

g. (0.70 mole) of ethyl alcohol, 39 ml. of sulfuric acid, and sufficient water to make 390 ml. into a mixture of 95 g. (1.38 moles) of sodium nitrite, 32.2 g. (0.70 mole) of ethyl alcohol and sufficient water to make 390 ml. The generator flask was warmed slightly with a warm water-bath from time to time to ensure a steady evolution of ethyl nitrite. After all of the ethyl nitrite had been passed into the alcoholic limonene solution, 10 ml. of water was added, and moist hydrogen chloride was passed into the solution. The reaction was quite exothermic, but the introduction of hydrogen chloride could be so regulated as to maintain a reaction temperature of 0 to -10° , preferably -5° . The moist hydrogen chloride was generated by dropping 114 ml. of concentrated hydrochloric acid (1.5 moles of HCl) into sulfuric acid and passing the evolved hydrogen chloride through concentrated hydrochloric acid. After addition of the hydrogen chloride was complete, the reaction mixture was stirred for about thirty minutes to permit the reaction temperature to drop to -10° . The precipitated *d*-limonene nitrosochloride, 80 g. (80% yield), was filtered with suction and washed with cold ethyl alcohol. The addition of 10 ml. of water to the reaction mixture prior to introduction of hydrogen chloride was found to be absolutely necessary to the isolation of a good yield of product. When anhydrous conditions were maintained, yields of only 9–11% were realized.

A similar procedure using methyl nitrite gave yields of *d*-limonene nitrosochloride of the order of 70%.

Preparation of *l*-Carvoxime.—*d*-Limonene nitrosochloride was dehydrohalogenated by the pyridine procedure of Wallach⁹ to afford *l*-carvoxime in 90–95% yield; m.p. 74° (reported¹¹ m.p. 72°).

Hydrolysis of Carvoxime.—The following procedures were found satisfactory for the hydrolysis of *l*-carvoxime to *l*-carvone:

Procedure A: A mixture of 10 g. (0.06 mole) of *l*-carvoxime and 100 ml. of 5% aqueous oxalic acid was heated to reflux for two hours. At the end of this time, the reaction

mixture was steam distilled, and the distillate was extracted with ether. The ethereal solution was dried over sodium sulfate and fractionally distilled to give 7.1 g. (78%) of *l*-carvone.

Procedure B: A mixture of 37 g. (0.22 mole) of carvoxime and 500 ml. of 5% oxalic acid was steam distilled without previous reflux. The distillate was treated as described above to give 20.5 g. of *l*-carvone. Nine grams of carvoxime was recovered from the residue from steam distillation. The yield of *l*-carvone was 80% based on the unrecovered *l*-carvoxime.

The *l*-carvone prepared by either procedure showed the following properties: b.p. $88-90^{\circ}$ (4 mm.); n_D^{20} 1.4989; d_4^{25} 0.9673; $[\alpha]_D^{25} -54.2^{\circ}$. The properties reported¹² for natural *l*-carvone are: b.p. $97-98^{\circ}$ (9 mm.); n_D^{20} 1.4988; d_4^{15} 0.9652; $[\alpha]_D^{20} -62.46^{\circ}$. Our *l*-carvone gave a semicarbazone, m.p. $140-141.5^{\circ}$; reported¹³ m.p. $141-142^{\circ}$.

A mixture of 20 g. (0.12 mole) of *l*-carvoxime and 100 ml. of 5 *N* hydrochloric acid was heated to reflux for 15 minutes. The mixture was steam distilled, the distillate was extracted with ether, and the ethereal solution was dried over anhydrous sodium sulfate. Removal of the ether left 13.3 g. of an oil which was completely soluble in 5% aqueous sodium hydroxide. This oil was characterized as carvacrol through the formation of 2-methyl-5-isopropylphenoxylacetic acid, m.p. $152.0-152.5^{\circ}$; reported¹⁴ m.p. $150-151^{\circ}$. The yield of crude carvacrol was 74%. An attempt to prevent isomerization of carvone to carvacrol by steam distilling the hydrochloric acid solution without reflux led also to carvacrol in 77% yield.

An attempted oxime exchange between benzaldehyde and carvoxime in glacial acetic acid as solvent was unsuccessful; carvoxime was almost quantitatively recovered.

