gen atoms was found. However, in some instances, the reaction was more vigorous in that it proceeded at a lower temperature and further toward completion.

With lithium aluminum hydride, the keto–enol tautomers investigated behaved as though they were only partially enolized, whereas similar compounds with the Grignard reagent act as though they exist in the enol form only.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, EMORY UNIVERSITY]

Claisen Condensation of Methyl Esters

BY E. EARL ROYALS

Investigations of the acetoacetic ester condensation[1] have been largely confined to the study of ethyl esters; particularly, relatively few methyl ester condensations have been reported in the literature. The present commercial availability of sodium methoxide, and observations[2] that sodium methoxide is a condensation catalyst considerably less sensitive to adverse experimental conditions than sodium ethoxide make further investigation of methyl ester condensations desirable. The present research was undertaken to determine the utility of sodium methoxide as a reagent for the condensation of the simpler methyl esters, and, more specifically, to develop methods of synthesis for certain keto-esters which have not previously been satisfactorily prepared by direct ester condensation.

McElvain and co-workers made an extensive study of the self-condensation of ethyl esters in the presence of sodium ethoxide under both equilibrium and forcing conditions.[3] Our results on the self-condensation of methyl esters, shown in Table I, are quite similar to those of McElvain in the ethyl ester series. Our forcing procedure, however, is considerably simpler and requires less of the pure ester than the one described by McElvain.

The condensation of methyl benzoate with methyl acetate has been reported to give yields of methyl benzoylacetate ranging from 45 to 85% depending on the conditions employed.[4] Dorsch and McElvain[5] condensed ethyl benzoate in the presence of sodium ethoxide with ethyl acetate, propionate, and *n*-butyrate and obtained yields of 37, 19 and 4%, respectively, of the α-benzoyl esters. We have investigated the condensation of methyl benzoate with methyl acetate, propionate and *n*-butyrate; our results are summarized in Table II. The methyl propionate condensation was chosen for pilot work. The yield of methyl α-benzoylpropionate from equivalent quantities of the two esters and sodium methoxide was found to be essentially the same whether the reactants were directly mixed, or whether the propionate was added dropwise to a mixture of methoxide and benzoate. The yield was not increased by lengthening the reaction time from four to twenty-four hours. It was found, however, that the use of excess methyl propionate and sodium methoxide greatly increased the yield of methyl α-benzoylpropionate (calculated on methyl benzoate); indeed, the second and third equivalents of propionate were utilized in inter-ester condensation with almost the same efficiency as the first. Similar results were obtained in the condensation of methyl acetate with methyl benzoate; somewhat lower yields were obtained, however, than in the corresponding methyl propionate condensations. The best conditions found for the condensation of methyl benzoate with methyl propionate were applied to the analogous methyl *n*-butyrate condensation. A negligible yield of methyl α-benzoylbutyrate was obtained. It was observed, however, that even with a reaction period of forty hours, considerable quantities of methyl *n*-butyrate were recovered unreacted, indicating that the low yield of inter-ester condensation product might be due to an unfavorable equilibrium rather than to a preference of methyl *n*-butyrate for self-condensation. Accordingly, methyl *n*-butyrate (4 moles) was condensed with methyl benzoate (1 mole) in the presence of sodium methoxide (2

TABLE I

SELF-CONDENSATIONS OF METHYL ESTERS IN THE PRESENCE OF SODIUM METHOXIDE

Methyl ester	Moles ester per mole CH_3ONa	Temp., °C.	Time, hr.	% yield β-ketoester
Acetate	6	60	8	43
Acetate (forced)[a]	6	80	8	43–50
Propionate	4	80	16	29
Propionate	6	80	16	42
Propionate (forced)	6	100	16	71
n-Butyrate (forced)	6	125	30	79
Phenylacetate (forced)	2	100[b]	6	80

[a] See text and Experimental Part for description of forcing conditions. [b] Pressure slowly reduced from atm. to final value of 10 mm.

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(1) See Hauser and Hudson in Adams, "Organic Reactions," John Wiley and Sons, New York, N. Y., 1942, Chap. 9.

(2) Freri, *Gazz. chim. ital.*, **68**, 616 (1938); Royals, THIS JOURNAL, **67**, 1508 (1945).

