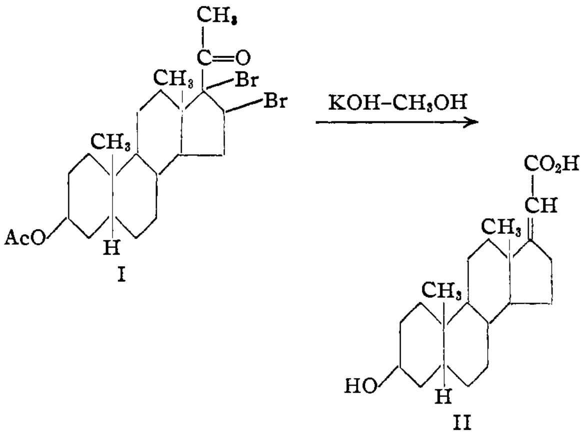
[CONTRIBUTION FROM THE WHITMORE LABORATORIES OF THE PENNSYLVANIA STATE COLLEGE]

Rearrangement of α,β-Dibromoketones[1]

BY R. B. WAGNER

During the course of studies of certain steroidal bromoketones, it was found that 16,17-dibromopregnan-3(β)-ol-20-one acetate (I) under vigorous alkali treatment yields 3(β)-hydroxy-Δ^{17-20}-pregnen-21-oic acid (II) by a rearrangement which had not been previously observed.[2]



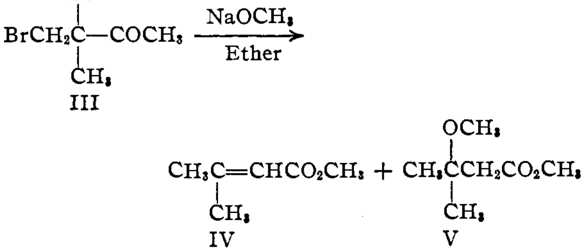
I

II

The present paper describes the extension of this rearrangement to aliphatic and simpler alicyclic α,β-dibromoketones, namely, 3,4-dibromo-3-methyl-2-butanone (III), 3,4-dibromo-3-methyl-2-pentanone (VI) and 1-acetyl-1,2-dibromocyclohexane.

The dibromo compounds were prepared by the reaction of equimolar quantities of bromine and the corresponding α,β-unsaturated ketones. The adjacent positions of the bromine atoms in these compounds are indicated by their almost quantitative removal with hot methanolic sodium iodide to give the original unsaturated ketone.[2]

When 3,4-dibromo-3-methyl-2-butanone (III) was added to an ether suspension of two moles of sodium methoxide at 10–20° and the products were allowed to stand for thirty hours, a mixture of the methyl esters of β,β-dimethylacrylate (IV) (42%) and β-methoxyisovalerate (V) (16%) was obtained; with a reaction time of two and a half hours, a mixture consisting of 64% of IV and 2% of V was obtained.



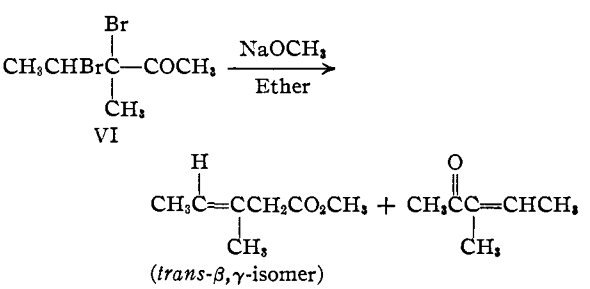
$$BrCH_2\overset{Br}{\underset{CH_3}{C}}{-}COCH_3 \xrightarrow[\text{Ether}]{NaOCH_3}$$

III

$$CH_3\underset{CH_3}{C}{=}CHCO_2CH_3 + CH_3\overset{OCH_3}{\underset{CH_3}{C}}CH_2CO_2CH_3$$

IV V

Similarly, using the shorter reaction time, 3,4-dibromo-3-methyl-2-pentanone (VI) gave 3-methyl-3-penten-2-one (VIII) (15%) and the methyl ester of *trans*-3-methyl-3-pentenoic acid (VII) (55%); none of the corresponding isomeric unsaturated ester could be isolated. Under the same conditions, 1-acetyl-1,2-dibromocyclohexane yielded exactly analogous products, namely, the methyl ester of 1-cyclohexenylacetic acid (34%) and methyl 1-cyclohexenyl ketone (19%).



$$CH_3CHBr\overset{Br}{\underset{CH_3}{C}}{-}COCH_3 \xrightarrow[\text{Ether}]{NaOCH_3}$$

VI

$$CH_3\overset{H}{C}{=}\underset{CH_3}{C}CH_2CO_2CH_3 + CH_3\overset{\overset{O}{\|}}{C}\underset{CH_3}{C}{=}CHCH_3$$

(*trans*-β,γ-isomer)
VII VIII

The methyl esters from these rearrangements were characterized by hydrogenation, saponification and oxidation procedures and, in each case, direct comparison with synthetic products and their derivatives were made. With the exception of the β-methoxy ester (V), the products could be obtained by procedures described in the literature.[3,4]

Methyl β-methoxyisovalerate (V) has been synthesized in small yields by the addition of methanol to methyl β,β-dimethylacrylate (IV) in the presence of sodium methoxide. It has been shown that the addition of alcohols to methyl acrylate is a general reaction for the preparation of β-alkoxypropionates.[5] However, the reaction of the disubstituted acrylate is much slower.

