The quinoline derivatives were characterized by preparation of the picrates and methiodides, by analysis of the latter for iodide ion, and by oxidation to 3-quinolinecarboxylic acid.

Experimental

Materials.—The trimethylol compounds were supplied by the Heyden Corporation. A sample of 2-(hydroxymethyl)-2-methylpropanediol-1,3 was also prepared by condensation of an excess of formaldehyde with propionaldehyde in the presence of calcium hydroxide; m. p. after recrystallization from dioxane, 198–199°.

Reaction of 2-(Hydroxymethyl)-2-methylpropanediol-1,3.—A mixture of 7 g. of the alcohol, 10 g. of aniline, 11 ml. of nitrobenzene and 20 ml. of sulfuric acid was heated to 160°. A vigorous reaction set in, necessitating removal of the heating bath and external cooling of the flask. After this subsided the mixture was heated at 160–170° for six hours. The reaction mixture was made basic with 30% sodium hydroxide solution, steam distilled, the distillate acidified with dilute sulfuric acid and extracted with 30 ml. of chloroform. The acid solution was then cooled to 5° and diazotized with 10% sodium nitrite solution until an excess persisted for twenty minutes as shown by starch-iodide paper. At the end of this time the solution was heated slowly to boiling on the steam-bath. It was then made strongly basic with 30% sodium hydroxide solution and steam distilled. The distillate was extracted with three 50-ml. portions of ether and the extract dried over sodium sulfate. Removal of the ether gave 2.6 g. (28%) of crude product. Distillation at 12–13 mm. gave 2.3 g. (25%) of 3-ethylquinoline, b. p. 126–131°. The picrate was prepared by addition of a saturated solution of picric acid in alcohol to an alcoholic solution of the base; yellow needles from alcohol, m. p. 199.5–200.5°. The methiodide was prepared by reaction of the base with methyl iodide at room temperature and recrystallized from alcohol; m. p. 190–191.5°.

Anal. Calcd. for $C_{12}H_{14}NI$: I, 42.41. Found: I, 42.12.

Oxidation.—One gram of the base was dissolved in 50 ml. of 4% sulfuric acid and to it was added a solution of 4 g. of sodium dichromate in an equal volume of the same acid. The solution was heated for fifty hours on the steam-bath, then made basic with concentrated ammonium hydroxide. The hot suspension of hydrous chromic oxide was filtered off with suction and the cake washed with 30 ml. of dilute ammonia. The filtrate and washings were boiled with charcoal, filtered, acidified with acetic acid and cooled. The precipitated acid was filtered off and dried over sulfuric acid; m. p. 279–280° after recrystallization from alcohol–benzene.

Anal. Calcd. for $C_{10}H_7O_2N$: neut. equiv., 173. Found: neut. equiv., 171.

Reaction of 2-(Hydroxymethyl)-2-ethyl-propanediol-1,3.—Eight grams of the alcohol, 12 g. of aniline, 12 g. of nitrobenzene, and 25 ml. of sulfuric acid were treated as described above. The product was 1.5 g. (15%) of light yellow oil boiling at 137–140° under 11 mm. pressure. Picrate, yellow needles from alcohol, gave a m. p. 174–175°; methiodide gave a m. p. 131–132°. Oxidation with chromic acid as described above gave 3-quinolinecarboxylic acid, m. p. 279–280°.

Anal. Calcd. for $C_{13}H_{16}NI$: I, 40.52. Found: I, 40.21.

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Diethyl Acetals of α-Formyl Esters

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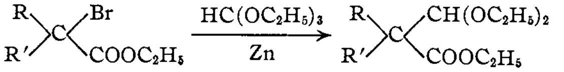
Tschitschibabin,[1] using a modification of the Reformatsky reaction, prepared the diethyl acetals of ethyl formylacetate and ethyl α-formylpropionate from the appropriate α-bromo ester, zinc, and ethyl orthoformate in yields of 38 and 64%, respectively. The reaction can be represented as



I

Shdanowitsch[2] reported that the reaction was successful with ethyl α-bromoisobutyrate.

In the present investigation this reaction has been applied successfully to eight α-bromo esters including the three previously investigated. Although diethyl α,α′-dibromoadipate and bromomalonic ester reacted with zinc and ethyl orthoformate, no acetal was detected.

