[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Aldol-type Condensations with Disubstituted Formamides

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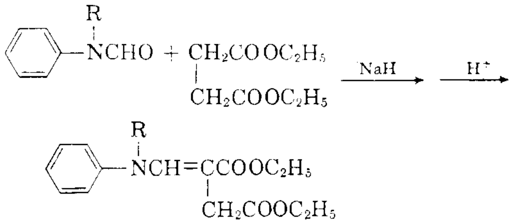
The well-known aldehyde-like character of formic acid and its derivatives has been demonstrated synthetically in the base-catalyzed condensation of certain disubstituted formamides.

The aldehyde character of formic acid and its derivatives is well known and has in the past been the basis for qualitative tests for these substances.[1] This resemblance of formic acid and its derivatives to aldehydes suggested their use in syntheses in which compounds containing quite reactive carbonyl groups usually are employed.

Such a synthesis is the Stobbe condensation, a reaction of the aldol type.[2] The disubstituted formamides were chosen as formic acid derivatives which might successfully be used in a Stobbe-like condensation. It was found that when an alkylformanilide, such as N-ethylformanilide, or a diarylformamide, such as diphenylformamide, was condensed with diethyl succinate using sodium hydride as the condensing agent, then a disubstituted aminomethylenesuccinic ester was produced in a yield of 40 to 45%. The structure of the product in each case was established by analysis and infrared and ultraviolet spectra. The structure of diethyl N-ethylanilinomethylenesuccinate was proved conclusively by its independent synthesis from diethyl formylsuccinate and N-ethylaniline. This condensation is dissimilar to the Stobbe condensation, for the product is a diester and all known Stobbe condensation products are half-acid esters.



Chelintsev and Osetrova have reported the condensation of N,N-diphenylacetamide with acetophenone in the presence of sodium to give acetoacetophenone.[3] The conditions of their condensation approximate those of the present study. An attempt therefore was made to isolate from the reaction product of the N-methylformanilide reaction, diethyl formylsuccinate, which would result from a similar condensation. Its presence in only very minute amount was indicated by the preparation of a *p*-nitrophenylhydrazone. Evidently, this Claisen type of condensation proceeds to only a very minor extent.

The apparent generality of the condensation of alkylformanilides with compounds containing active methylene groups can be inferred from the formation of N-methylanilinovinyl phenyl ketone from the reaction of acetophenone with N-methylformanilide.

When a dialkylformamide was allowed to react with diethyl succinate or acetophenone and sodium hydride, none of the aldol-like condensation was observed. From the products from dimethylformamide and diethyl succinate there was isolated no more than a 3.3% yield of diethyl formylsuccinate. As noted above, this compound is probably formed by a condensation of the Claisen type, although the possibility exists that it is an artifact of the isolation procedure produced by hydrolysis of a small amount of diethyl dimethylaminomethylene succinate actually formed in the reaction. An attempt to condense N-formylpiperidine with acetophenone under the usual conditions failed and increasing the rigor of the reaction conditions led only to the cleavage of the acetophenone to benzoic acid by the sodium hydride and to the formation of a non-nitrogenous product of high boiling point and unknown structure.

The mechanism of the condensation of substituted formamides with compounds containing active methylene groups must be similar to the usual aldol condensation and so does not need to be detailed here. It suffices merely to emphasize the importance of aryl substitution: formamides with aryl substituents lead to products by both the aldol and Claisen-like condensations, the former in great predominance, while formamides without aryl substitution give products by the latter condensation only.

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Experimental[4]

Preparation of the Disubstituted Formamides.—All the formamides were prepared by dissolving 0.35 mole of the secondary amine in 80 ml. of 98–100% formic acid, heating for several hours on the steam-bath and then removing the excess formic acid in vacuum and distilling the residue. In this fashion were prepared N-ethylformanilide, b.p. 98° (2.4 mm.), n^{25}D 1.5407, 88% yield; N-methylformanilide, b.p. 94.5–95.5° (1.5 mm.), n^{25}D 1.5575, 90% yield; N-formylpiperidine, b.p. 51–54° (0.6 mm.), $n^{23.5}$D 1.4715, 65% yield. Diphenylformamide and dimethylformamide were obtained commercially.

Preparation of Diethyl N-Ethylanilinomethylenesuccinate. a. Aldol-type Condensation.—In a 300-ml. flask 7.2 g. (0.3 mole) of sodium hydride was mixed with 78.4 g. (0.45 mole) of diethyl succinate and 22.4 g. (0.15 mole) of N-ethylformanilide. Ten drops of dry ethanol was added and the reaction was stirred for 3 hours and then allowed to stand for 3 days. The pasty reaction mixture was cooled in ice and

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[1] E. H. Rodd, "Chemistry of Carbon Compounds," Vol. 1A, Elsevier Press, New York, N. Y., 1956, p. 543.