None of the corresponding γ-methoxy isomer, methyl γ-methoxyisovalerate, was detected among the rearrangement products from III. For comparison purposes, this compound has been synthesized by the following series of reactions.

The γ-methoxy ester and its acid are completely different from the rearrangement product (V) and its acid.

It is noteworthy that the double bond in the unsaturated esters from the last two mentioned rearrangement reactions is in the β,γ-position,

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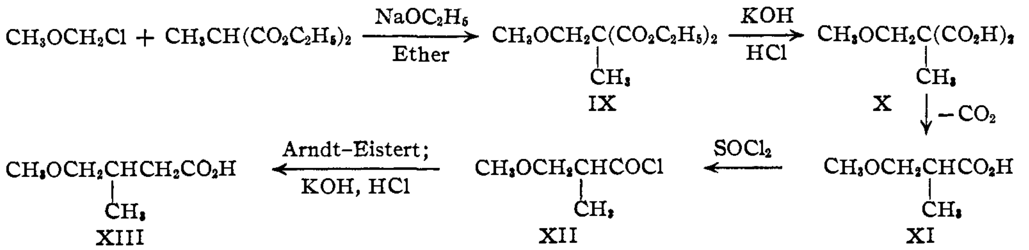
[1] Presented before the Division of Organic Chemistry, American Chemical Society, New York City, September, 1947.

[2] Marker, Wagner and Wittbecker, THIS JOURNAL, **64**, 2093 (1942).

[3] Kon, Linstead and Wright, *J. Chem. Soc.*, 599 (1934).

[4] Auwers and Ellinger, *Ann.*, **387**, 200 (1912); these authors report for methyl 1-cyclohexenylacetate, b. p. 93° (15 mm.), $n^{20}D$ 1.4679 and d^{20} 1.002.

[5] Rehberg, Dixon and Fisher, THIS JOURNAL, **68**, 544 (1946).

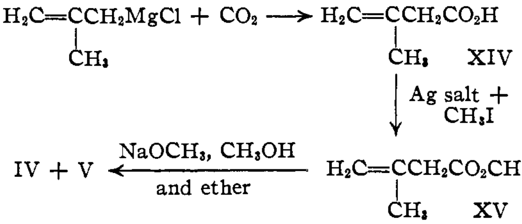


$$CH_3OCH_2Cl + CH_3CH(CO_2C_2H_5)_2 \xrightarrow[\text{Ether}]{NaOC_2H_5} \underset{\text{IX}}{CH_3OCH_2\underset{CH_3}{C}(CO_2C_2H_5)_2} \xrightarrow[HCl]{KOH} \underset{\text{X}}{CH_3OCH_2\underset{CH_3}{C}(CO_2H)_2}$$

$$\text{X} \xrightarrow{-CO_2} \underset{\text{XI}}{CH_3OCH_2\underset{CH_3}{C}HCO_2H} \xrightarrow{SOCl_2} \underset{\text{XII}}{CH_3OCH_2\underset{CH_3}{C}HCOCl} \xrightarrow[\text{KOH, HCl}]{\text{Arndt-Eistert;}} \underset{\text{XIII}}{CH_3OCH_2\underset{CH_3}{C}HCH_2CO_2H}$$

whereas the first reaction gives an ester having α,β-unsaturation. This anomaly in this series has been investigated further and it has been found that the corresponding β,γ-isomer (XV) of methyl β,β-dimethylacrylate when placed under conditions similar to those used for the bromoketone rearrangement *undergoes a shifting of the double bond to the α,β-position.* In addition, methyl β-methoxyisovalerate (V) is formed during this reaction in the same proportions as noted in the rearrangement reaction. From this experiment, it may be concluded that if the β,γ-unsaturated ester is formed here as in the other cases, it would immediately undergo a secondary reaction to give the α,β-isomer (IV) and the β-methoxy ester (V). Furthermore, since methanol adds to the α,β-isomer (IV) under these conditions of long and short reaction periods to form the β-methoxy ester (V) in 24 and 8% yields, respectively, this source (IV) for the latter (V) is indicated in both the isomerization and the rearrangement reaction. On the other hand, the double bond in the higher β-alkylated-β,γ-unsaturated esters, homologs of XV, does not migrate under these mild conditions; in fact, even under more vigorous alkali treatment, the "equilibrated" mixture favors the β,γ-isomer.[3] However, it should be noted that the double bond in the steroidal unsaturated acid (II) is in the α,β-position, which again appears to be the more stable position.

