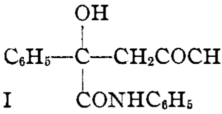
[CONTRIBUTION FROM THE NICHOLS LABORATORY OF NEW YORK UNIVERSITY]

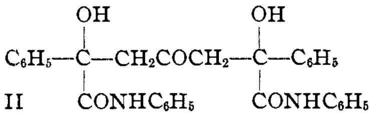
Condensations of Benzoylformanilide with Acetone, Ethyl Phenylacetate and Diethyl Malonate

BY JOHN V. SCUDI AND H. G. LINDWALL

Acetone condenses with benzoylformanilide in the presence of diethylamine to yield 2-phenyl-2-hydroxy-4-pentanoneanilide (I), which is analogous to the product obtained with acetophenone.[1] The aldol nature of I is shown by its dissociation into the original reactants when heated with aqueous alkali; it forms a phenylhydrazone and, further, it condenses with benzoylformanilide to yield II.



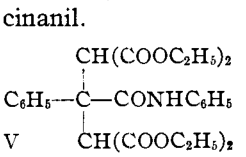
I $C_6H_5-\underset{CONHC_6H_5}{\overset{OH}{C}}-CH_2COCH_3$



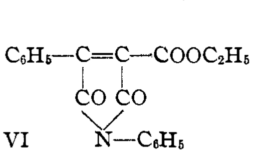
II $C_6H_5-\underset{CONHC_6H_5}{\overset{OH}{C}}-CH_2COCH_2-\underset{CONHC_6H_5}{\overset{OH}{C}}-C_6H_5$

The condensation of benzoylformanilide with ethyl phenylacetate, catalyzed by diethylamine, produces α,β-diphenylmaleinanil (III); this method, while giving a good yield, is too slow to appear practical. Reduction of III gives IV, which was found to be identical with the anil of α,β-diphenylsuccinic acid, prepared by the method of Lapworth and McRae.[2]

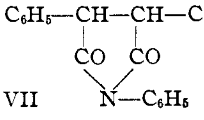
Diethyl malonate and benzoylformanilide condense in the ratio of two moles to one, yielding V. Compound V upon being heated *in vacuo* is decomposed into α-carbethoxy-β-phenylmaleinanil (VI) which remains as a residue after diethyl malonate and a low-boiling liquid (probably ethyl alcohol) have distilled over. The corresponding α-carbethoxy-β-phenylsuccinanil (VII) results from the reduction of VI. Hydrolysis of this ester (VII) by hydrochloric acid effects also decarboxylation to yield the known phenylsuccinanil.



V $C_6H_5-\underset{CH(COOC_2H_5)_2}{\overset{CH(COOC_2H_5)_2}{C}}-CONHC_6H_5$



VI



VII

The condensation reactions of benzoylformanilide find a parallel in the case of isatin which also condenses with acetone[3] and diethyl malonate.[4]

Experimental Part

2-Phenyl-2-hydroxy-4-pentanoneanilide (I).—A mixture of 5 g. of benzoylformanilide in 10 cc. of acetone and 5 drops of diethylamine was allowed to stand at room temperature for six hours. The white product was crystallized from toluene as hairy needles, m. p. 137–138°; slightly soluble in ether, more in benzene; yield, 80%.

Anal. Calcd. for $C_{17}H_{17}O_3N$: C, 72.08; H, 6.01. Found: C, 72.17; H, 5.90.

Phenylhydrazone of I.—A mixture of 12.5 g. of phenylhydrazine, 12.5 cc. of glacial acetic acid, 25 cc. of water and 5 g. of I, was allowed to stand for one hour at room temperature. The solid product was recrystallized from an alcohol–ethyl acetate solution (4:1 by volume); white needles, m. p. 174–175°, with decomp.; soluble in alcohol and toluene; yield, 60%.

Anal. Calcd. for $C_{23}H_{23}O_2N_3$: N, 11.26. Found: N, 11.43, 11.45.

2,6-Dihydroxy-2,6-diphenyl-4-heptanonedianilide-1,7 (II).—Compound I (2 g.) and 2.5 g. of benzoylformanilide, dissolved in a minimum amount of alcohol with 5 drops of diethylamine, were allowed to stand at room temperature for two weeks. The yield of product was 25%, but is improved by longer time; white needles after crystallization from alcohol, m. p. 171–172°.

Anal. Calcd. for $C_{31}H_{28}O_5N_2$: C, 73.23; H, 5.51. Found: C, 73.29; H, 5.57.

α-β-Diphenylmaleinanil (III).—A mixture of 1 g. of benzoylformanilide, 1 g. of ethyl phenylacetate and 3 drops of diethylamine produced a 90% yield of III after three months of standing at room temperature; yellow needles after recrystallization from alcohol, m. p. 178–179°.

Anal. Calcd. for $C_{22}H_{15}O_2N$: C, 81.23; H, 4.61. Found: C, 81.23; H, 4.73.

α-β-Diphenylsuccinanil (IV).—To a hot solution of 1 g. of III in 50 cc. of alcohol was added 1 g. of sodium hyposulfite in 30 cc. of boiling water. The yellow color disappeared at once; addition of cold water caused a white precipitation; white needles from ethyl alcohol or from glacial acetic acid; m. p. 234–235°; yield, 80%.

Anal. Calcd. for $C_{22}H_{17}O_2N$: C, 80.73; H, 5.20; N, 4.28. Found: C, 80.96; H, 5.46; N, 4.29, 4.45.