(3) McElvain, THIS JOURNAL, **51**, 3124 (1929); Briese and McElvain, *ibid.*, **55**, 1697 (1933); Roberts and McElvain, *ibid.*, **69**, 2007 (1937).

(4) Ref. 1, pp. 278, 283.

(5) Dorsch and McElvain, THIS JOURNAL, **54**, 2960 (1932).

TABLE II

CONDENSATIONS OF ALIPHATIC METHYL ESTERS WITH METHYL BENZOATE IN THE PRESENCE OF SODIUM METHOXIDE

Methyl ester	Moles ester and CH_3ONa per mole benzoate	Temp., °C.	Time, hr.	Product, b. p. °C.	mm.	$C_6H_5COCHRCO_2CH_3$ $n^{25}D$	Yield, %
Acetate	1	60	4	117–122[a]	2.5	1.5355[a]	19
Acetate[b]	1	60	6	113–115	2.0	1.5361	21
Acetate[c]	3	60	6	127–130	5.0	1.5354	45
Propionate	1	80	4	130–131[d]	4.0	1.5200	24
Propionate	1	80	24	117–120	2.0	1.5206	22
Propionate[b]	1	80	6	125–127	3.0	1.5206	19
Propionate[e]	2	80	6	120	2.5	1.5206	41
Propionate[c]	3	80	6	120–123	2.0	1.5206	61
n-Butyrate[c]	3	100	6	110–129	3.0		9
n-Butyrate (forced)	2[f]	120	30	115–120[g]	1.0	1.5215	41

[a] von Auwers and Jacobsen, *Ann.*, **426**, 234 (1922), report, b. p. 151.5–151.8° (13 mm.), $n^{20}D$ 1.5394. [b] Aliphatic ester added dropwise to reaction mixture. [c] Aliphatic ester and sodium methoxide added in three equal portions to reaction mixture. [d] Characterized through 4-methyl-3-phenyl-isoxazalone-5, m. p. 121–122°. Haller and Bauer, *Compt. rend.*, **152**, 1446 (1911), report m. p. 123–124°. [e] Aliphatic ester and sodium methoxide added in two equal portions to reaction mixture. [f] Plus 2 moles excess methyl *n*-butyrate. [g] Characterized through 4-ethyl-3-phenyl-isoxazolone-5, m. p. 90.5–92.0°. Haller and Bauer, *loc. cit.*, report m. p. 91°.

moles), the methanol formed in the reaction being azeotropically distilled with the excess methyl *n*-butyrate during a reaction period of thirty hours. A yield of 41% of methyl α-benzoylbutyrate was obtained.

The results here reported for condensations of methyl benzoate with aliphatic methyl esters indicate that such inter-ester condensations, involving one ester incapable of self-condensation, may be of more general usefulness than previous investigations would indicate. Our results on inter-ester condensations are to be regarded as exploratory; further investigations along this line are in progress in our laboratory.

Experimental

Materials.—The methyl esters used were either purchased from the Eastman Kodak Company or were prepared by standard procedures. All of the esters were dried over calcium chloride, distilled, then dried over and distilled from phosphorus pentoxide through an 18-inch column packed with a nichrome spiral of the Podbielniak type. The sodium methoxide was a commercial product purchased from the Mathieson Alkali Works, Niagara Falls, N. Y.

Procedures.—The experiments described below will illustrate the general methods used. Self-condensations under non-forcing conditions were run essentially according to the procedure[3c] described by Roberts and McElvain. The forced self-condensation of methyl phenylacetate was run according to the general procedure[3b] of Briese and McElvain.