(12) J. L. Simonsen, "The Terpenes," Second Ed., Vol. I, The University Press, Cambridge, Mass., 1947, p. 396.

(13) H. Rupe and K. Dorschky, *Ber.*, **39**, 2112, 2372 (1906).

(14) C. F. Koelsch, *THIS JOURNAL*, **53**, 304 (1931).

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(11) O. Wallach, *Ann.*, **305**, 324 (1899).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, EMORY UNIVERSITY]

Studies in Mixed Ester Condensations. II¹

BY E. EARL ROYALS, JOHN C. HOPPE, A. D. JORDAN, JR.,² AND A. G. ROBINSON, III²

A study has been made of the acylation of several aliphatic methyl esters with methyl benzoate, methyl furoate, methyl isobutyrate and methyl isovalerate as acylating agents. The lower aliphatic methyl esters have been benzoylated in satisfactory yields under forcing conditions with benzene as azeotropic distillation agent for removal of methyl alcohol and with sodium methoxide as catalyst; a ratio of three moles of aliphatic ester per mole of methyl benzoate was necessary for satisfactory yields. Methyl furoate is a much more active acylating agent for aliphatic esters than is methyl benzoate; yields of the order of 30% of α -furoylated esters were obtained under non-forcing conditions without the use of an excess of the aliphatic ester, while yields of 60–70% were readily obtained using a threefold excess of the aliphatic ester under forcing conditions. Acetic, propionic, *n*-valeric and *n*-caproic esters have been isobutyrylated in approximately 30% yields using a threefold excess of the aliphatic ester and forcing conditions; attempted isobutyrylation of methyl *n*-butyrate led to an inseparable mixture of mixed and self condensation products. Acetic, propionic and *n*-caproic esters were isovalerylated in 21–30% yields using a threefold excess of the aliphatic ester and forcing conditions; attempted isovalerylation of methyl *n*-butyrate and methyl *n*-valerate led to inseparable mixtures of mixed and self condensation products.

It has previously been shown¹ that satisfactory yields of methyl α -benzoylpropionate and of methyl α -benzoyl-*n*-butyrate may be obtained by direct ester condensation provided that an excess of the aliphatic ester is used. It was found that the previously reported poor yields for benzoylation of *n*-butyric esters is due to an unfavorable equilibrium rather than to a preference of the *n*-butyric ester for self condensation, and that a yield of 41% of the mixed condensation product may be

obtained by using a fourfold excess of methyl *n*-butyrate and conducting the condensation under forcing conditions.

Although esters fail completely to undergo sodium alkoxide catalyzed acetoacetic ester condensation in benzene solution under non-forcing conditions, it has been found that benzene, rather than an excess of the aliphatic ester, may be used as azeotropic distillation agent for forced benzoylations of aliphatic esters. The use of benzene as azeotropic distillation agent for these forced mixed ester condensations is of considerable practical advantage, since smaller supplies of pure aliphatic ester are required. Assuming that benzoic and aliphatic esters are of comparable reactivity as

(1) For the first paper in this series, see E. E. Royals, *THIS JOURNAL*, **70**, 489 (1948).

(2) Taken in part from theses presented by A. D. Jordan, Jr., and A. G. Robinson, III, to the Graduate Faculty of Emory University in partial fulfillment of the requirements for the degree of Master of Science, 1950 and 1951, respectively.

acylating agents and that consequently self and mixed ester condensation proceed with comparable rapidity in an attempted benzoylation of an aliphatic ester, the "theoretical" ratio of reactants and catalyst for such a mixed ester condensation should be three moles of aliphatic ester and two moles of sodium methoxide per mole of methyl benzoate. Using this ratio of reactants and conducting the condensation in benzene with slow azeotropic distillation of the methyl alcohol formed through a short fractionating column led to 46.9, 48.6 and 36.4% yields, respectively, for the benzoylation of methyl propionate, methyl *n*-butyrate and methyl *n*-valerate. The preferred procedure for these condensations was to dissolve two-thirds of the aliphatic ester in benzene and add this solution dropwise to the remainder of the reaction mixture during the period of reaction, the methyl alcohol-benzene azeotrope being continuously removed through the column. Benzoylations of the higher aliphatic esters were unsatisfactory because of the tendency of the higher β -ketoesters to decompose to ketones during the fractional distillation necessary for the separation of mixed and self condensation products. This is in accord with the experience of Briese and McElvain.³