[2] W. S. Johnson and G. H. Daub, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., p. 1.

[3] G. V. Chelintsev and E. D. Osetrova, *Compt. rend. acad. sci. U.R.S.S.*, **4**, 419 (1936); *C. A.*, **31**, 3467 (1937).

[4] The boiling points and melting points recorded are uncorrected.

decomposed by the dropwise addition of 30 ml. of glacial acetic acid followed by 100 ml. of water. A white solid was removed from the ether and water layers by filtration. These layers were then separated.

The acid–water layer was shown to contain no organic material by evaporation of the ether extract of the layer after basifying with ammonia.

The ether layer was evaporated to near dryness, chilled and filtered. The solid so obtained was combined with the solid originally isolated from the acidified reaction mixture. The combined solids when recrystallized from ethanol weighed 15.4 g. (0.6 mole) and melted at 128–129.5°. This is the self-condensation product of diethyl succinate and consumed 27% of the starting diethyl succinate in its formation.

The filtrate from the preceding separation was distilled through a Claisen-head and gave a 24.3% recovery of diethyl succinate (b.p. 56–59° (0.6 mm.), n^{25}_{D} 1.4331) and then after an intermediate fraction (probably the formamide) with constantly rising boiling point, a viscous, yellow liquid was obtained, b.p. 175–176° (0.8 mm.), n^{27}_{D} 1.5372, n^{25}_{D} 1.5393, 21.5 g. (0.703 mole), 47%. This material could not be induced to crystallize and was insoluble in concentrated ammonium hydroxide. Its analysis checked for diethyl N-ethylanilinomethylenesuccinate. The infrared spectrum had the following maxima: 5.75 (unconjugated carbonyl) and 5.95 μ (conjugated carbonyl) with no oxygen or nitrogen-bound hydrogen absorption. The ultraviolet spectrum showed a maximum at 294 mμ (ε 16,950) consistent with the structure as deduced from the analytical data.

Anal. Calcd. for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.85; H, 7.89; N, 4.53.

All but 2–3% of the initial diethyl succinate was accounted for in this experiment.

b. Amine Condensation.[5]—A mixture of 20.1 g. (0.095 mole) of diethyl formylsuccinate[6] and 12.2 g. (0.10 mole) of N-ethylaniline was heated at 100° for 1.5 hours on the steambath and then allowed to stand overnight at room temperature. The reaction mixture was diluted with ether and washed with dilute sodium bicarbonate solution. The ether solution was dried, evaporated and the product distilled, b.p. 165–167° (1.5 mm.), n^{27}_{D} 1.5378, yield 15.0 g. (0.049 mole), 52%, calculated for diethyl N-ethylanilinomethylenesuccinate. The infrared and ultraviolet spectra were identical to those of the material prepared under (a).

Anal. Calcd. for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.62; H, 7.51; N, 4.53.

Preparation of Diethyl N-Methylanilinomethylenesuccinate.—This material was prepared identically to the N-ethyl analog and the product (b.p. 170–173° [0.7 mm.], n^{25}_{D} 1.5408) was obtained in 38% yield.

Anal. Calcd. for $C_{16}H_{21}NO_4$: C, 65.95; H, 7.27; N, 4.81. Found: C, 66.00; H, 7.10; N, 4.84.

In a similar experiment on double quantities a Vigreux column was used in the distillation, but the material distilling between the fractions containing diethyl succinate (37.8 g.) and the product (41.5 g., 47.5%) could not be separated into any distinct fraction: it boiled from 70–170° (1 mm.) and weighed 28.7 g. The fraction boiling below 140° (8.6 g.) was diluted with ether and extracted with sodium bicarbonate solution. The basic extract was acidified and in turn extracted with ether. This ether solution was evaporated to give about 0.5 g. of liquid. This material yielded a *p*-nitrophenylhydrazone in a small amount that melted crude at about 89–91°. The literature[7] reports 100° for the pure *p*-nitrophenylhydrazone of diethyl formylsuccinate. The melting point is low but would indicate that some diethyl formylsuccinate is present. The infrared spectrum indicated it was present but impure.

The higher fraction 140–170° from the distillation above could not be separated into any single pure compound, although a fraction boiling 150–153° (0.9 mm.) had an analysis very similar to diethyl N-methylanilinomethylenesuccinate except for lower carbon.