From six of the α-bromo esters, acetal esters (I) were obtained in yields of 44–58% (Table I). On hydrolysis by alkali followed by acidification and treatment with 2,4-dinitrophenylhydrazine in 20% sulfuric acid, the acetal esters were converted to the 2,4-dinitrophenylhydrazones of simple aldehydes. Thus the derivative of isobutyraldehyde was obtained from the diethyl acetal of ethyl α-formyl isobutyrate. With the diethyl acetal of ethyl α-formyl-*n*-valerate, which was expected to give the 2,4-dinitrophenylhydrazone of *n*-valeraldehyde, only an impure product was obtained.

The acetal esters, when treated with 2,4-dinitrophenylhydrazine in 20% aqueous sulfuric acid, gave 2,4-dinitrophenylhydrazones without hydrolysis of the ester group. Their properties are listed in Table II.

Tschitschibabin[1] reported that the product from ethyl α-bromoacetate was contaminated with ethyl β-ethoxyacrylate formed by splitting out of ethanol from the acetal. Under the conditions used in the present investigation the product was about an equal mixture of ethyl β-ethoxyacrylate and the diethyl acetal of ethyl formylacetate. This mixture could be converted completely to the acrylate ester by heating at 190–200° (gentle refluxing) for one hour.

The product isolated from ethyl bromocyanoacetate was ethyl α-cyano-β-ethoxyacrylate.

This reaction constitutes a good preparative method for diethyl acetals of α-formyl esters. It is especially valuable when there are two alkyl groups in the α position, since esters such as ethyl isobutyrate undergo base-catalyzed formylation only with difficulty.[3]

Experimental

Diethyl Acetals of α-Formyl Esters.—In all runs listed in Table I the following procedure was used which gave better temperature control than the method of Tschitschibabin which did not use any solvent. About 100 g.

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(1) Tschitschibabin, *J. prakt. Chem.*, **73**, 326 (1906).

(2) Shdanowitsch, *J. Russ. Phys.-Chem. Soc.*, **42**, 1279 (1910).

(3) Hudson and Hauser (THIS JOURNAL, **63**, 3156 (1941)) obtained a 16% yield of ethyl α-formylisobutyrate using triphenylmethylsodium as the agent to condense ethyl formate and ethyl isobutyrate.

TABLE I

DIETHYL ACETALS OF α-FORMYL ESTERS

α-Bromo ester (ethyl α-bromo-)	Acetal ester (diethylacetal of ethyl α-formyl-)	Yield, %	B. p., °C. 20 mm.	Saponification equivalent Calcd.	Saponification equivalent Found	Formula	Analyses, %[a] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Propionate	Propionate	44[b]	99–102	204	200	$C_{10}H_{20}O_4$				
n-Butyrate	*n*-Butyrate	51	112–117	218	217	$C_{11}H_{22}O_4$	60.52	60.58	10.16	10.37
Isobutyrate	Isobutyrate	58.5[c]	104–107	218	220	$C_{11}H_{22}O_4$	60.52	60.00	10.16	10.01
n-Valerate	*n*-Valerate	56.5	116–120	232	228[d]	$C_{12}H_{24}O_4$	62.04	61.73	10.41	10.28
n-Caproate	*n*-Caproate	46.5	132–136	246	246	$C_{13}H_{26}O_4$	63.38	63.28	10.64	10.23
Hexahydrobenzoate	Hexahydrobenzoate	52.5	149–152		[e]	$C_{14}H_{26}O_4$	65.08	65.07	10.14	10.17

[a] Microanalyses by Micro-Tech Laboratories, Skokie, Illinois. [b] Prepared by Tschitschibabin.[1] [c] Obtained by Shdanowitsch.[2] [d] This ester required twenty hours refluxing in 0.5 *N* aqueous ethanolic sodium hydroxide for complete saponification instead of the usual two hours. [e] Attempts to quantitatively saponify this ester with alkali were unsuccessful.