Forced Self-Condensation of Methyl Propionate.—A mixture of 317 g. (3.6 mole) of methyl propionate and 32.4 g. (0.6 mole) of sodium methoxide was placed in a 500-cc. flask under an 18-inch, nichrome spiral packed column with a Whitmore-Lux type head. The entire apparatus was protected from atmospheric moisture by suitably placed calcium chloride tubes. The reaction flask was heated in an oil-bath at 100°. The reaction mixture became homogeneous within about one hour. The column was operated at a jacket temperature of 65° with slow take-off and frequent total reflux. A total of 112 g. of distillate was collected (vapor temperature 65–68°) during a reaction period of sixteen hours. The residue on cooling to room temperature set to a solid cake. This cake was broken up, 150 cc. of ether added, and the slurry was cooled in an ice-bath. An ice-cold solution of 50 cc. of glacial acetic acid in 100 cc. of water was added in portions with stirring. Stirring was continued at ice-bath temperature until the solid material had all dissolved. The organic layer was separated, and the aqueous layer was twice extracted with 100-cc. portions of ether. The ether solutions were combined, washed once with water, and dried over sodium sulfate. Removal of the drying agent and ether, followed by distillation of the residue through the spiral-packed column referred to above gave 61 g. (70.5%) of methyl α-propionylpropionate, b. p. 74–76° (10 mm.), $n^{25}D$ 1.4211.

Condensation of Methyl Benzoate with Methyl Propionate.—A mixture of 68 g. (0.5 mole) of methyl benzoate, 44 g. (0.5 mole) of methyl propionate, and 27 g. (0.5 mole) of sodium methoxide was placed in a 500-cc., three necked flask fitted with a modified Hershberg stirrer[6] and reflux condenser protected by a calcium chloride tube. The reaction mixture was stirred in an oil-bath at 80° for six hours. After two hours, and again after four hours, additional quantities of 44 g. of methyl propionate and 27 g. of sodium methoxide were added. The reaction mixture was cooled to room temperature, and 100 cc. of ether was added to give a fluid system. This slurry was cooled in an ice-bath, then poured into an ice-cold solution of 125 cc. of glacial acetic acid in an equal volume of water. (This hydrolysis step is critical; early attempts to effect the hydrolysis by dropwise addition of the cold acetic acid solution to the reaction mixture with stirring in an ice-bath led to the formation of large amounts of benzoic acid, presumably from acid cleavage of the keto-ester.) When all of the solid material had disappeared (about five minutes), the organic layer was separated, and the aqueous layer was twice extracted with 100-cc. portions of ether. The ether solutions were combined, washed once with water, then with saturated sodium bicarbonate solution until free of acid, and again with water. The ether solution was dried over sodium sulfate, then overnight over drierite. Removal of the drying agent and ether, and distillation of the residue through the column referred to above gave 58 g. (60.5%) of methyl α-benzoylpropionate, b. p. 120–123° (2 mm.), $n^{25}D$ 1.5206. A forerun, 35 g., was obtained, b. p. 63–69° (4 mm.), $n^{25}D$ 1.4735, the physical constants indicating a mixture of methyl α-propionylpropionate and unreacted methyl benzoate.

Forced Condensation of Methyl *n*-Butyrate with Methyl Benzoate.—A mixture of 191 g. (1.88 mole) of methyl *n*-butyrate, 64 g. (0.47 mole) of methyl benzoate, and 53.5 g. (0.94 mole) of sodium methoxide was placed in

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

a 500-cc., two-necked flask under the column described above. A modified Hershberg stirrer was mounted in the second neck of the flask. The reaction mixture was stirred and heated in an oil-bath at 120–130° for thirty hours, while distillate was slowly taken off through the column jacketed at 65°. A total of 64 g. of distillate was collected. The residue was cooled in an ice-bath and worked up by the procedure described above under the condensation of methyl propionate with methyl benzoate.

Distillation of the reaction product through the spiral-packed column referred to above gave: (I) 8 g., probably methyl benzoate, b. p. 67–85° (9 mm.), (II) 47 g. methyl α-butyrylbutyrate, b. p. 85–90° (9–7 mm.), (III) 6 g. intermediate, (IV) 40 g. (41.3% on methyl benzoate) of methyl α-benzoylbutyrate, b. p. 115–120° (1 mm.), $n^{25}\text{D}$ 1.5215.

Summary

Sodium methoxide has been used to effect the acetoacetic ester type of condensation of several methyl esters. Procedures have been described for the self condensation of methyl propionate and of methyl *n*-butyrate to give good yields of β-ketoesters without the use of very large excesses of the esters. It has been found possible to effect satisfactory syntheses of methyl α-benzoylpropionate and of methyl α-benzoyl-*n*-butyrate by direct ester condensation.

