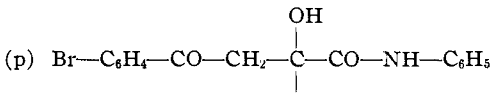
[CONTRIBUTION FROM THE NICHOLS LABORATORY OF NEW YORK UNIVERSITY]

A Synthesis of Certain Pyrrolones from Acetophenone and Benzoylformanilide[1]

BY J. T. BASHOUR AND H. G. LINDWALL

In the course of studies of the condensation reactions of certain cyclic alpha-keto amides[2] it became of interest to investigate the properties of an open-chain alpha-keto amide and benzoylformanilide was chosen. Benzoylformanilide will undergo a condensation reaction with acetophenone and *p*-bromoacetophenone to yield in each instance an aldol-type product (2-phenyl-2-hydroxy-3-(*p*-bromobenzoyl)-propaneanilide) (I). Condensation was effected through use of the Knoevenagel[3] catalysts or dilute sodium hydroxide solution, at room temperature.



$$\text{(p) Br—C}_6\text{H}_4\text{—CO—CH}_2\text{—}\overset{\text{OH}}{\underset{\text{C}_6\text{H}_5}{\text{C}}}\text{—CO—NH—C}_6\text{H}_5$$

I

The aldol nature of the condensation product (I) was indicated by its properties, for it tends to be decomposed under the influence of heat into the original reactants, and when the compound is heated for several minutes in 2.5% aqueous alcoholic sodium hydroxide solution it is decomposed nearly completely into the components. The compound further forms a mono-phenylhydrazone although, strangely enough, attempts to prepare a semicarbazone have been unsuccessful. Application of the Grignard reagent (CH_3-Mg-Br) for the determination of active hydrogens yielded an average of 2.3 moles of gas per mole of compound I. Assuming the fraction of a mole of gas to be the result partly of enol compound and partly experimental error, evidence is presented for the alcoholic and amidic hydrogens of Structure I. Attempts to prepare an acetate were without success, as might be expected.

Since I is a tertiary alcohol, it should be easy to dehydrate it to obtain the corresponding unsaturated structure. In the course of the acetylation attempts no definite new compound was obtained, but when I was treated with alcoholic hydrogen chloride there was obtained a product (II) which from the composition ($C_{24}H_{20}O_2NBr$) appeared to have been formed by dehydration followed by the introduction of an ethyl group. Using methyl alcohol as the solvent, a different but similar compound (III) was formed. The composition $C_{23}H_{18}O_2NBr$ indicated that this was a lower homolog. It was then found possible to conduct the reaction in two stages. Compound I, heated in dry benzene–ether solution with hydrogen chloride, yielded a product (IV) having the composition $C_{22}H_{16}O_2NBr$, and this could be converted into either the ethyl derivative II or the methyl derivative III by the action of the appropriate alcohol and hydrogen chloride. Compounds II and III were further interconvertible by alcoholysis.

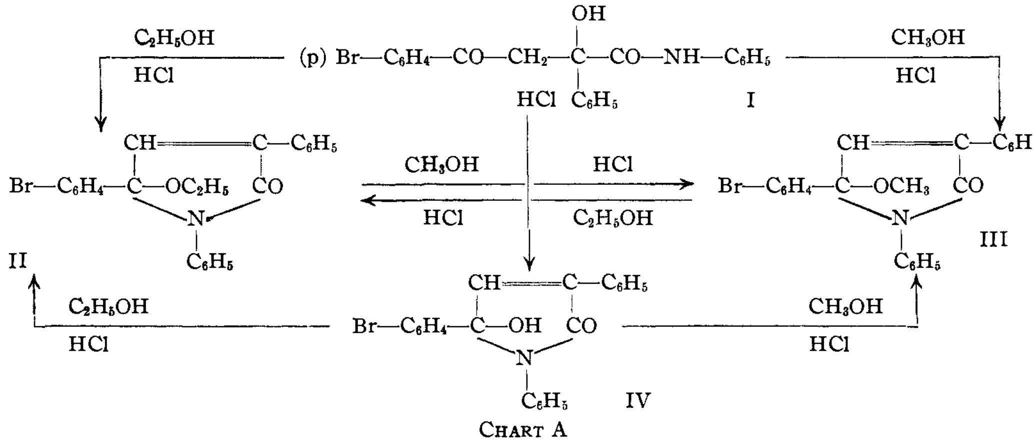


CHART A

Compound IV was found to have one active hydrogen on being tested with the Grignard reagent, while no such hydrogens were present in