Methyl 2-furoate was found to be a considerably more active acylating agent for aliphatic esters than is methyl benzoate. Reasonably satisfactory yields (20–39%) of α -furoylated esters were obtained by treatment of 1 mole of the aliphatic ester with 1 mole of methyl furoate in the presence of 2 moles of sodium methoxide at the boiling point of the aliphatic ester and under non-forcing conditions for a period of five hours. Under these conditions, negligible self condensation of the aliphatic ester was observed, and considerable quantities of unreacted aliphatic ester were recovered. Increasing the reaction time led to no increase in the yield of condensation product. Furoylation of aliphatic esters using a threefold excess of the aliphatic ester and under the forcing conditions found most satisfactory for benzoylation led to excellent yields (60–70%) of α -furoyl esters. Furoylation of methyl acetate with methyl furoate under forcing conditions gave quite low yields (41.1%) of methyl α -furoylacetate; furoylation of ethyl acetate with methyl furoate, however, under the same conditions gave an excellent yield of ethyl α -furoylacetate. We have consistently experienced difficulty in forced acylations of methyl acetate with various acylating esters; ethyl acetate gives considerably better results. This difference between methyl and ethyl acetates is probably attributable to the difficulty of rigid purification of methyl acetate and to the low boiling point of this ester and its azeotropes permitting escape from the reaction mixture during forced condensations. These difficulties are much less pronounced with the ethyl ester. Our results for furoylation of various aliphatic esters are summarized in Table I.

Isobutyric and isovaleric esters fail⁴ to undergo

(3) R. R. Briese and S. M. McElvain, *THIS JOURNAL*, **55**, 1697 (1933).

(4) D. C. Roberts and S. M. McElvain, *ibid.*, **59**, 2007 (1937); S. M. McElvain, *ibid.*, **51**, 3124 (1929).

TABLE I
MIXED CONDENSATIONS OF METHYL 2-FUROATE WITH ALIPHATIC METHYL ESTERS

Aliphatic ester	Moles ester per mole of furoate	Reaction time (hr.)	Product, α -furoyl ester B.p., °C.	Mm.	Yield, %
Acetate	1	5	118–121	4	20.4 ^a
Acetate ^b	3	8	116–118	3.5	41.1 ^a
Acetate ^c	3	8	128–129	7	68.2 ^a
Propionate	1	5	116–117	3.5	26.5 ^d
Propionate ^b	3	8	121–123	4	70.4 ^d
<i>n</i> -Butyrate	1	5	129–130	6	38.8 ^e
<i>n</i> -Butyrate ^b	3	8	126–128	5	60.2 ^e
<i>n</i> -Valerate	1	5	137–138	5	32.8 ^f
<i>n</i> -Valerate ^b	3	8	136–139	6	62.4

^a Characterized through the formation of 1-phenyl-3-furylpyrazolone-5, m.p. 182–182.5°; S. S. Sandelin, *Ber.*, **33**, 492 (1900), reports m. p. 179°. ^b Condensation run under forcing conditions. ^c Ethyl acetate rather than methyl acetate used in this condensation. ^d Characterized through the formation of α -furoylpropionamide, m.p. 185.5–186°; A. Mironescu and G. Ioanid, *Bull. soc. chim., Roumania*, **17**, 107 (1935), report m.p. 183°. ^e Characterized through the formation of α -furoyl-*n*-butyramide, m.p. 191.5–192°; Mironescu and G. Ioanid, *ibid.*, **17**, 107 (1935), report m.p. 188°. ^f *Anal.* Calcd. for $C_{11}H_{18}O_4$: C, 62.84; H, 6.71. Found: C, 62.72; H, 6.85.