2-Phenyl-2-formanilido-1,1,3,3-tetracarbethoxypropane (V).—Five grams of benzoylformanilide, 5 g. of diethyl malonate and 5 drops of diethylamine in 10 cc. of ethyl alcohol produced a solid mass of V in three hours at

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(1) Bashour and Lindwall, THIS JOURNAL, **57**, 178 (1935).

(2) Lapworth and McRae, *J. Chem. Soc.*, **121**, 1699 (1922).

(3) Braude and Lindwall, THIS JOURNAL, **55**, 325 (1933).

(4) Lindwall and Hill, *ibid.*, **57**, 735 (1935).

room temperature; crude yield, 95%. After washing with ether, the product was crystallized from 60% acetone; colorless crystals, m. p. 107–108°, soluble in alcohol.

Anal. Calcd. for $C_{25}H_{33}O_9N$: C, 63.74; H, 6.31. Found: C, 64.08; H, 6.50.

α-Carbethoxy-β-phenylmaleinanil (VI).—A sample of V (3 g.) was subjected to vacuum distillation; a water-white distillate was obtained, distilling at 101–102° at 25 mm. Fractional distillation of this liquid showed it to consist largely of diethyl malonate, verified by conversion to malonamide. A low-boiling fraction was evidently ethyl alcohol. The residue from the vacuum distillation was dissolved in 20 cc. of diethyl ether, and diluted with 100 cc. of petroleum ether. Hard yellow crystals separated after two hours of cooling; it recrystallized from 80% alcohol as yellow rhombic crystals, m. p. 111°, soluble in alcohol, ether, benzene; yield, 75%.

Anal. Calcd. for $C_{19}H_{15}O_4N$: C, 71.03; H, 4.67; N, 4.36. Found: C, 71.09; H, 4.79; N, 4.31, 4.56.

α-Carbethoxy-β-phenylsuccinanil (VII).—One gram of VI was dissolved in 15 cc. of boiling alcohol and to this was added 1 g. of sodium hyposulfite in 5 cc. of hot water. The mixture was heated for five minutes until it became colorless. Upon addition of 75 cc. of water and cooling, a white oil separated, which gradually solidified to white needles from 10% alcohol, m. p. 104–105°, soluble in alcohol, ether, acetone, ethyl acetate, chloroform, benzene; yield, 85%.

Anal. Calcd. for $C_{19}H_{17}O_4N$: C, 70.59; H, 5.26; N, 4.33. Found: C, 70.60; H, 5.28; N, 4.26.

Phenylsuccinanil from VII.—A solution of 1 g. of VII in 15 cc. of alcohol and 15 cc. of concd. hydrochloric acid was refluxed for one hour and then evaporated to dryness on a steam-bath. The residue was extracted with three 10-cc. portions of boiling water. Concentration of the extract to one-third its volume and cooling gave white needles, m. p. 137–138°; yield, 40%. There was no lowering of melting point when mixed with a known sample.

Summary

Benzoylformanilide condenses in the presence of diethylamine with one mole of acetone and two moles of diethyl malonate to give products analogous to those of isatin. The diethyl malonate product is decomposed by heat, losing a molecule of diethyl malonate and forming a maleinanil derivative through ring closure.

Ethyl phenylacetate reacts slowly with benzoylformanilide under similar conditions to yield symmetrical diphenylmaleinanil.

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The Preparation of High Molecular Weight Acyloins

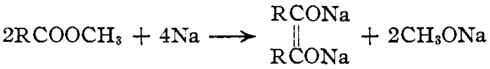
BY V. L. HANSLEY

The simultaneous reaction and condensation of aliphatic esters by means of sodium to give α,β-keto alcohols, the so-called acyloins, has been limited in previous investigations to esters of acids of six or less carbon atoms. Previous work along this line has been summarized by Corson and his co-workers.[1]

By the use of different solvents and by making radical changes in reaction conditions, we have been able to extend this series of acyloins from 12 to 36 carbon atoms and to shorten the reaction time considerably.

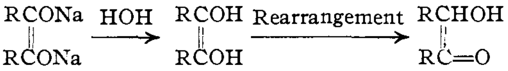
The reaction between sodium and the esters takes place essentially quantitatively according to the following equation, and neither reactant need be employed in excess.

(a)



$$2RCOOCH_3 + 4Na \longrightarrow \begin{array}{c}RCONa\\ \|\\ RCONa\end{array} + 2CH_3ONa$$

(b)



$$\begin{array}{c}RCONa\\ \|\\ RCONa\end{array} \xrightarrow{HOH} \begin{array}{c}RCOH\\ \|\\ RCOH\end{array} \xrightarrow{\text{Rearrangement}} \begin{array}{c}RCHOH\\ |\\ RC{=}O\end{array}$$

While previously recommended methods for the preparation of butyroin and other low molecular weight acyloins[2] do not suggest any difficulty in the preparation of the higher molecular weight acyloins, the work of Corson and his co-workers[1] indicates that the described methods of preparation fail when applied to these higher esters.

The failure of these investigators to obtain acyloins from acids of greater than six carbon atoms was apparently due to the insolubility of the reaction products at the temperatures employed in the particular reaction media used. Previous investigators carried out their reactions in ether or benzene at room temperature or lower, allowing even days for the reaction to take place. A few previous attempts were also made to carry

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(1) Corson, Benson and Goodwin, THIS JOURNAL, **52**, 3988 (1930); *cf* Snell and McElvain, *ibid.*, **53**, 750 (1931).

(2) Snell and McElvain, "Organic Syntheses," J. Wiley & Sons, Inc., 440 Fourth Ave., New York City, 1933, Vol. XIII, pp. 24–26.