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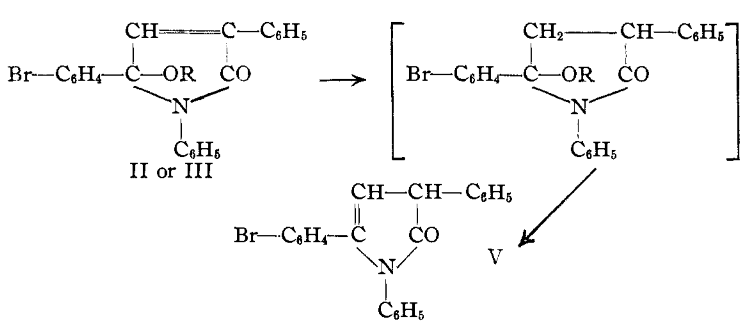
[1] From a dissertation presented by J. T. Bashour in partial satisfaction of the requirements for the Ph.D. degree at New York University.

[2] Lindwall and Maclennan, THIS JOURNAL, **54**, 4739 (1932).

[3] Knoevenagel, *Ann.*, **281**, 25 (1894); **288**, 321 (1895); *Ber.*, **31**, 2585, 2595 (1898); **37**, 4464 (1904).

substances II and III. None of the three compounds exhibits ketonic characteristics. On the basis of these properties and other considerations, formulas were assigned as shown in Chart A.

The reduction of either II or III with zinc dust and glacial acetic acid yielded a compound, V, the composition of which indicated that the reaction involved the introduction of two atoms of hydrogen and the loss of a molecule of ethyl or methyl alcohol. No phenylhydrazone could be formed. The compound reduces potassium permanganate in acetone solution, but does not decolorize a solution of bromine in carbon tetrachloride. It appeared likely that the substance was formed as follows



This indicates that the reduction product, V, has the structure of 1,3-diphenyl-5-(*p*-bromophenyl)-pyrrolone-2. Since the bromine-free compound has been prepared by Almström[4] by another method of synthesis, the above series of reactions was repeated using the condensation product from acetophenone and benzoylformanilide. The final product, of which V is the bromo derivative, proved to be identical with a sample of 1,3,5-triphenylpyrrolone-2 prepared by the method of Almström.

Experimental Part

2-Phenyl-2-hydroxy-3-benzoylpropaneanilide (VI) and 2-Phenyl-2-hydroxy-3-(*p*-bromobenzoyl)-propaneanilide (I).—A mixture consisting of 10 g. of benzoylformanilide, an equimolecular quantity of acetophenone or *p*-bromoacetophenone, 10 cc. of absolute ethyl alcohol, and 1.5 cc. of diethylamine was allowed to stand at room temperature for two days. The crude product which separated was recrystallized from a mixture of carbon tetrachloride and ligroin (5 to 3 by volume). Products I and VI are alike in appearance, white needles, and are soluble in benzene, ethyl alcohol and ethyl acetate. Both are decomposed into the original reactants upon being heated in solution, consequently there is difficulty in obtaining a pure product; yield, 85%.

Compound VI.—M. p. 143–145°. *Anal.* Calcd. for $C_{22}H_{19}O_3N$: C, 76.52; H, 5.51; N, 4.06; active hydrogen atoms, 2. Found: C, 76.69; H, 5.64; N, 4.13; active hydrogen atoms,[5] 2.3, 2.4, 2.3.

Compound I.—M. p. 133–135°. *Anal.* Calcd. for $C_{22}H_{18}O_3NBr$: C, 62.28; H, 4.48; Br, 18.87; active hydrogen atoms, 2. Found: C, 62.55; H, 4.06; Br, 18.74, 18.98; active hydrogen atoms, 2.3, 2.3, 2.4.

Phenylhydrazone of I.—One gram of I was dissolved in 7 cc. of ethyl alcohol and to this was added 7 cc. of a solution of phenylhydrazine in aqueous acetic acid (3.6 cc. of phenylhydrazine and 2 cc. of glacial acetic acid in 10 cc. of water) and the mixture warmed on the steam-bath for one and one-half hours. The solid which separated upon cooling was recrystallized from ethyl alcohol as long white needles of m. p. 179–180°.

