the multiplicity of structure types encountered here.

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[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

Synthesis of Unsymmetrical α-Ketols by the Mixed Acyloin Reaction

BY JOHN W. LYNN[1] AND JAMES ENGLISH, JR.

The conditions for optimum yield in a mixed acyloin reaction have been determined for ethyl benzoate and ethyl propionate. The reaction has been extended to several analogous esters and consideration given to the problem of chain-extension by use of this reaction.

A survey of the literature concerning the acyloin reaction[2] revealed only limited application to the synthesis of unsymmetrical α-ketols. Other reported methods for the preparation of compounds of this class frequently suffer from the disadvantage of requiring relatively inaccessible starting materials.[3–8] The mixed acyloin reaction has previously been employed only by Baudart[9] in his synthesis of several unsaturated long-chain fatty acids and by Kapron[10] who used the analogous bimolecular reduction of an ester–ketone mixture.

In the present work a model pair of esters, ethyl benzoate and ethyl propionate was employed, and a study made of the effect of varying the solvent, reaction time, and concentration of each reactant. The mixed coupling products isolated from the reaction were phenylpropionylcarbinol, 1-phenylbutanedione-1,2 and 1-phenylbutanediol-1,2. Benzoin and propionoin were also obtained, the yields being quite small in comparison with the yield of mixed coupling product. The remainder of the material could be accounted for as an acidic fraction and polymeric residue from the distillation. A summary of the results of this study is given in Table I. The yields given represent fractions isolated by distillation from the hydrolyzed reaction mixture. The fractions consisted mainly of the component indicated, as was shown by preparation of solid derivatives. The difficulty of making a clean separation of acyloin products has been noted previously.[11] Since the products are readily interconvertible the success of synthetic application of the reaction would depend upon the total yield of mixed coupling product.

Phenylpropionylcarbinol was synthesized independently by the reaction of ethylmagnesium bromide with mandelamide.[2] Oxidation and reduction of this compound gave, respectively, 1-phenylbutanedione-1,2 and 1-phenylbutanediol-1,2, shown to be identical with the products from the acyloin reaction by a comparison of their physical constants and by mixed melting points of solid derivatives.

TABLE I

VARIATION OF REACTION CONDITIONS[a]

Variable	α-Ketol, %	α-Diketone, %	α-Glycol, %
Benzene solvent	16	1	1
Ether solvent	10	5	
Xylene solvent	7.5	6	
Reaction time, 2 hours	7.5	8.5	
Reaction time, 4 hours	16	1	1
Reaction time, 8 hours	9.5	3.5	3.0
Calculated reactant ratio	16	1	1
100% excess sodium	3	3.0	5.0
100% excess ethyl benzoate	12		8.0
100% excess ethyl propionate	23.0		10
200% excess ethyl propionate	22.0		

[a] Reaction times were 3–4 hours except where indicated.

Since benzene proved to be the best of the usable solvents it was used exclusively in later experiments. The duration of reaction period appears to affect only the ratio of α-ketol, α-diketone and α-glycol obtained. It is logical to expect a short reaction time to favor the formation of a greater percentage of α-diketone since it has been shown that diketones are the primary reaction products which are subsequently reduced to the α-ketols[11,12] and α-glycols.

Assuming that the mechanism proposed by Blicke[13] and Kharasch[12] is correct, the calculated proportion of reactants required to form the α-ketol is two moles of sodium per mole of ester mixture. It is apparent that an excess of sodium adversely affects the percentage of mixed-coupling product obtained; an excess of ethyl propionate, however, causes a striking increase in yield. This marked increase in yield may be accounted for by the fact that the metal ketyl produced by the reaction of sodium and ethyl propionate would be expected to possess a much greater reactivity than the ketyl from ethyl benzoate, since the latter may exist as a relatively stable resonance hybrid.[14,15]

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(1) Taken from a thesis submitted by John W. Lynn to the faculty of the Graduate School of Yale University in partial fulfillment of the requirements for the Ph.D. degree.