The β,γ-isomer (XV), methyl 3-methyl-3-butenoate, has been synthesized for these studies by the carbonation of methallyl Grignard reagent followed by esterification of the resulting acid through its silver salt. This ester is readily differentiated from the rearrangement ester (IV).



$$H_2C{=}\underset{CH_3}{C}CH_2MgCl + CO_2 \longrightarrow \underset{\text{XIV}}{H_2C{=}\underset{CH_3}{C}CH_2CO_2H} \xrightarrow{\text{Ag salt} + CH_3I} \underset{\text{XV}}{H_2C{=}\underset{CH_3}{C}CH_2CO_2CH_3} \xrightarrow[\text{and ether}]{NaOCH_3,\ CH_3OH} \text{IV} + \text{V}$$

The mechanism by which the rearrangement occurs is not definitely settled although suggestions have been made.[6,7]

Acknowledgment.—Combustion analyses (C, H, N) were performed by R. N. Walters.

Experimental[8]

Unsaturated Ketones.—(a) **3-Methyl-3-buten-2-one** was prepared by the dehydration of 3-methyl-4-butanol-2-one, b. p. 80° (10 mm.), $n^{20}D$ 1.4340, d^{20} 0.9951. The crude ketol prepared by the procedure of Morgan and Griffith[9] was found to be satisfactory for dehydration. The reaction was carried out by adding 1 kg. of the ketol, preheated to 95°, continuously in a slow stream to a hot mixture of 50 g. of fused potassium bisulfate and 4 g. of hydroquinone contained in a flask equipped with the usual Claisen distilling head and condenser. The reaction mixture was heated during the addition causing the distillation of the olefinic ketone and water mixture. When the addition of the ketol was complete and the head temperature had risen to 110°, the reaction was stopped and the product layers were separated. The organic mixture was fractionated through a column with a 45 × 1.8 cm. section packed with 3/32″ glass helices, removing additional water in the fore-cut. There was obtained an 80% yield of the unsaturated ketone, b. p. 58° (200 mm.), $n^{20}D$ 1.4232 and d^{20} 0.8540.[10]

(b) **3-Methyl-3-penten-2-one** was prepared in an 87% yield by distilling directly from a reaction mixture consisting of 290 g. of 3-methyl-4-pentanol-2-one, 2 cc. of 38% aqueous hydrobromic acid and 2 g. of hydroquinone. The crude olefinic ketone was fractionated to give material having b. p. 97° (200 mm.), $n^{20}D$ 1.4489 and d^{20} 0.8758.

The pure ketol, b. p. 76° (10 mm.), $n^{20}D$ 1.4350 and d^{20} 0.9704, was prepared in a 67% yield from methyl ethyl ketone and acetaldehyde by the procedure of Kyrides[11] using satisfactorily five times the stated quantities. The reaction mixture was concentrated by a flash evapora-

TABLE I

DIBROMO KETONES

Compound	B. p., °C. (M. p. °C.)	Mm.	d^{20}	Yield, %	Bromine analyses, % (Stepanoff) Calcd.	Found	
2,3-Dibromo-3-methyl-2-butanone (III)	53	1	1.803	97	65.7	65.6	65.7
2,3-Dibromo-3-methyl-2-pentanone (VI)[a]	78–82	5	1.701	90	62.0	61.8	61.7
1-Acetyl-1,2-di-bromo-cyclohexane[b]	(48)		...	60	56.3	56.8	56.9

[a] This material could be distilled in 10-g. batches without serious decomposition. [b] 1-Acetyl-1,2-dibromocyclohexene (formula not shown) was prepared by brominating the unsaturated ketone dissolved in an equal volume of chloroform. Most of the solvent was removed at a bath temperature of 20° and the remainder at 15 mm. during three days at 30°. The crystalline dibromide was triturated and washed with cold pentane. A sample of this material was heated under reflux for one hour with excess sodium iodide in methanol. The liberated iodine (titrated with standard sodium thiosulfate) corresponded to the theoretical quantity for the complete removal of both bromine atoms. The original olefinic ketone was isolated as its semicarbazone, m. p. and mixed m. p., 217°.

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[6] McPhee and Klingsberg, *ibid.*, **66**, 1132 (1944).

[7] Marker, Crooks and Wagner, *ibid.*, **64**, 213 (1942).

[8] All melting points and boiling points are uncorrected.

[9] Morgan and Griffith, *Chemistry and Industry*, **57**, 885 (1938).

[10] McMahon, *et al.*, THIS JOURNAL, **70**, 2971 (1948), report b. p. 38° (85 mm.), $n^{20}D$ 1.4325 and d^{20} 0.8541.

[11] Kyrides, *ibid.*, **55**, 3431 (1933).