Anal. Calcd. for $C_{28}H_{24}N_3O_2Br$: N, 8.17. Found: N, 8.06.

1,3-Diphenyl-5-hydroxy-5-(*p*-bromophenyl)-pyrrolone-2 (IV).—Three grams of I, 17 cc. of dried benzene, and 50 cc. of absolute ether were mixed and dry hydrogen chloride was passed through the mixture for one hour at room temperature. After standing overnight at room temperature, the solution was warmed on a steam-bath until all the ether had been driven off. Upon cooling, a solid separated which was recrystallized three times from ethyl alcohol, yield 1.5 g. of fine white needles, m. p. 195–196°. Upon melting, IV forms a clear colorless liquid which darkens rapidly to a charred mass. The compound does not add bromine in carbon tetrachloride solution, but reduces potassium permanganate slowly in acetone.

Anal. Calcd. for $C_{22}H_{16}O_2NBr$: C, 65.04; H, 3.94; N, 3.45; active hydrogen atoms, 1.0. Found: C, 65.18; H, 4.19; N, 3.37; active hydrogen atoms, 1.1, 1.0, 1.0.

1,3,5-Triphenyl-5-ethoxypyrrolone-2 (VII), 1,3-Diphenyl 5-(*p*-bromophenyl)-5-ethoxypyrrolone-2 (II) and 1,3-Diphenyl-5(*p*-bromophenyl)-5-methoxypyrrolone-2 (III), from VI or I.—The procedure was the same for the preparation of each of these compounds, with variation in reagents used. A mixture of 3 g. of VI (or I), 17 cc. of absolute ethyl alcohol (or methyl alcohol in the case of III), and 50 cc. of ether was saturated with dry hydrogen chloride at room temperature, and was allowed to stand for approximately twenty-four hours. The solution was then evaporated to dryness at room temperature, and the product recrystallized from ethyl alcohol. Compound III was crystallized from methyl alcohol, yield, 75%.

Compound VII.—Thick colorless crystals; m. p. 106–107°. Soluble in hot alcohol, benzene and acetone. *Anal.* Calcd. for $C_{24}H_{21}O_2N$: C, 81.13; H, 5.91. Found: C, 81.24; H, 6.22.

Compound II.—Thick colorless crystals; m. p. 148–149.5°. *Anal.* Calcd. for $C_{24}H_{20}O_2NBr$: C, 66.37; H, 4.60; N, 3.23; Br, 18.44; mol. wt., 433.9; active hydrogen atoms, 0.0. Found: C, 66.36, 66.46; H, 4.35, 4.44; N, 3.32; Br, 18.41, 18.45; mol. wt., 401; active hydrogen atoms, 0.2, 0.1.

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(4) Almström, *Ann.*, **400**, 133 (1913).

(5) Zerewitinoff, *Ber.*, **40**, 2028 (1907); **41**, 2239 (1908).

Compound III.—Colorless crystals, resembling II; m. p. 139–140°. Soluble in benzene and ethyl alcohol. It does not add bromine in carbon tetrachloride, and is similar to VII and II in this respect. *Anal.* Calcd. for $C_{23}H_{18}O_2NBr$: C, 65.73; H, 4.28; N, 3.33. Found: C, 65.58; H, 4.41; N, 3.23.

1,3-Diphenyl-5-(*p*-bromophenyl)-5-ethoxypyrrolone-2 (II) and 1,3-Diphenyl-5-(*p*-bromophenyl)-5-methoxypyrrolone-2 (III) from IV.—Two grams of IV, 12 cc. of absolute alcohol (ethyl alcohol for II, methyl for III), and 34 cc. of absolute ether were mixed and saturated at room temperature with dry hydrogen chloride. After standing at room temperature overnight, the solution was evaporated at steam-bath temperature to crystallization. The product was then recrystallized from the appropriate alcohol, yields 80% approx. The products were identified by melting points and mixed melting points with products described above.

1,3-Diphenyl-5-(*p*-bromophenyl)-5-ethoxypyrrolone-2 (II) from III, and 1,3-Diphenyl-5-(*p*-bromophenyl)-5-methoxypyrrolone-2 (III) from II.—The procedure described immediately above was carried out, substituting first III, and then II, for IV. When III was thus treated with absolute ethyl alcohol–ether saturated with dry hydrogen chloride, compound II was obtained. Similarly, when II was treated with absolute methyl alcohol and ether and dry hydrogen chloride, III was the product. Products were identified by melting point methods.