(2) S. M. McElvain, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1942, Vol. IV, p. 242.

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(7) J. S. Buck and W. S. Ide, THIS JOURNAL, **52**, 4107 (1930).

(8) M. Bouis, *Bull. soc. chim.*, **51**, 1177 (1932).

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(10) J. Kapron, *ibid.*, **223**, 421 (1946).

(11) J. M. Snell and S. M. McElvain, THIS JOURNAL, **53**, 750 (1931).

(12) M. S. Kharasch, E. Sternfield and F. R. Mayo, *J. Org. Chem.*, **5**, 362 (1940).

(13) F. F. Blicke, *ibid.*, **47**, 229 (1925).

(14) A. E. Remick, "Electronic Interpretations of Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 532.

(15) M. J. S. Dewar, "Electronic Theory of Organic Chemistry," Clarendon Press, Oxford, 1949, p. 243.

The presence of an excess of the relatively shorter-lived, reactive radical apparently allows a greater opportunity for the more stable aromatic ketyl to couple with it.

The reaction was extended to two other pairs of esters. A mixture of ethyl benzoate and ethyl acetate on reduction with sodium gave phenylacetylcarbinol in only 6% yield. The reduction of a mixture of ethyl benzoate and ethyl butyrate, however, gave phenylbutyrylcarbinol in 18% yield. All the α-ketols were characterized as their 2,4-dinitrophenylosazones.

An obvious application of the mixed acyloin reaction is its use as a method of chain-extension. In order to accomplish this, one of the ester pair must possess a terminal functional group which is unreactive toward sodium. Baudart[9] successfully employed the ethoxyl and vinyl groups in this manner. In the present investigation the ester-acetal, ethyl diethoxyacetate, and the ester-ortho-ester, ethyl triethoxyacetate, were investigated and found to be useless in this respect; the reactions yielded only polymeric material. It was found, however, that aliphatic N,N-dialkylamides were totally unaffected by sodium under the conditions employed.

The ethyl ester-N,N-diethylamides of oxalic and succinic acid were prepared and reacted alone with sodium to determine the nature of the symmetrical coupling products. In both cases the expected α-diketones, N,N'-tetraethyl-α-β-diketosuccinamide and N,N'-tetraethyl-γ,δ-diketosuberamide, were obtained yields of 30 and 16%, respectively.

Though the mixed acyloin reaction between the ester-amides described above and ethyl benzoate yielded the expected mixed-coupling products the yields were extremely small and purification of the products was difficult. In both cases the expected α-diketones, N,N-diethyl-β-phenyl-α,β-diketopropionamide and N,N-diethyl-δ-phenyl-γ,δ-diketovaleramide, were obtained.

Experimental[16]

Mixed Acyloin Reaction.—All operations were carried out under anhydrous conditions, the apparatus being maintained under a slight positive pressure of dry oxygen-free nitrogen.[17] The esters employed were purified by the method of McElvain[18] and all solvents were redistilled and anhydrous. The procedure here described was followed for each run except for modification as shown in Table I. One-half the required amount of sodium was made into a fine sand by rapidly stirring the molten metal under xylene in a three-neck flask fitted with a condenser, nitrogen inlet, Hershberg stirrer and dropping funnel. After the cooled xylene was decanted the sodium was rinsed with benzene, (or other solvent), and then placed under the same solvent. The system was then swept with nitrogen for one-half hour prior to the dropwise addition of the esters to the warm mixture during stirring. A marked color change from yellow to orange to brown generally occurred shortly after the addition was completed. The remainder of the sodium sand suspended in the solvent was then added in small portions from a dropping funnel with a large-bore stopcock. The mixture was stirred at the reflux for the appropriate period (see Table I and individual compounds) then chilled and hydrolyzed by adding dropwise an excess of cold 30% sulfuric acid while stirring under nitrogen. The resulting clear yellow solution was decanted from the precipitated sodium sulfate and extracted with 20% sodium carbonate to remove free acids which are always formed to some extent. After drying over sodium sulfate the excess solvent was distilled from the neutral fraction and the residual oil fractionally distilled to yield the observed products. No attempt was made to determine the amounts of benzoin or lower symmetrical acyloin formed. The yield of symmetrical products was distinctly smaller than that of the mixed ketols. The bulk of the material polymerized and formed a residue in the distilling flask. The various products were identified by their boiling points, refractive indices and solid derivatives.

