that the alkylation products of disodio salts of unsymmetrical diketones reflect primarily the result of irreversible and unequilibrated dianion formation. However, their findings may have no bearing on the question of stability of β-diketone dianions.

Experimental Section[10]

Alkylation of Disodio Salts of Unsymmetrical β-Diketones.—In Schemes I–IV are summarized the per cent composition of the

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[7] It was not determined whether in the previous work with dipotassio salts the minor alkylation product had been overlooked because gas chromatography had not been used or whether the minor products had not been present because more bulky groups were contained in the alkyl halides and β-diketones.

[8] A similar experiment was conducted with potassio salts; the salts were heavily precipitated in the reaction mixture. The product ratio was 83:17.

[9] H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341 (1965).

[10] Melting points were taken on a Mel-Temp capillary melting point apparatus and are uncorrected. Analyses are by Dr. Ing. A. Schoeller Mikro-Labor, Kronach, West Germany, and by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were obtained with a Perkin-Elmer Model 137 Infracord using the potassium bromide pellet method for solids, and neat liquid between sodium chloride plates for liquids. Vapor phase chromatograms were obtained on an F and M Model 500 gas chromatograph equipped with thermal conductivity detectors using 2-ft silicone gum rubber, 5-ft Apiezon L, and 5-ft Carbowax 20M columns. Reaction products with the exception of **11** (R = $n\text{-}C_4H_9$ and $CH_2C_6H_5$) were identified by comparison of retention times with those of authentic samples. The product ratios were determined by integration of the curves of the gas chromatograms. Several chromatograms were made in each case; average values are reported.

products obtained for various alkylations. The details are described below.

A. **Methylation.**—To a stirred suspension of 0.20 mole of sodium amide[11] in 400 ml of liquid ammonia was added 11.4 g (0.10 mole) or 2,4-hexanedione (**2**) in 20 ml of ether. After 30 min, 14.2 g (0.10 mole) of methyl iodide in 20 ml of ether was added rapidly to the stirred solution. The reaction mixture was stirred 30 min, 250 ml of ether was added, and the ammonia was evaporated on the steam bath. The ethereal suspension was cooled in ice, and a mixture of 100 g of ice and 30 ml of cold, concentrated hydrochloric acid was added. The ethereal layer was separated and the aqueous layer was extracted three times with ether. The combined ethereal solution was dried with anhydrous magnesium sulfate and filtered, and the ether was evaporated. Vpc of the crude residue showed the presence of **2**, 3,5-heptanedione (**3**), and 5-methyl-2,4-hexanedione (**4**); the ratios of **3** and **4** were calculated (see Scheme I). In another experiment methyl iodide was added 3 min after addition of diketone **2** to afford **3** and **4** in the ratio 88:12. The total yield of **3** and **4** in these reactions ranged from 56 to 66%.

Similarly, 5-methyl-2,4-hexanedione (**4**) was methylated as described above for **2**, methyl iodide being added after 50 min. The combined yield of **5** and **6** was 56%, bp 76–79° (20 mm) (see Scheme II).

The methylation of 2-methyl-3,5-heptanedione (**5**) was conducted similarly, methyl iodide being added after 30 min. Isomers **7** and **8** could not be separated by vpc. The total yield of **7** and **8** was 58%. Since the products could not be separated, 5 g of the crude product was refluxed with 25 ml of 20% potassium hydroxide for 5 hr. The solution was cooled and extracted with ether. The ether was evaporated and vpc of the residue showed that the ratio of butanone:3-methyl-2-butanone:pinacolone was 20:79:1. Most of the butanone probably came from **5**, not **8**, because hydrolysis of an authentic sample of **8** by the same procedure gave a ratio of butanone:pinacolone of 12:88. It is estimated that the ratio of **7** to **8** was about 99:1 (see Scheme III).

The methylation of 1-phenyl-2,4-pentanedione (**9**) was effected similarly, methyl iodide being added after 30 min. Vpc of the product showed that there was a negligible amount of **10** (R = CH_3). However, **11** (R = CH_3) failed to be resolved from starting material. A solution of 0.8 g of the crude product in 25 ml of 10% aqueous potassium hydroxide was refluxed 15 hr. The solution was cooled and washed with ether. The extract was concentrated and analyzed by vpc (see Scheme IV, R = CH_3). No 2-butanone was obtained and the ratio of 3-phenyl-2-butanone to phenylacetone was 91:9. The copper chelate, prepared from 1 g of the crude diketone and an aqueous solution of copper acetate, gave an infrared spectrum essentially identical with that of the authentic copper chelate of **11** (R = CH_3) (see below).