EMORY UNIVERSITY, GA. RECEIVED JUNE 12, 1947

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Some Dialkylaminoalkyl Sulfides and Ethers Derived from Quinoline and Acridine Heterocycles

BY R. O. CLINTON AND C. M. SUTER

Although the literature contains references to a very large number of heterocyclic nitrogen compounds substituted by basic side chains linked to the nucleus by an imino (—NH—) group, few compounds of this type in which the linkage is oxygen or sulfur have been described. It was the purpose of the present study to determine the effect of replacement of the —NH— by the —O— or —S— linkage upon the therapeutic activity of these compounds, particularly toward the malaria parasite.

The literature[1] describes several quinolines in which 2-dialkylaminoethoxy side chains are linked to the nucleus in the 2- or 4-position, and further substituents (*e. g.*, methyl, phenyl, carboxamide) appear in the quinoline ring. Bachman, *et al.*,[2] have reported the preparation of 3-amino-4-(3-diethylamino-2-hydroxypropylmercapto)-quinoline by the alkylation of the corresponding aminoquinolinethiol with 3-diethylamino-1,2-epoxypropane. In addition, several quinolyl sulfides of related types are listed by Wiselogle,[3]

TABLE I

7-CHLOROQUINOLINES

No.	4-Substituent	Max., mμ	$\epsilon \times 10^{-3}$	Min., mμ	$\epsilon \times 10^{-3}$
1	2-(2-Diethylaminoethylmercapto)-ethoxy[a]	231	63.00	264	1.50
		305	9.49	307	9.18
		310	9.30		
2	4-Diethylamino-1-methylbutyloxy[a]	232	32.18	264	0.85
		310	6.66		
3	2-Diethylaminoethylmercapto[a,b]	241	42.3	268	1.90
		332	17.59		
4	2-Di-*n*-hexylaminoethylamino[a,c]	221	29.60	231	24.40
		235	25.25	245	15.72
		248	15.79	278	2.10
		326	18.15	330	16.24
		339	18.20		
5	4-Diethylamino-1-methylbutylmercapto[a]	241	36.80	275	19.65
		345	16.21	347	16.15
		349	16.20		
6	4-Diethylamino-1-methylbutylmercapto[d,e]	230	30.38	280	3.77
		315	9.98	320	9.90
		322	9.94		
7	4-Diethylamino-1-methylbutylamino[a,f]	220	32.25	231	18.05
		235	18.85	243	13.80
		256	16.28	280	1.85
		330	17.83	336	15.90
		343	19.45		
8	4-Diethylamino-1-methylbutylamino[d]	218	39.40	246	15.10
		255	17.91	275	1.33
		330	11.90		
	6-CHLORO-2-METHOXYACRIDINES				
	9-Substituent				
9	2-Diethylaminoethylmercapto[a]	222	22.13	240	13.83
		275	68.97	310	1.01
		381	14.13	404	3.77
		445	5.58		
10	4-Diethylamino-1-methylbutylmercapto[a]	225	19.31	240	13.76
		276	64.26	315	0.83
		376	12.40	406	4.10
		445	5.79		
11	4-Diethylamino-1-methylbutylamino[a,g]	220 (?)	...	242	10.19
		280	55.07	318	2.69
		344	4.99	364	1.26
		424	9.40	436	8.65
		444	8.87		

[a] In 0.01 N hydrochloric acid. [b] Inflection at 380–385 mμ, $\epsilon = 450$. [c] Huber, Bair and Laskowski, THIS JOURNAL, **67**, 1619 (1945). [d] In 0.01 N sodium hydroxide. [e] Inflection at 375–380 mμ, $\epsilon = 900$. [f] These values agree well with those reported by Drake, *et al.*, THIS JOURNAL, **68**, 1214 (1946). [g] *Cf.* Scudi and Jelinek, *J. Biol. Chem.*, **152**, 27 (1944).

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[1] U. S. Patents 1,572,768 (Reissue 16,394), 1,688,469, 1,841,970, 1,860,286, 1,891,980; Bachman, *et al.*, *J. Org. Chem.*, **9**, 302 (1944).

[2] Bachman, Welton, Jenkins and Christian, THIS JOURNAL, **69**, 366 (1947).

[3] Wiselogle, "Survey of Antimalarial Drugs," Vol. II, Part 2, pp. 1107–1108 (1946).