TABLE II

PHYSICAL CONSTANTS AND YIELDS OF PRODUCTS FROM REARRANGEMENT STUDIES

Bromo ketone reacted	Products	B. p.		$n^{20}D$	d^{20}	M_D		Yield, %
		°C.	Mm.			Calcd.	Obs.	
III	Methyl *β*,*β*-dimethylacrylate (IV)	60	50	1.4378	0.9425	31.10[b]	31.78	64(42)[c]
	Methyl *β*-methoxyisovalerate (V)	67	20	1.4161	.9786	37.82	37.49	2(16)[c]
VI	3-Methyl-3-penten-2-one (VIII)	63	50	1.4489	.8758	29.45[b]	30.05	15
	Methyl *trans*-3-methyl-2-pentenoate (VII)	74	50	1.4306	.9949	35.71	35.92	55
XVI[a]	1-Acetyl-1-cyclohexene	78	10	1.4904	.9685	36.49[b]	37.10	23
	Methyl 1-cyclohexenylacetate	84	10	1.4668	1.001	42.75	42.73	35

[a] 1-Acetyl-1,2-dibromocyclohexane (formula not shown). [b] Exaltations for the conjugated systems in these compounds would raise the calculated values (*cf.* ref. 4). [c] Yields in parentheses are those obtained when the reaction mixture was allowed to stand thirty hours.

tion technique[12] and distilled through a column with a 53 × 1.8 cm. section packed with $^1/_8$″ glass helices.

(c) **1-Acetyl-1-cyclohexene** was prepared in a 50% yield from cyclohexane, acetyl chloride and anhydrous aluminum chloride by the directions of Christ and Fuson[13] and was purified by fractionation through a column with a 53 × 1.8 cm. section packed with $^3/_{32}$″ glass helices; b. p. 88.5° (20 mm.) and $n^{20}D$ 1.4904.[14]

Preparation of the Dibromo Ketones.—The unsaturated ketone, 2–3 moles, contained in a 1-liter three-necked flask which was equipped wth a stirrer, dropping funnel and thermometer and surrounded by an ice–salt-bath, was treated in a dropwise manner with an equimolar quantity of bromine at 0° during six hours. Additional data are summarized in Table I.

Reaction with Sodium Methoxide.—To a suspension of 4 moles of sodium methoxide (Mathieson Alkali Works, 95%) in anhydrous ether was added 2 moles of the dibromo ketone. The reaction mixture was stirred vigorously and was cooled by a salt–ice-bath. The addition was completed in one and one-half hours, keeping the temperature at 20°. An acid–base titration of a 2-ml. aliquot showed the almost complete absence of the basic reagent. After stirring an additional hour, the mixture was poured onto ice, the layers were separated, and the water layer was ether extracted. The total ethereal solution was dried over anhydrous potassium carbonate and the ether was removed through a column. The concentrate was rapidly distilled *in vacuo* through a Claisen apparatus to free it from any high-boiling and bromine-containing material. The crude distillate was then carefully fractionated through a column with a 43 × 1.8 cm. section packed with $^3/_{32}$″ glass helices. Additional data are summarized in Table II.

Identification of Products from the Rearrangement Reactions.[15] (a) **Methyl *β*,*β*-Dimethylacrylate** (IV).—Hydrogenation of IV using Adams catalyst gave methyl 3-methylbutanoate, b. p. 116° (732 mm.), $n^{20}D$ 1.3920, d^{20} 0.8807, further characterized by its *p*-toluide, m. p. and mixed m. p., 109–110°. Saponification gave dimethylacrylic acid, m. p. and mixed m. p., 70°, and methanol, b. p. 64° (739 mm.) and $n^{20}D$ 1.3265. Oxidation with magnesium permanganate gave acetone isolated as its 2,4-dinitrophenylhydrazone, m. p. and mixed m. p., 126–127°.

The **anilide** was crystallized from ether as needles, m. p. and mixed m. p. with an authentic sample, 131–132°.

The *p*-toluide was crystallized from ethanol as needles, m. p. and mixed m. p. with an authentic sample, 106–107°.

Anal. Calcd. for $C_{12}H_{15}ON$: N, 7.40. Found: N, 7.59, 7.58.

(b) **Methyl *β*-Methoxyisovalerate** (V).—The properties of V are the same as those for the product synthesized by the route described below.

Anal. Calcd. for $C_7H_{14}O_3$: $2CH_3O$, 42.4; sapn. equiv., 146. Found: $2CH_3O$ (Zeisel), 42.4; sapn. equiv., 149.

The *p*-toluide was crystallized from benzene–pentane as needles, m. p. and mixed m. p., 51–52°.

Anal. Calcd. for $C_{13}H_{19}O_3N$: N, 5.90. Found: N, 6.14.

(c) **3-Methyl-3-penten-2-one** (VIII).—The properties of VIII agree with those for the product synthesized as described above. The **semicarbazone** was crystallized from ethanol, m. p. and mixed m. p., 200–201°.[16]

(d) **Methyl *trans*-3-Methyl-3-pentenoate** (VII).—Hydrogenation of VII using Adams catalyst gave methyl 3-methylpentanoate isolated as its anilide which was crystallized from benzene–pentane, m. p. and mixed m. p., 86–87°. Ozonolysis gave acetaldehyde isolated as the 2,4-dinitrophenylhydrazone, m. p. and mixed m. p., 167–168°.