B. **Butylation of 1-Phenyl-2,4-pentanedione (9).**—To a suspension of 0.10 mole of sodium amide in 400 ml of liquid ammonia was added 8.8 g (0.05 mole) of diketone **9** in 20 ml of ether. After 20 min, 6.85 g (0.05 mole) of butyl bromide in 20 ml of ether was added rapidly. The reaction mixture was worked up as described above for methylation to afford 8.9 g (77%) of 5-phenyl-2,4-nonanedione (**11**, R = n-C_4H_9), bp 125–128° (0.6 mm). Vpc of the crude product showed none of the isomeric **10**. The retention time of **11** (R = n-C_4H_9) was significantly different from those of **10** (R = C_4H_9) and **9**.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C. 77.73; H, 8.46.

Diketone **11** (R = n-C_4H_9) (1 g) was refluxed in an aqueous 10% potassium hydroxide solution for 3 hr. The mixture was cooled and extracted with small portions of ether. The ethereal solution was dried and filtered, and the ether was evaporated. Vpc of the residue showed a small peak for acetone and a large peak for 3-phenyl-2-heptanone but no 2-heptanone. The semicarbazone of 3-phenyl-2-heptanone was prepared and after recrystallization from aqueous ethanol melted 156–158°. The mixture melting point with an authentic sample prepared as described below was not depressed.

3-Phenyl-2-heptanone, bp 138–141° (20 mm), was independently prepared in 32% yield from 4.6 g (0.20 g-atom) of sodium in absolute ethanol, 26.8 g (0.20 mole) of phenylacetone, and 27.4 g (0.20 mole) of butyl bromide by the method of Levy and Jullien.[12] The semicarbazone melted at 156–158° after recrystallization from aqueous ethanol (lit.[12] mp 156–158°).

C. **Benzylation of 9.**—This experiment was effected with benzyl chloride essentially as described above for the butylation of **9** to afford 10.2 g (77%) of 5,6-diphenyl-2,4-hexanedione **11** (R = $CH_2C_6H_5$), bp 164–167° (1 mm). Vpc of the product gave only a single peak.

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C. 81.16; H. 6.75.

Diketone **11** (R = $CH_2C_6H_5$) was hydrolyzed with aqueous potassium hydroxide. Vpc of the product showed a large peak for 3,4-diphenyl-2-butanone and a small peak for acetone. The semicarbazone melted at 145–147° after recrystallization from aqueous ethanol. The mixture melting point with an authentic sample, which is described below, was undepressed.

3,4-Diphenyl-2-butanone was prepared essentially by the procedure employed above for 3-phenyl-2-heptanone, except benzyl chloride was substituted as the alkylating agent. The procedure afforded 22.7 g (50%) of ketone, bp 190–193° (20 mm) [lit.[12] bp 188–189° (20 mm)]. The semicarbazone melted at 146–148° after recrystallization from aqueous ethanol (lit.[12] mp 144–145°).

Competitive Disodio Salt Formation between Acetylacetone (12) and 3,5-Heptanedione (3).—A suspension of 0.15 mole of sodium amide in 400 ml of liquid ammonia was added from an inverse addition flask[13] to a solution of 0.05 mole each of acetylacetone (**12**) and 3,5-heptanedione (**3**) in 400 ml of liquid ammonia. After 30 min, 6.85 g (0.05 mole) of butyl bromide in 20 ml. of ether was added rapidly. The reaction mixture was worked up as described in the first experiment. Vpc of the crude product showed the ratio of 2,4-nonanedione (**13**) to 6-methyl-3,5-decanedione (**14**) was 61:39. A repeat of this experiment showed the ratio of 62:38.

Attempted Equilibration of Monosodio Salt 12′ and Disodio Salt 3″.—To a suspension of 0.10 mole of sodium amide in 400 ml of liquid ammonia was added 6.4 g (0.05 mole) of 3,5-heptanedione (**3**) in 20 ml of ether. After 30 min. 6.1 g (0.05 mole) of monosodioacetylacetone (**12′**), prepared by reaction of the diketone with metallic sodium, was added from an erlenmeyer flask through Gooch tubing. After 1 hr, 6.85 g (0.05 mole) of butyl bromide was added and the reaction mixture was worked up as described in the first experiment. Vpc of the crude product showed acetylacetone (**12**), 3,5-heptanedione (**3**), and 6-methyl-3,5-decanedione (**14**) but no 2,4-nonanedione (**13**).