TABLE II

2,4-DINITROPHENYLHYDRAZONES OF α-FORMYL ESTERS

α-Formyl ester (Ethyl α-formyl-)	2,4-Dinitrophenylhydrazone Appearance, yellow	M. p.,[b] °C.	Formula	Analyses, %[a] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Propionate	Needles	110–111.5	$C_{12}H_{14}O_6N_4$	46.45	46.64	4.55	4.47
n-Butyrate	Flakes	106–108	$C_{13}H_{16}O_6N_4$	48.14	48.35	4.97	4.80
Isobutyrate	Needles	104.5–105	$C_{13}H_{16}O_6N_4$	48.14	48.10	4.97	5.02
n-Valerate	Needles	121–123	$C_{14}H_{18}O_6N_4$	49.70	49.62	5.36	5.25
n-Caproate	Blades	86.5–88	$C_{15}H_{20}O_6N_4$	51.13	51.10	5.71	5.60
Hexahydrobenzoate	Needles	150–152	$C_{16}H_{20}O_6N_4$	52.74	52.80	5.53	5.54

[a] Microanalyses by Micro-Tech Laboratories, Skokie, Illinois. [b] The 2,4-dinitrophenylhydrazones were recrystallized to constant m. p. from methanol.

of granulated zinc was washed with dilute hydrochloric acid, and then rinsed three times each with water, methanol and acetone. The zinc was dried at 100° and 20 mm. for ten minutes and used immediately. A crystal of iodine and 25 cc. of dry benzene were added to the zinc. The benzene was heated to reflux and a solution of 0.2 mole of the α-bromoester and 40 cc. (0.24 mole) of ethyl orthoformate[4] in 75 cc. of dry benzene was added dropwise at a rate to maintain vigorous refluxing. A little heat was applied along with vigorous stirring to keep the zinc agitated. The addition took about forty-five minutes. A few minutes after the addition was completed a gum precipitated making further stirring impossible. After adding 25 additional grams of zinc prepared as described above, heat was applied and the mixture refluxed for six hours.

The mixture was cooled and the clear liquid decanted into a mixture of 200 cc. of ether and 100 g. of ice. The flask was rinsed with ether (the gummy precipitate contains very little of the product and need not be removed from the flask). An excess of acetic acid was added at 0° The ether layer was washed with water and cold sodium bicarbonate solution, dried over sodium sulfate, and the product distilled at 20 mm. after removal of solvent.

Ethyl β-Ethoxyacrylate.—The product obtained from ethyl bromoacetate using the standard procedure boiled sharply at 88–89° (12 mm.). However a saponification equivalent of samples from different runs gave values ranging from 150–170 (calcd. for ethyl β-ethoxyacrylate, 144; for the diethyl acetal of ethyl formylacetate, 190). The yield from 16.7 g. (0.2 mole) of ethyl bromoacetate was 13 g. (this is a 39% yield assuming that it is an equal mixture of the acrylate and acetal). The product was gently refluxed for one hour at 190–200° during which ethanol slowly distilled. The ethyl β-ethoxyacrylate was then distilled as a colorless oil (b. p. 189–193°) weighing 8.5 g. (over-all yield from ethyl bromoacetate is 30%). The saponification equivalent was 142 (calcd. 144).

Ethyl α-Cyano-β-ethoxyacrylate.—Ethyl bromocyanoacetate (5.9 cc., 0.05 mole) and 8.25 cc. of ethyl orthoformate were dissolved in 70 cc. of dry benzene. Zinc (25 g.) prepared in the usual way was added to the mixture. A very vigorous reaction started which required external cooling. After the initial reaction had subsided, the mixture was refluxed for two hours. The reaction mixture was cooled and extracted with cold dilute acetic acid followed by cold sodium bicarbonate solution. The benzene solution was treated with Norite and dried over magnesium sulfate. Filtration and removal of solvent left 2.0 g. (37%) of discolored crystals of ethyl α-cyano-β-ethoxyacrylate. Recrystallization from absolute ethanol gave white, massive crystals (m. p. 49–50°) which gave no m. p. depression with an authentic sample prepared by the method of Claisen.[5]

2,4-Dinitrophenylhydrazone of Hexahydrobenzaldehyde.—The hexahydrobenzaldehyde was prepared from cyclohexylmagnesium bromide and ethyl orthoformate and also from the diethyl acetal of ethyl α-formylhexahydrobenzoate by saponification and decarboxylation on acidification. The 2,4-dinitrophenylhydrazone crystallized from methanol in yellow needles, m. p. 168–169°.

Anal. Calcd. for $C_{13}H_{16}O_4N_4$: C, 53.60; H, 5.20. Found: C, 53.47; H, 5.43.

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(4) The reagents must be free of all hydroxylic solvents. Commercial samples of ethyl orthoformate were frequently found to contain large amounts of ethanol. This must be removed by fractional distillation.

(5) de Bollemont, *Bull. soc. chim.*, [3] **25**, 20 (1901).