Anal. Calcd. for $C_7H_{12}O_2$: sapn. equiv., 128. Found: sapn. equiv., 128.

The amide was crystallized from benzene–pentane as plates, m. p. 130–131°.

The *p*-toluide was crystallized from aqueous ethanol as plates, m. p. and mixed m. p. with the *p*-toluide of the *trans*-isomer, 91–92°.

The anilide was crystallized from benzene–pentane as needles, m. p. and mixed m. p. with the anilide of the *trans*-isomer, 99–100°.

(e) **Methyl 1-Cyclohexenylacetate.**[4]—Saponification gave methanol, b. p. 64° (739 mm.) and $n^{20}D$ 1.3268.

The anilide was crystallized from aqueous ethanol as long needles, m. p. and mixed m. p. with an authentic sample,[17] 118–119°.

Anal. Calcd. for $C_{14}H_{17}ON$: C, 78.10; H, 7.96. Found: C, 77.38; H, 7.82.

The *p*-toluide was crystallized from aqueous ethanol as needles, m. p. and mixed m. p. with an authentic sample,[17] 101–102°.

Anal. Calcd. for $C_{15}H_{19}ON$; C, 78.56; H, 8.35. Found: C, 78.59; H, 8.14.

(f) **Methyl 1-Cyclohexenyl Ketone.**—The semicarbazone was crystallized from ethanol, m. p. and mixed m. p., 221°.[14]

3-Methyl-3-butenoic Acid (XIV) and Reactions.—Methallylmagnesium chloride was prepared in an 81% yield by treating 900 g. (10 moles) of methallyl chloride in 10 liters of anhydrous ether with 243 g. (10 moles) of magnesium turnings at 14–16° during ten hours. The reaction was carried out with vigorous stirring in a three-

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(12) Whitmore, *et al.*, *Ind. Eng. Chem.*, **38**, 942 (1946).

(13) Christ and Fuson, THIS JOURNAL, **59**, 895 (1937).

(14) Kon, *J. Chem. Soc.*, 1801 (1926), reports b. p. 81° (13 mm.), $n^{20}D$ 1.49042 and d^{10} 0.9685; semicarbazone, m. p. 217°.

(15) All derivatives were prepared by the methods described by Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 2nd ed., 1940.

(16) Hinkel, *J. Chem. Soc.*, 818 (1931), reports the semicarbazone, m. p. 201°.

(17) The 1-cyclohexenylacetic acid used for the preparation of these derivatives was prepared from cyclohexylideneacetic acid by the procedure of Beesley, Ingold and Thorpe, *J. Chem. Soc.*, 1080 (1915); b. p. 136° (12 mm.).

gallon copper vessel. The Grignard reagent was obtained as a solid suspended in the ether. This was added with vigorous stirring during thirty minutes to 10 kg. of powdered Dry Ice contained in a second copper vessel equipped with a large vent to the hood. The resulting complex was decomposed with ice and concentrated hydrochloric acid mixture (requires 1 liter of concd. hydrochloric acid). After saturating the water layer with sodium chloride, the ether layer was separated and the acid portion was extracted by washing with a solution of 600 g. of sodium carbonate (final *p*H of wash, 8.01). The alkaline extract was layered with 6 liters of ether and acidified by vigorous stirring with 1 liter of concd. hydrochloric acid (final *p*H, 1.5). The ethereal solution was evaporated, and the residue was dried by removing the water as an azeotropic mixture with benzene and then distilled through a Claisen apparatus to give 400 g. of material (40% yield) boiling 68–70° (5 mm.), m. p. 20.2–21.3° and n^{20}D 1.4308.

Anal. Calcd. for $C_5H_8O_2$: neut. equiv., 100. Found: neut. equiv., 100, 101.

Ozonolysis of this material yielded formaldehyde isolated as its dimedone derivative.

(a) **Conversion to the Methyl Ester (XV).**—To a stirred solution of 213 g. (2.13 moles) of 3-methyl-3-butenoic acid in 4 liters of distilled water was added 85 g. (2.13 moles) of C. P. sodium hydroxide dissolved in 2 liters of distilled water followed by a solution of 392 g. (2.31 moles) of silver nitrate in 1 liter of distilled water. The precipitate was filtered and triturated twice successively with water, absolute ethanol and ether. The silver salt suspended in 2.5 liters of anhydrous ether contained in a 5-liter, three-necked flask, equipped with a stirrer and condenser, was treated with excess methyl iodide (2.3 moles) under reflux for seventy-two hours. After twenty-four hours a yellow precipitate of silver iodide predominated. The reaction mixture was filtered, the ether was evaporated, and the product was fractionated through a column with a 43 × 1.8 cm. section packed with $^3/_{32}''$ glass helices to give entirely one product, 115 g., b. p. 41° (27 mm.), n^{20}D 1.4168 and d^{20} 0.931; 47% yield. *M*D calcd., 31.10; obs., 31.18.