Anal. Found: C, 64.52, 64.58; H, 7.32, 7.37; N, 4.81.

Preparation of Diethyl N,N-Diphenylaminomethylenesuccinate.—In the same fashion as in the experiment with N-ethylformanilide, diethyl succinate was condensed with 29.6 g. (0.15 mole) of diphenylformamide. The reaction was stirred 10 days before the semi-solid reaction mixture was acidified with dilute acetic acid. The filtrate from the removal of the diethyl succinoylsuccinate was extracted with ether and the residue from the dried, evaporated ether solution was distilled. The product boiled at 206–208° (1.1 mm.), n^{25}_{D} 1.5870, and was formed in a 41% yield. The infrared spectrum was identical in the carbonyl region to that of the N-methyl and N-ethyl analogs.

Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.61; H, 6.56; N, 4.13.

Preparation of β-(N-Methylanilino)-vinyl Phenyl Ketone.—A mixture of 19.4 g. (0.144 mole) of N-methylformanilide and 3.45 g. (0.144 mole) of sodium hydride was stirred and 0.35 ml. of ethanol was added, followed after a short interval by 17.3 g. (0.144 mole) of acetophenone in 35 ml. of ether. The reaction was heated to reflux for 4 hours, then cooled, diluted with 200 ml. of ether and inverted into an iced solution of 14.4 ml. of glacial acetic acid in 100 ml. of water. The ether extract of this acidification was dried and evaporated. The product was distilled to give, after a forerun of starting materials, a fraction boiling from 170–243° (0.8 mm.) which crystallized. The crystalline product was purified by recrystallization from petroleum-ether (60–64°), m.p. 90–92°, yield 7.5 g. (22%).

Anal. Calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80,85; H, 6.28; N, 5.69.

Reactions of N-Formylpiperidine. a. With Diethyl Succinate.—N-Formylpiperidine was allowed to react in like amounts and under the same conditions as in the condensation of N-ethylformanilide with an identical isolation procedure; 87% of the starting diethyl succinate was accounted for, 50% as the self-condensation product and 37.4% as recovered ester. Distillation of the liquid product gave in addition to diethyl succinate a small amount (6.3 g.) of material boiling from 75–175° (1.0 mm.) from which crystallized on standing some diethyl succinoylsuccinate. It was probably the main high-boiling component. The residual oil was not investigated further.

b. With Acetophenone.—In a duplicate experiment to the condensation of acetophenone with N-methylformanilide, N-formylpiperidine gave only starting materials on isolation. In a similar experiment except that the reaction was refluxed for 56 hours during which time the ether evaporated, the temperature was allowed to rise to well over 100°. The usual decomposition procedure gave a liquid which was distilled. Acetophenone was recovered along with a fraction boiling at 105° (1.5 mm.), m.p. 121–122° (which proved on analysis, mixture m.p. and infrared to be benzoic acid), and a fraction boiling 135–240° (1.5 mm.). Redistillation of the latter gave a very small amount of material, b.p. 220–240° (1.2 mm.), which contained no nitrogen. (*Anal.* Found: C, 91.56; H, 6.64). The anticipated product had not been formed.

Reaction of Dimethylformamide and Diethyl Succinate.—Dimethylformamide was allowed to react with diethyl succinate in the same molecular proportions as was N-ethylformanilide except that the reaction was allowed to stir 3 days at room temperature. Then a solution of 30 ml. of acetic acid in 100 ml. of water was added in one portion. The insoluble solid (diethyl succinoylsuccinate) was filtered and dried (27.7 g.). The filtrate was extracted with ether and the ether solution in turn extracted with dilute sodium bicarbonate solution. The base-insoluble portion was isolated from the dried ether solution and distilled (b.p. 71–72° (1.6 mm.), n^{25}_{D} 1.4175, 14.5 g.). It was all diethyl succinate. The basic aqueous solution was acidified with dilute hydrochloric acid, extracted with ether and the ether extract dried and evaporated. The oily residue was distilled and about 1.0 g. of material was obtained, b.p. 108–118° (1.7 mm.), n^{25}_{D} 1.4442. This material analyzed correctly for and had the physical constants of diethyl formylsuccinate. The infrared spectrum is likewise identical to that of authentic material. Neighboring fractions which were in all probability mainly this material weighed 1.2 g. Even on this basis the yield of diethyl formylsuccinate would be only 3.3%.

Anal. Calcd. for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.33; H, 7.07.

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(6) T. B. Johnson and C. F. Speh, *Am. Chem. J.*, **38**, 607 (1907).

(7) E. Carriere, *Ann. chim.*, [9] **17**, 46 (1922).