Phenylpropionylcarbinol, from the reaction of ethyl benzoate and ethyl propionate with sodium, was isolated as described above as a yellow liquid boiling from 124–134° (10 mm.), $n^{20}\mathrm{D}$ 1.5240. An independent synthesis by the reaction of mandelamide with ethylmagnesium bromide, as described by Tiffeneau,[3] gave a product with identical properties.

The 2,4-dinitrophenylosazone of the α-ketol prepared by either method melted from 220–221° (dec.) after crystallization from ethyl acetate, and a mixed melting point showed no depression.

Anal. Calcd. for $C_{22}H_{18}O_8N_8$: N, 21.29. Found: N 21.30.

1-Phenylbutanedione-1,2 was isolated as a yellow oil boiling from 105–120° (10 mm.), $n^{19}\mathrm{D}$ 1.5180, by the fractional distillation of the neutral oil from the sodation of ethyl benzoate and ethyl propionate. A product with identical properties was obtained by the oxidation of phenylpropionylcarbinol with cupric acetate in acetic acid.[19]

The 2,4-dinitrophenylosazone was found to be identical with that obtained from phenylpropionylcarbinol and the dioxime had the same melting point, 205–206°, as reported.[20]

1-Phenylbutanediol-1,2 was obtained by fractional distillation of the neutral fraction as a discolored liquid boiling from 140–150° (10 mm.), $n^{19}\mathrm{D}$ 1.5368; which corresponds closely to the properties reported.[21] This glycol was also prepared by the reduction of phenylpropionylcarbinol with lithium aluminum hydride in 70% yield.

The same dicarbanilate was isolated in the usual manner from both glycols and after crystallization from dilute ethanol was obtained as white crystals melting from 173–174°.

Anal. Calcd. for $C_{24}H_{24}O_2N_4$: C, 71.30; H, 5.98; N, 6.95. Found: C, 71.53; H, 6.19; N, 7.08.

Phenylacetylcarbinol was obtained from the mixed acyloin reaction (four hours at temperature of refluxing benzene) between ethyl benzoate and ethyl acetate (100% excess) in 6% yield. The yellow oil was found to boil at 66° (0.2 mm.), $n^{26}\mathrm{D}$ 1.5205. A reported synthesis[22] of this compound gave the boiling point as 126° (14 mm.).

The 2,4-dinitrophenylosazone was found to melt from 253–254° dec. after crystallization from ethyl acetate.

Anal. Calcd. for $C_{21}H_{16}O_8H_8$: C, 49.60: H, 3.15; N, 22.0. Found: C, 49.31; H, 3.10; N, 22.0.

Phenylbutyrylcarbinol was prepared in 18% yield by a mixed acyloin reaction (two hours at temperature of refluxing benzene) between ethyl benzoate and ethyl butyrate (100% excess). The yellow oil boiled from 60–75° (0.05 mm.), $n^{25}\mathrm{D}$ 1.5040. the reported boiling point being from 150–162° (28 mm.).[3]

The 2,4-dinitrophenylosazone was found to melt at 235° dec. after crystallization from ethyl acetate.

Anal. Calcd. for $C_{23}H_{20}O_8N_8$: N, 20.91. Found: N, 20.87.