Anal. Calcd. for $C_6H_{10}O_2$: C, 63.13; H, 8.83. Found: C, 62.94; H, 9.10.

The *p*-toluide was prepared from the ester and crystallized from aqueous ethanol as needles, m. p. 95°. A mixture with the *p*-toluide of β,β-dimethylacrylic acid, m. p. 107°, melted 68–90°.

Anal. Calcd. for $C_{12}H_{15}ON$: N, 7.40. Found: N, 7.40.

(b) **Conversion to β,β-Dimethylacrylic Acid.**—A mixture of 10 g. of 3-methyl-3-butenoic acid, 20 ml. of dry ether and 10 g. of 90% sulfuric acid was allowed to stand at room temperature for forty-eight hours. The reaction mixture was diluted with water and extracted with ether, after saturating the water layer with ammonium sulfate. The acid fraction was then transferred to the aqueous sodium salt solution and back to an ethereal solution, which was evaporated to yield 9.7 g. of dimethylacrylic acid, crystallized from water; m. p. and mixed m. p., 68–70°; 97% yield.

(c) **Conversion to Methyl β,β-Dimethylacrylate and Methyl β-Methoxyisovalerate.**—For reasons discussed above, this reaction was carried out under conditions similar to those used for the rearrangement of the bromo ketones. Since the formation of the unsaturated ester is accompanied by an equimolar quantity of methanol, this was added. Thus a mixture 109 g. (0.96 mole) of methyl 3-methyl-3-butenoate, 32 g. (1.0 mole) of methanol, 10 g. of sodium methoxide and 500 ml. of ether was stirred at room temperature for thirty hours. The reaction mixture was processed as before and the product on fractionation gave 60 g. (0.55 mole) of methyl β,β-dimethylacrylate, b. p. 60° (50 mm.), n^{20}D 1.4381 (53% yield) and 32 g. (0.22 mole) of methyl β-methoxyisovalerate, b. p. 66° (20 mm.), n^{20}D 1.4157 (23% yield).

Under similar conditions using a two and a half-hour reaction time, the yield of the unsaturated ester was 80 and 10% for the β-methoxy ester.

When methyl β,β-dimethylacrylate was treated under the same conditions, the yields were 63% of the unsaturated ester and 24% of the β-methoxy ester for the long reaction period and 81 and 8%, respectively, for the short time.

Methyl β-Methoxyisovalerate (V).—A solution of 3 g. of sodium in 32 g. (1.0 mole) of methanol was added to 83 g. (0.85 mole) of methyl β,β-dimethylacrylate at 28° during ten minutes. The mixture was kept at room temperature for four days, then acidified with 15 cc. of concd. hydrochloric acid and filtered. The filtrate was fractionated to give starting material and 15 g. (0.11 mole) of methyl β-methoxyisovalerate, b. p. 67° (20 mm.), n^{20}D 1.4161 and d^{20} 0.9777; *M*D calcd., 37.8; obs., 37.5.

Anal. Calcd. for $C_7H_{12}O_3$: $2CH_3O$, 42.4; C, 57.5; H, 9.65. Found: $2CH_3O$ (Zeisel), 44.0, 44.2; C, 58.1; H, 10.0.

The *p*-toluide was prepared and crystallized from benzene–pentane as needles, m. p. 51°. This gave no depression in melting point with the *p*-toluide of the corresponding rearrangement product.

Synthesis of γ-Methoxyisovaleric Acid (XIII). (a) **Ethyl Methoxymethylmethylmalonate (IX).**—Finely divided sodium, 115 g. (5 atoms) in 2 liters of anhydrous ether was treated with 855 g. (5.0 moles) of ethyl methylmalonate.[18] The mixture was refluxed and stirred for eight hours at which time all of the sodium had reacted. To the semi-solid sodio-derivative was added 440 g. (5.5 moles) of monochloromethyl ether,[19] b. p. 60–65° (739 mm.), during one hour at reflux temperature. The reaction was vigorous and the mixture became more fluid with the formation of sodium chloride; it was stirred overnight at room temperature.

Titration of a 1-ml. aliquot indicated that only 0.33 mole of base remained. The mixture was acidified with 30 ml. of acetic acid and then treated with water. The ethereal solution was dried rapidly with anhydrous calcium chloride and distilled rapidly through a Claisen apparatus. Material boiling between 94 and 120° (50 mm.), was carefully fractionated to give a 50% yield of product, b. p. 115–117° (16 mm.), n^{20}D 1.4220.