Methylation of Dipotassio-2,4-hexanedione.—To a solution of 0.20 mole of potassium amide[14] in 400 ml of liquid ammonia was added 11.4 g (0.10 mole) of 2,4-hexanedione (**2**) in 20 ml of ether. After 30 min, 14.2 g (0.10 mole) of methyl iodide in 20 ml of ether was added. The reaction mixture was worked up as described in the first experiment. Vpc of the product showed the ratio of **3** to **4** of 87:13.

Competitive Dipotassio Salt Formation between Acetylacetone (12) and 3,5-Heptanedione (3).—A 500-ml three-necked flask containing 0.15 mole of potassium amide in 400 ml of liquid ammonia was cooled in a Dry Ice–acetone bath while nitrogen was passed over the reaction mixture. A solution of 5 g (0.05 mole) of **12** and 6.4 g (0.05 mole) of **3** in 20 ml of ether was added in small portions from a pressure-compensating addition funnel. The cooling bath was removed. After 1 hr, 6.85 g (0.05 mole) of butyl bromide in 20 ml of ether was added rapidly. The reaction mixture was worked up as described in the first experiment. Vpc of the crude product showed the ratio of 2,4-nonanedione (**13**) to 6-methyl-3,5-decanedione (**14**) was 83:17.

Synthesis of Starting β-Diketones and Authentic Samples of Alkylation Products.—Acetylacetone (**12**) was commercially available. 2,4-Hexanedione (**2**) was prepared by methylation and 2,4-nonanedione (**13**) by butylation of acetylacetone as described previously.[4] Similarly, 6-methyl-2,4-decanedione (**14**) was prepared from dipropionylmethane (**3**) and butyl bromide.[6]

1-Phenyl-2,4-pentanedione (**9**) and 1-phenyl-2,4-nonanedione **10** (R = n-C_4H_9) were prepared from diphenyliodonium chloride and acetylacetone and 2,4-nonanedione, respectively, as described previously.[15]

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(11) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 122 (1954).

(12) J. Levy and P. Jullien, *Bull. Soc. Chim. France*, [4] **45**, 941 (1929).

(13) See C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *J. Am. Chem. Soc.*, **78**, 1653 (1956).

(14) C. R. Hauser and T. M. Harris, *ibid.*, **80**, 6360 (1958).

(15) K. G. Hampton, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **29**, 3511 (1964).

5-Phenyl-2,4-hexanedione (**11**, R = CH_3) was prepared by the condensation of 2-phenylpropionyl chloride[16] and *t*-butyl acetoacetate effected by sodium.[17] The product was refluxed with *p*-toluenesulfonic acid in toluene. The mixture was neutralized with sodium bicarbonate and filtered. The toluene was evaporated and the residue was distilled to afford 54% of product, bp 129–139° (13 mm). The copper chelate was recrystallized from ethanol, mp 153–154°.

Anal. Calcd for $C_{24}H_{26}CuO_4$: C, 65.21; H, 5.93; Cu, 14.38. Found: C, 65.48; H, 6.03; Cu, 14.34.

The diketones **3–8** and **10** (R = CH_3) were made by condensing the respective monoketones and esters by means of sodium amide[18] in ether as described previously.[19] There were two new β-diketones formed by this method. Ethyl propionate was condensed with 3-methyl-2-butanone to afford 2-methyl-3,5-heptanedione (**5**) in 29% yield. After the usual isolation procedure,[19] **5** was further purified by extraction into aqueous base and acidification of the aqueous solution; the product was redistilled, bp 75–78° (20 mm). The copper chelate melted at 148–149° after recrystallization from methanol.

Anal. Calcd for $C_{16}H_{26}CuO_4$: C, 55.55; H, 7.52; Cu, 18.38. Found: C, 55.53; H, 7.28; Cu, 18.15.

Ethyl propionate was condensed with pinacolone to afford 2,2-dimethyl-3,5-heptanedione (**8**) in 31% yield, bp 86–88° (25 mm). The copper chelate melted at 119.5–121° after recrystallization from methanol.

Anal. Calcd for $C_{18}H_{30}CuO_4$: C, 57.81; H, 8.08; Cu, 16.99. Found: C, 58.03; H, 7.88; Cu, 17.16.

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[16] S. P. Bakshi and E. E. Turner, *J. Chem. Soc.*, 171 (1961).

[17] See R. L. Shriner, A. G. Schmidt, and L. J. Roe, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p 266.

[18] Lithium amide was used in the preparation of 2,6-dimethyl-3,5-heptanedione (**7**) as described by H. D. Murdock and D. C. Nonhebel, *J. Chem. Soc.*, 2153 (1962).