Attempted Sodation of Aliphatic N,N-Dialkylamides.—N,N-Diethylpropionamide (b.p. 96° (23 mm.), $n^{20}\mathrm{D}$ 1.4425), was prepared from propionyl chloride and diethylamine[23] and N,N-diethylcyclohexanecarboxamide, a new compound (b.p. 94–95° (0.1 mm.), $n^{20}\mathrm{D}$ 1.4740) was prepared in quantitative yield from cyclohexanecarboxylic acid[24] by reaction of the acid chloride with diethylamine.

Anal. Calcd. for $C_{11}H_{21}ON$: C, 71.5; H, 12.3; N, 7.6. Found: C, 71.7; H, 11.8; N, 7.96.

Each amide was treated with sodium in the manner de-

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(16) All melting and boiling points are corrected.

(17) E. G. R. Ardagh, R. M. B. Roome and H. W. Owens, *Ind. Eng. Chem.*, **25**, 1116 (1933).

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(20) A. Collet, *Bull. soc. chim.*, **17**, 77 (1897).

(21) E. Urion and E. Baum, *C. A.*, **33**, 7286 (1939).

(22) H. Wren, *J. Chem. Soc.*, **95**, 1592 (1909).

(23) J. v. Braun, *Ber.*, **36**, 2287 (1903).

(24) A. Wake and A. Meyer, *Compt. rend.*, **145**, 193 (1907),

scribed but in neither case was any reaction observed, the amides being recovered unchanged.

N,N-Diethylcarbethoxyformamide was obtained as a colorless liquid (b.p. 137–138° (18 mm.), $n^{20}\text{D}$ 1.4432) in 74% yield from the reaction of carbethoxyformoyl chloride (b.p. 134–135° (760 mm.), $n^{20}\text{D}$ 1.4162), prepared by the method of Southwich,[25] and diethylamine in dry ether.

Anal. Calcd. for $C_8H_{15}O_3N$: N, 8.09. Found: N, 8.26.

N,N'-Tetraethyldiketosuccinamide was prepared in 31% yield from a acyloin reaction (16 hours at the temperature of refluxing benzene) of N,N-diethylcarbethoxyformamide. The orange oil boiled at 107° (0.002 mm.), $n^{20}\text{D}$ 1.4780.

The dioxime, prepared in the usual manner, melted from 228–229° dec. after crystallization from dilute ethanol.

Anal. Calcd. for $C_{12}H_{22}O_4N_4$: C, 50.35; H, 7.41; N. 19.54. Found: C, 49.76; H, 7.02; N, 19.59.

N,N-Diethyl-β-phenyl-αβ-diketopropionamide was obtained in 7% yield from the mixed, acyloin reaction (16 hours at the temperature of refluxing benzene) between N,N-diethylcarbethoxyformamide and ethyl benzoate. The viscous yellow oil boiled at 107° (0.1 mm.), $n^{20}\text{D}$ 1.5187.

Anal. Calcd. for $C_{13}H_{15}O_3N$: C, 66.95; H, 6.43; N, 6.00. Found: C, 67.60; H, 7.9; N, 6.60.

N,N-Diethyl-β-carbomethoxypropionamide was obtained as a colorless liquid (b.p. 107–110° (0.8 mm.), $n^{20}\text{D}$ 1.4555) in 85% yield from the reaction of β-carbomethoxypropionyl chloride (b.p. 92–93° (18 mm.) which was prepared by Caxson's method,[26] and diethylamine in dry ether.

Anal. Calcd. for $C_9H_{17}O_3N$: N, 7.49. Found: N, 7.31.

N,N'-Tetraethyl-γ,δ-diketosuberamide was the product obtained from the acyloin reaction (one hour at the temperature of refluxing benzene) of N,N-diethyl-β-carbomethoxypropionamide in 16% yield. The yellow viscous oil was found to boil from 178–195° (0.05 mm.).

The 2,4-dinitrophenylosazone was prepared and after crystallization from ethyl acetate melted from 236–238° dec.

Anal. Calcd. for $C_{28}H_{36}O_{10}N_{10}$: N, 20.18. Found: N, 20.85.