(b) **Methoxymethylmethylmalonic Acid (X).**—To a solution of 300 g. (7.5 moles) of sodium hydroxide in 200 ml. of water and 1 liter of 95% ethanol was added 530 g. (2.43 moles) of the above ester during one hour at room temperature. The mixture was stirred for two hours and allowed to stand overnight. After dissolving the solid mass in 400 ml. of water, the solution was concentrated to one liter on the steam-bath with air passing through it to remove the alcohol. The concentrate was cooled and acidified with 235 ml. (4.2 moles) of concentrated sulfuric acid dissolved in an equal volume of water and then continuously extracted with ether for four days. The ether extract was evaporated and the residue was crystallized; 393 g. (2.40 moles); yield, 99% of crude acid. An aliquot was recrystallized from ether–pentane, m. p. 104–105°.

Anal. Calcd. for $C_6H_{10}O_5$: C, 44.44; H, 6.22; neut. equiv., 81.0. Found: C, 44.53; H, 6.49; neut. equiv., 81.4, 82.4.

(c) **β-Methoxyisobutyric Acid (XI).**—The above crude acid, 383 g. (2.36 moles), was heated under a column with a 53 × 1.8 cm. section packed with $^1/_4''$ glass helices at 150–160° until the evolution of carbon dioxide ceased. The product was fractionated to give 228 g. (1.93 moles) of monocarboxylic acid, b. p. 83° (3 mm.) and n^{20}D 1.4192; 82% yield.

Anal. Calcd. for $C_5H_{10}O_3$: CH_3O, 26.3; neut. equiv., 118. Found: CH_3O (Zeisel), 26.3, 26.6; neut. equiv., 118, 119.

(d) **β-Methoxyisobutyryl Chloride (XII).**—A mixture of 118 g. (1.00 mole) of XI and 144 g. (1.20 moles) of pure thionyl chloride was warmed at 40° for forty-five minutes and then at 60° for an additional forty-five minutes. The excess thionyl chloride was removed *in vacuo* and the

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(18) Cox and McElvain, *Org. Syntheses*, Coll. Vol. II, 279 (1943).

(19) Marvel and Porter, *ibid.*, Coll. Vol. I, 377 (1941).

product was distilled to give material boiling at 48–59° (15 mm.), 122 g. (0.90 mole), representing a 90% yield.

Anal. Calcd. for $C_5H_9O_2Cl$: Cl, 26.0. Found: Cl (Stepanoff), 26.2, 26.2.

(e) γ-Methoxyisovaleric Acid (XIII).—The above acid chloride, 114 g. (0.84 mole), was treated in three batches with an ethereal solution of diazomethane and then with a methanol slurry of silver oxide according to the Arndt–Eistert[20] procedure. The resulting product consisted of a mixture of the chloro ketone and the desired methyl ester, 25 g., b. p. 69° (20 mm.); 25% yield.

Although the saponification equivalent agreed closely with the theoretical value, a chlorine analysis showed that the ester was contaminated with the chloro ketone. The latter was removed by converting the above methyl ester, 24 g., to the corresponding acid by refluxing with excess 10% alcoholic potassium hydroxide. The product was isolated in the usual manner and fractionated to give the γ-methoxy acid; 16 g., b. p. 123–125° (20 mm.), n^{20}_D 1.4235, d^{20} 1.034; M_D calcd., 33.09; obs., 32.52.

Anal. Calcd. for $C_6H_{12}O_3$: OCH_3, 23.5. Found: OCH_3 (Zeisel), 23.6.

β-Methoxyisovaleric Acid.—For comparison purposes, the ester, 21 g., was hydrolyzed with excess 20% alcoholic potassium hydroxide as above and the product was fractionated to give the β-methoxy acid, b. p. 125° (20 mm.), n^{20}_D 1.4333, d^{20} 1.045; M_D calcd., 33.09; obs., 32.81.

Anal. Calcd. for $C_6H_{12}O_3$: neut. equiv., 132. Found: neut. equiv., 132.

***cis*- and *trans*-3-Pentenoic Acid.**—These acids were prepared by general procedures described in the literature[3] and converted to their derivatives, not previously described, for comparisons with the corresponding derivatives of the rearrangement products. Ethyl β-methyl-β-hydroxyvalerate, b. p. 83–88° (13 mm.), prepared by the Reformatsky reaction according to the procedure of Natelson and Gottfried,[21] was converted to the acid by careful alkaline hydrolysis, avoiding the presence of a large excess of base at any time. For this the ester, 280 g. (1.75 moles), in 200 ml. of 95% ethanol was treated at reflux temperature with a solution of 70 g. (1.75 moles) of C. P. sodium hydroxide in 150 ml. of water in a dropwise manner, maintaining a faint coloration with phenolphthalein indicator. The mixture was concentrated by air passing through the hot solution. The cold concentrate was acidified with dilute sulfuric acid and ether extracted to give 200 g. (1.75 moles) of crude acid. This was dehydrated with acetic anhydride according to Wallach[22] to give a mixture of the *cis*- and *trans*-isomers of both the α,β- and β,γ-unsaturated acids. The non-crystalline material,[23] 80 g. (0.70 mole) was partially esterified during twelve hours at room temperature to separate the α,β- and β,γ-isomers as acid and ester, respectively.[2] The former, 53 g. (0.47 mole), was treated with 260 g. (4.65 moles) of potassium hydroxide in 750 ml. of water at 100° for three days; an equilibrium mixture of the *cis*- and *trans*-α,β-acids and the *cis*-β,γ-acid resulted (the *trans*-β,γ-acid is not present to any large extent).[3] The mixture was partially esterified with ethanol to give an acid fraction consisting of the α,β-isomers and a neutral fraction which was the desired ethyl *cis*-3-methyl-3-pentenoate, b. p. 61° (13 mm.), n^{20}_D 1.4298 and d^{20} 0.9183; wt., 25 g. (0.16 mole).