the acetoacetic ester condensation in the presence of sodium alkoxides even under forcing conditions. Consequently, these esters should serve as suitable acylating components for mixed ester condensations leading to only two products. Wahl attempted⁵ such a mixed ester condensation between ethyl acetate and ethyl isovalerate and reported a yield of only 9% of ethyl isovaleryl acetate. We have found that ethyl acetate, methyl propionate, methyl *n*-valerate and methyl *n*-caproate may be successfully isobutyrylated in approximately 30% yields by condensation of methyl isobutyrate with a threefold excess of the aliphatic esters under forcing conditions with benzene as azeotropic distillation agent and sodium methoxide as catalyst. Condensation of methyl isobutyrate with methyl *n*-butyrate by this procedure led to a mixture of mixed and self condensation products inseparable by fractional distillation. Similarly, methyl isovalerate was condensed with ethyl acetate, methyl propionate and methyl *n*-caproate to afford 21–30% yields of mixed condensation products. Condensations of methyl isovalerate with methyl *n*-butyrate and methyl *n*-valerate led to inseparable mixtures of mixed and self condensation products; the presence of both mixed and self condensation products was demonstrated by ketonic cleavage of the mixed β -ketoesters and identification of the resulting ketones. Our results for isobutyrylation and isovalerylation of various aliphatic esters are summarized in Table II.

Experimental

Materials.—The esters used were either purchased from the Matheson Company, Inc., Paragon Division, or were prepared by direct esterification or by interaction of an acid chloride with an alcohol in pyridine solution. The esters were dried over sodium sulfate or calcium chloride, then over drierite, fractionally distilled, and stored in glass-stoppered bottles over drierite until use. The sodium methoxide used was a commercial product purchased from the Mathieson Alkali Works, Niagara Falls, New York.

(5) A. Wahl and M. Doll, *Bull. soc. chim.*, **13**, 265 (1913).

TABLE II
 MIXED CONDENSATIONS OF METHYL ISOBUTYRATE AND METHYL ISOVALERATE WITH ALIPHATIC ESTERS^a

Acyating methyl ester	Ester acylated	Mixed condensation product ^b						Self condensation product ^b					
		°C.	Mm.	Yield, %	Analyses, %		°C.	Mm.	Yield, %	Analyses, %		°C.	Mm.
					Carbon	Hydrogen				Carbon	Hydrogen		
					Calcd.	Found				Calcd.	Found		
Isobutyrate	Et acetate	69	2.0	34.2	60.73	60.47	8.86	8.92	48	3.5	30.8	55.38	55.83
Isobutyrate	Me propionate	73-75	2.0	30.2	60.73	60.41	8.86	8.67	56	2.5	29.2	58.33	58.28
Isobutyrate	Me <i>n</i> -valerate	79-82	2.0	28.6	64.52	64.61	9.78	9.39	105-108	5.0	28.4	66.00	65.83
Isobutyrate	Me <i>n</i> -caproate	85-87	1.5	31.4	66.00	65.98	10.00	10.34	118-121	1.5	31.8	68.46	68.72
Isovalerate	Et acetate	74-75	2.0	30.2	62.79	62.83	9.30	9.52	47	2.0	28.1	55.38	55.34
Isovalerate	Me propionate	79	1.5	28.1	62.79	62.61	9.30	9.34	56	2.0	28.5	58.33	58.39
Isovalerate	Me <i>n</i> -caproate	96-98	2.0	21.2	67.29	67.32	10.28	10.69	120	2.0	17.0	68.46	68.32

^a The ratio of reactants for each condensation was one mole of acylating ester per three moles of acylated ester and two moles of sodium ethoxide. ^b In each case the mixed and self condensation products were characterized by ketonic hydrolysis and identification of the resulting ketones through formation of known derivatives.

Experimental Procedures.—All of the condensations here reported were performed in essentially the same manner. The experiments described in detail below are illustrative of the general procedures.