1,3-Diphenyl-5-(*p*-bromophenyl)-pyrrolone-2 (V) from 1,3-Diphenyl-5-(*p*-bromophenyl)-5-ethoxypyrrolone-2 (II).—A mixture of 100 cc. of glacial acetic acid, 10 g. of powdered zinc, and 7 g. of II (or of III) was heated at a gentle boil for four hours, during which time 30 g. more of zinc was added in small portions at intervals of fifteen minutes. The supernatant liquid was decanted while hot and the residue extracted several times with hot glacial acetic acid. The combined solutions were poured into water and allowed to stand overnight. The solid which precipitated was recrystallized from ethyl alcohol, yield 85%, white plates of m. p. 151.5–152.5°. Compound V is soluble in carbon tetrachloride, benzene, pyridine and toluene.

Anal. Calcd. for $C_{22}H_{16}ONBr$: C, 67.70; H, 4.10; N, 3.59; mol. wt., 389.9; active hydrogen atoms, 0.0. Found: C, 67.92; H, 4.00, 3.82; N, 3.43; mol. wt., 361; active hydrogen atoms, 0.1, 0.2, 0.2.

1,3,5-Triphenylpyrrolone-2 (VIII) from 1,3,5-Triphenyl-5-ethoxypyrrolone-2 (VII).—Compound VIII was prepared from VII by the same method as used above for the preparation of V from II. VIII was recrystallized from glacial acetic acid, m. p. 197–198°.

Summary

Acetophenone condenses with benzoylformanilide to give an aldol-like compound which will form an hydroxypyrrolone ring upon treatment with dry hydrogen chloride. Alkoxypyrrolones result if alcoholic hydrogen chloride is employed. These alkoxypyrrolones yield 1,3,5-triphenylpyrrolone-2 as their common reduction product.

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[CONTRIBUTION FROM THE UNIVERSITY OF MARYLAND STATION OF THE INSECTICIDE DIVISION, BUREAU OF CHEMISTRY AND SOILS]

Croton Resin. I. Toxicity Studies Using Goldfish[1]

BY JOSEPH R. SPIES

The oil of the croton bean[2] has been the subject of numerous investigations during the last century. Its purgative action as well as its vesicant and toxic properties were noted by earlier investigators, and various attempts have been made to isolate the active principle. Recently Cherbuliez[3] and his co-workers have isolated an extremely active, nonhomogeneous, resin from both the oil and beans which is undoubtedly responsible for their vesicant and toxic properties.[4]

In a search for new natural insecticides, in which a number of plant materials were examined,[5] it became apparent that the croton bean[6] contains a substance which surpasses rotenone in its toxicity to goldfish. The process of Cherbuliez was modified to obtain the resin for this study, and it was shown by tests on goldfish that no appreciable quantity of toxic material was lost in the process.

In the hope that some resolution of components

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(1) From a thesis submitted by Joseph R. Spies to the Graduate School of the University of Maryland in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

(2) *Croton tiglium* (Linné) is a species of the *Croton* genus of the *Euphorbiaceae* family. The seed or bean is sometimes used as a fish poison.

(3) Cherbuliez, Ehninger and Bernhard, *Helv. Chim. Acta*, **15**, 658 (1932).

(4) Boehm and Flaschenträger, *Arch. Path. Pharmakol.*, **157**, 115 (1930), claim to have isolated the pure toxic principle from croton oil by purely physical means which they did not describe.

(5) (a) Drake and Spies, *J. Econ. Entomol.*, **25**, 129 (1932); (b) Spies, *ibid.*, **26**, 285 (1933).

(6) Dr. G. P. Jung of the Bureau of Entomology of China kindly furnished the major supply of beans for this study. According to Jung a "croton emulsion" made from the beans is used as an insecticide in China; other sources from which the beans were obtained: (a) Schimmel & Co., A. G., Miltitz bei Leipzig (through Fritzsche Bros., N. Y.), shelled beans, yield of resin 0.6%; (b) Anandji Virgi & Co., Box 153, Bombay, India, shelled beans, yield of resin 0.94%; (c) H. C. Neibert, Milbuk, P. I. *Cf.* Jung, *Lingnan Sci. J.*, [3] **13**, 557 (1934).