Ozonolysis of this material gave acetaldehyde, isolated as its 2,4-dinitrophenylhydrazone, m. p. and mixed m. p., 165–168°.

The *cis*-*p*-toluide was crystallized from aqueous ethanol as needles, m. p. 100.5–101.5°. A mixture with the *p*-toluide from the rearrangement product (IV) or the authentic *trans*-*p*-toluide described below showed a melting point depression of thirty degrees.

Anal. Calcd. for $C_{13}H_{17}ON$: C, 76.80; H, 8.43. Found: C, 76.94; H, 8.47.

The *cis*-anilide was crystallized from aqueous ethanol as needles, m. p. 99–100°. A mixture with the anilide of *trans*-3-methyl-3-pentenoic acid (m. p. 101°) melted 97–98°, a slight depression.

Anal. Calcd. for $C_{12}H_{15}ON$: C, 76.15; H, 7.91. Found: C, 76.30; H, 8.00.

The *cis*-amide was crystallized from benzene–pentane as plates, m. p. 126–127°. A mixture with the amide from the rearrangement product (m. p. 131°) melted 127–130°.

Anal. Calcd. for $C_6H_{11}ON$: N, 12.38. Found: N, 12.13.

The *trans*-acid and its derivatives were obtained by dehydrating a second batch of the hydroxy ester, 256 g. (1.60 moles), with a suspension of 170 g. (1.25 moles) of phosphorus pentoxide in 750 ml. of dry benzene,[24] hydrolyzing the unsaturated esters, and partially esterifying the crude acids, 103 g. (0.90 mole), during five hours at room temperature.[3] The resulting mixture of β,γ-unsaturated esters, 49 g. (0.31 mole), b. p. 62–65° (16 mm.), was treated with a slight excess of 10% ethanolic potassium hydroxide for four days at room temperature. The acid fraction was isolated and crystallized from pentane to give the desired *trans*-acid, m. p. 35°; wt., 10 g.

Anal. Calcd. for $C_6H_{10}O_2$: neut. equiv., 114. Found: neut. equiv., 113, 114.

Ozonolysis of this material gave acetaldehyde, isolated as its 2,4-dinitrophenylhydrazone, m. p. and mixed m. p., 165–168°.

The *trans* *p*-toluide was crystallized from aqueous ethanol as flat needles, m. p. 91.5–92.5°; this did not depress the melting point of the *p*-toluide of the rearrangement product (VII).

Anal. Calcd. for $C_{13}H_{17}ON$: N, 6.91. Found: N, 7.17.

The *trans* anilide was crystallized from aqueous ethanol as needles, m. p. 100–101°; this did not depress the melting point of the *p*-toluide of the rearrangement product (VII).

Anal. Calcd. for $C_{12}H_{15}ON$: N, 7.41. Found: N, 7.38.

Summary

1. Treatment of α-alkyl-α,β-dibromoketones with a suspension of sodium methoxide in ether causes a rearrangement to give the methyl ester of a β-alkyl-β,γ-unsaturated acid. In addition, the original olefinic ketone may be regenerated.

2. The simplest compound in this series, namely, 3,4-dibromo-3-methyl-2-butanone (III), takes an anomalous course in giving methyl β,β-dimethylacrylate (IV) and methyl β-methoxyisovalerate (V). It has been shown that the corresponding β,γ-isomer, methyl 3-methyl-3-butenoate (XV), if formed in the rearrangement reaction, would undergo further reaction to give these products.

3. Methyl *trans*-3-methyl-3-pentenoate and the corresponding *cis*-isomer have been definitely characterized and the identity of the former with an ester from the rearrangement studies has been established.

4. Methyl β-methoxyisovalerate and its γ-methoxy homolog have been synthesized for comparison purposes.

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RECEIVED FEBRUARY 21, 1949

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[20] Bachman and Struve in "Organic Reactions," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 52.

[21] Natelson and Gottfried, THIS JOURNAL, **61**, 970 (1939).

[22] Wallach, *Ann.*, **365**, 261 (1909).

[23] The crystalline material, 27 g. (0.23 mole), consisted largely of *trans*-3-methyl-2-pentenoic acid.

[24] Treatment of the pure hydroxy ester with gaseous hydrochloric acid gave incomplete dehydration; *cf.* ref. 21.