[19] J. T. Adams and C. R. Hauser, *J. Am. Chem. Soc.*, **66**, 1220 (1944); R. Levine, J. A. Conroy, J. T. Adams, and C. R. Hauser, *ibid.*, **67**, 1510 (1945). Compounds **6** and **10** (R = CH_3) were prepared by Dr. J. T. Adams

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Synthesis of 4-Substituted 1,1-Dimethyl-*trans*-2-decalones *via* Conjugate Addition of Grignard Reagents

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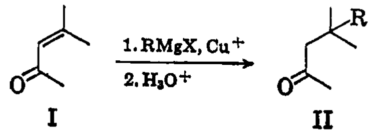
1,1-Dimethyl-*trans*-3-octal-2-one (**7a**) was prepared and used to study the stereochemistry of the cuprous ion catalyzed 1,4 addition of Grignard reagents to α,β-unsaturated ketones as a function of the bulk of the organomagnesium compound. The synthesis involved methylation of 1(9)-octal-2-one (**1**) followed by reduction of the resulting 1,1-dimethyl-8-octal-2-one (**2**) first with lithium aluminum hydride and then with hydrogen over a platinum catalyst. The alcohol obtained from this sequence gave 1,1-dimethyl-*trans*-2-decalone (**5a**) upon oxidation and this ketone afforded the required octalone **7a** *via* bromination and dehydrobromination. Methylmagnesium iodide afforded principally the 1,4 adduct, 1,1,4α-trimethyl-*trans*(10β-H)-2-decalone (**10**), in which the newly introduced methyl group is axially oriented. With isopropylmagnesium bromide a nearly 1:1 mixture of the isomeric, 1,4 adducts was obtained from octalone **7a**. Phenylmagnesium bromide afforded 1,1-dimethyl-4β-phenyl-*trans*(10β-H)-2-decalone (**19**) in which the newly introduced phenyl group possesses the equatorial conformation.

The cuprous ion catalyzed addition of Grignard reagents to α,β-unsaturated ketones constitutes a useful method for introducing an alkyl group to the β-position of a ketone (*e.g.*, I → II).[2] Information concerning the stereochemistry of this reaction is available from recent reports which deal with the addition of methylmagnesium iodide to Δ^1-3-keto steroids.[3] The major product can be related to the starting unsaturated ketone in each instance[4] by assuming the Grignard reagent attacks the least hindered face of the double bond to give a 1,4 adduct in which the new carbon–carbon bond possesses an axial conformation. Other studies not related to steroids support this picture of the reaction.[5]



I II

Stereoelectronic factors may also play a part in the mechanism of conjugate addition to unsaturated ketones by Grignard reagents.[6] The results cited above could be explained satisfactorily according to this postulate, although a simple kinetic argument based upon steric hindrance of the double bond would serve equally well.

Because of our interest in its possible application to natural products synthesis we undertook a study of the alkylation reaction exemplified by I → II. We were particularly concerned with three points: (1) the relative importance of stereoelectronic factors; (2) the relationship between the size of the Grignard reagent and the stereochemistry of 1,4 addition; and (3) the effect of the cuprous ion catalyst on the stereochemistry of 1,4 addition.

We chose 1,1-dimethyl-*trans*-3-octal-2-one (**7a**, Chart I) as the substrate for these studies. This octalone seemed particularly appropriate for the following reasons. (a) The *trans*-fused rings offer a rigid, conformationally unambiguous system. (b) Yields of 1,4 adducts should be high because the conjugated double bond is relatively exposed and the *gem*-dimethyl group should hinder 1,2 addition. (c) The pathway leading to axial introduction of the alkyl group at the β carbon appears (from inspection of Dreiding models) more hindered than the alternative pathway leading to

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[1] National Science Foundation Predoctoral Fellow, 1964–1965.

[2] *Cf.* M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, pp 196–238; H. O. House, D. D. Traficante, and R. A. Evans, *J. Org. Chem.*, **28**, 348 (1963).

[3] (a) R. Wiechert, U. Kerb, and K. Kieslish, *Chem. Ber.*, **96**, 2765 (1963); (b) W. J. Wechter, *J. Org. Chem.*, **29**, 163 (1964); (c) H. Mori, *Chem. Pharm. Bull.* (Tokyo), **10**, 386 (1962).

[4] For a recent structure revision, see W. J. Wechter, G. Slomp, F. A. MacKellar, R. Weichert, and U. Kerb, *Tetrahedron*, **21**, 1625 (1965).

[5] H. O. House and H. W. Thompson, *J. Org. Chem.*, **28**, 360 (1963).

[6] A. J. Birch and M. Smith, *Proc. Chem. Soc.*, 356 (1962); E. Toromanoff, *Bull. Soc. Chim. France*, 708 (1962).