Condensation of Methyl Furoate with Methyl *n*-Butyrate (Unforced).—A mixture of 63 g. (0.5 mole) of methyl furoate and 27 g. (0.5 mole) of sodium methoxide was placed in a 500-ml., three-necked flask equipped with a modified Hershberg stirrer,⁶ a dropping funnel, and a reflux condenser protected by a calcium chloride tube. Fifty-one grams (0.5 mole) of methyl *n*-butyrate was added from the dropping funnel during one hour while the reaction mixture was vigorously stirred and maintained at a temperature of 100° by means of a heating mantle. Heating and stirring were continued for an additional four hours after the last of the methyl *n*-butyrate had been added. The reaction mixture was cooled to room temperature and poured onto crushed ice mixed with 60 ml. of concentrated hydrochloric acid. This mixture was stirred until all solids disappeared, and was allowed to stand until an organic layer clearly separated. The organic layer was separated, and the aqueous layer was extracted with two 100-ml. portions of ether. The organic layer and the ether extracts were combined, washed with a saturated solution of sodium bicarbonate until free of acid, then washed with water. The ether solution was dried over sodium sulfate, then over drierite. Removal of the drying agent and ether and distillation of the residue through a 61-cm. column packed with glass helices gave: (1) 12 g. of a mixture of methyl furoate and methyl α -butyryl-*n*-butyrate, b.p. 45-62° (8 mm.), (2) 7 g. of intermediate material, and (3) 38 g. (38.8%) of methyl α -furoyl-*n*-butyrate, b.p. 129-130° (6 mm.).

Other unforced condensations of methyl furoate with aliphatic esters were performed in a similar manner. In certain

cases, the reaction mixtures became quite thick, and sufficient benzene was added toward the end of the reaction period to permit pouring of the reaction mixture.

Forced Condensation of Methyl Furoate with Methyl *n*-Butyrate.—A mixture of 63 g. (0.5 mole) of methyl furoate, 54 g. (1.0 mole) of sodium methoxide, 51 g. (0.5 mole) of methyl *n*-butyrate and 100 ml. of dry benzene was placed in a 500-ml., three necked flask fitted with a modified Hershberg stirrer and dropping funnel and mounted under an 18-inch total-condensation partial-takeoff column packed with a nichrome wire spiral. Total reflux of the reaction mixture was established until the vapor temperature became constant. A solution of 102 g. (1 mole) of methyl *n*-butyrate in 200 ml. of dry benzene was added dropwise during 4.5 hours while the reaction mixture was vigorously stirred and material was taken off through the column at such a rate that the vapor temperature did not exceed 65° (preferable vapor temperature, 58-60°). The reaction was continued for 3.5 hours after the last of the methyl *n*-butyrate solution had been added. The reaction mixture was worked up by the procedure described above to give 59 g. (60.2%) of methyl α -furoyl-*n*-butyrate, b.p. 126-128° (5 mm.).

Forced condensations of methyl isobutyrate and methyl isovalerate with other aliphatic esters were run according to this essential procedure. In those cases that the self and mixed condensation products boiled near together, separations were effected using a Todd column,⁷ 90 cm. (5 mm.) with a monel spiral packing. Effectiveness of the separations was checked in each case by elemental analysis of the self and mixed condensation products and by ketonic hydrolysis of each product and identification of the resulting ketones.

(7) Floyd Todd, *ibid.*, **17**, 175 (1945).

(6) E. B. Hershberg, *Ind. Eng. Chem., Anal. Ed.*, **8**, 313 (1936).

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NOTES

The Detection of Carbohydrate Esters and Lactones after Separation by Paper Chromatography¹

By M. ABDEL-AKHER² AND F. SMITH

In connection with investigations into carbohydrates containing lactone or ester groupings by paper partition chromatography it was necessary to develop a method for the detection of minute amounts of these substances. The hydroxamic

acid test^{3,4} for esters which has been shown to be useful in following the reduction of certain carbohydrate esters with lithium aluminum hydride⁵ has now been modified for the location of esters and lactones on paper chromatograms.⁶ After carrying out the separation of esters or lactones or ester lactones by partition chromatography in the usual manner^{7,8}

(3) F. Feigl, V. Anger and O. Frehden, *Microchemie*, **15**, 9 (1934).

(4) D. Davidson, *J. Chem. Ed.*, **17**, 81 (1940).

(5) M. Abdel-Akher and F. Smith, *Nature*, **166**, 1037 (1950).

(6) Cf. S. Hestrin, *J. Biol. Chem.*, **180**, 249 (1949).

(7) R. Consden, A. H. Gordon and A. J. P. Martin, *Biochem. J.*, **38**, 224 (1944).

(8) S. M. Partridge and R. C. Westhall, *ibid.*, **42**, 235 (1948).

(1) Paper No. 2667, Scientific Journal Series, Minnesota Agricultural Experiment Station.

(2) M. A.-A. wishes to express his sincere thanks to the Fouad I University, Cairo, for a scholarship.