N,N-Diethyl-δ-phenyl-γ,δ-diketovaleramide was obtained from the mixed acyloin reaction (two hours at the temperature of refluxing benzene) of N,N-diethyl-β-carbomethoxypropionamide and ethyl benzoate as a yellow oil boiling from 89–94° (0.1 mm.), $n^{25}\text{D}$ 1.5284.

Anal. Calcd. for $C_{15}H_{19}O_3H$: C, 68.96; H, 7.27; N, 5.36. Found: C, 69.09; H, 7.03; N, 5.27.

The more volatile neutral fraction was separated from a considerable polymeric residue by use of a molecular still. Polymerization also occurred during the fractional distillation of this fraction which resulted in a yield of less than 1% of the desired product.

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[25] P. L. Southwick and L. L. Seivard, THIS JOURNAL, **71**, 2535 (1949).

[26] J. Caxson, "Organic Syntheses," **25**, 19 (1945).

NEW HAVEN, CONN. RECEIVED APRIL 9, 1951

[CONTRIBUTION NO. 797 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Studies in the Cyclopentane Series. II.[1] The Synthesis of Two Isomeric 3-(4-Phenoxybutyl)-cyclopentane-1,2-dicarboxylic Acids

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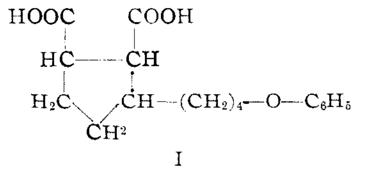
The synthesis of two of the four theoretically possible racemic 3-(4-phenoxybutyl)-cyclopentane-1,2-dicarboxylic acids is described and their structures are partially established. An additional example of a hydrazine-catalyzed *cis–trans* inversion in the cyclopentane series is also presented.

Four geometrical isomers of 3-(4-phenoxybutyl)-cyclopentane-1,2-dicarboxylic acid (I) may be expected. Two of these possess a *cis*, the other two a *trans* configuration of the carboxyl groups. The pairs differ in the orientation of the phenoxybutyl sidechain, which may bear either a *cis* or a *trans* relationship with respect to the carboxyl group in position 2. The present communication describes the preparation of two of these isomers.



I

Diethyl adipate was condensed with diethyl oxalate and the ensuing triester (II) converted into diethyl (3-carbethoxypropyl)-malonate (III) by heating in the presence of powdered glass. The structure of (III) followed from its conversion into adipic acid by hydrolysis and decarboxylation.

The alkylation with 4-phenoxybutyl iodide of (III) proceeded normally and the resulting disubstituted malonic ester (IV) was transformed into dimethyl 2-(4-phenoxybutyl)-adipate (V) by hydrolysis, decarboxylation and reësterification. Treatment with sodium methoxide in ether of the dimethyl ester (V) afforded methyl 5-(4-phenoxybutyl)-cyclopentanone-2-carboxylate (VI), which was purified through its copper chelate complex.

The cyclization of the dimethyl ester (V) may occur in two different ways, and, consequently, could lead to the formation of either methyl 5-(4-phenoxybutyl)-cyclopentanone-2-carboxylate (VI) or methyl 2-(4-phenoxybutyl)-cyclopentanone-2-carboxylate (VII). Although theoretical considerations favor the former possibility, it seemed desirable to establish the structure of the reaction product. This was done by comparing the properties of methyl 2-(4-phenoxybutyl)-cyclopentanone-2-carboxylate (VII), prepared by the alkylation with 4-phenoxybutyl iodide of methyl cyclopentanone-2-carboxylate, with those of the ketoester obtained from the Dieckmann cyclization of (V). The two ketoesters exhibited different properties, but both compounds on hydrolysis were converted into 2-(4-phenoxybutyl)-cyclopentanone (VIII). These

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[1] For Paper I see J. Müller, W. Behnke, M. Donin and K. Hofmann, THIS JOURNAL, **73**, 2487 (1951).

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