Condensations at the α-Carbon of Phenylacetanilide, Phenylacetamide, and Phenylacetic Acid through Their Dialkali Salts in Liquid Ammonia[1a]

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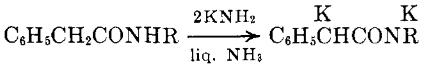
Condensations at the α-carbon of phenylacetanilide, phenylacetamide, and phenylacetic acid were accomplished through their dialkali salts. Phenylacetanilide was benzylated with benzyl chloride to produce the C-benzyl derivative. This amide and also phenylacetamide were benzoylated with methyl benzoate to form β-ketoamides and were condensed with benzophenone (aldol type) to give β-hydroxyamides, which were dehydrated to afford α,β-unsaturated amides. Phenylacetic acid was benzoylated, and the resulting β-keto acid was decarboxylated to give desoxybenzoin. The benzoyl derivative of phenylacetanilide was cyclized to form 3,4-diphenylcarbostyril. The α,β-unsaturated amides were cyclized to give 2,3-diphenylindenone.

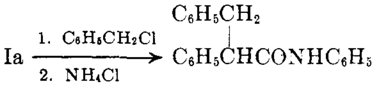
Previous papers have described certain condensations at the α-carbon of phenylacetic acid,[2] phenylacetamide,[3] and phenylacetanilide[3b] through their dialkali salts. The present paper describes several new condensations of these compounds. The two amides were converted to their dipotassio salts (Ia,b) by means of two molecular equivalents of potassium amide in liquid ammonia.



$$C_6H_5CH_2CONHR \xrightarrow[\text{liq. } NH_3]{2KNH_2} C_6H_5\overset{K}{C}HCO\overset{K}{N}R$$

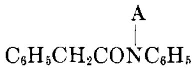
Ia, $R = C_6H_5$
b, $R = H$

Dipotassio salt Ia was benzylated with benzyl chloride to form the C-benzyl derivative (II) in 88% yield.



$$Ia \xrightarrow[2.\ NH_4Cl]{1.\ C_6H_5CH_2Cl} C_6H_5\overset{C_6H_5CH_2}{\overset{|}{C}}HCONHC_6H_5$$

II



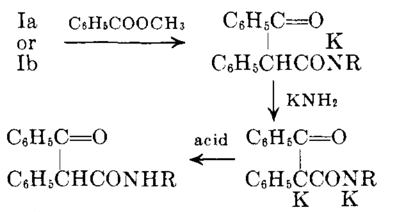
$$C_6H_5CH_2CO\overset{A}{\overset{|}{N}}C_6H_5$$

III

That the product was the C-benzyl derivative (II), not the possible N-benzyl derivative (III, A = CH_2-C_6H_5), was indicated by essential agreement of its melting point with the reported[4] value and by its infrared spectrum, which showed a band at 3.08 μ for the N–H group.[5]

Structure II was confirmed by independent synthesis by treatment of α-benzylphenylacetic acid[2a] with thionyl chloride, followed by aniline.

Next, both dipotassio salts (Ia and Ib) were benzoylated with methyl benzoate in the presence of potassium amide to form β-ketoamides (IVa and IVb) in yields of 23 and 50%, respectively.

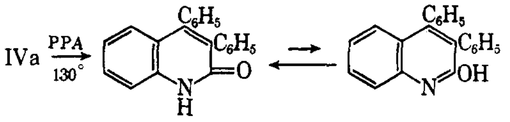


$$\begin{matrix}Ia \\ or \\ Ib\end{matrix} \xrightarrow{C_6H_5COOCH_3} \overset{C_6H_5C=O}{\overset{|}{C_6H_5CHCO\overset{K}{N}R}} \xrightarrow{KNH_2} \overset{C_6H_5C=O}{\overset{|}{\underset{K}{C_6H_5C}CO\underset{K}{N}R}} \xrightarrow{acid} \overset{C_6H_5C=O}{\overset{|}{C_6H_5CHCONHR}}$$

IVa, $R = C_6H_5$
b, $R = H$

That the products were the C-benzoyl derivatives (IVa,b) not the possible N-benzoyl derivatives (III, A = COC_6H_5), was supported by essential agreement of their melting points with reported values,[6,7] by positive enol tests, and by infrared bands for the N–H group[5] at 3.05 and 3.00 μ, respectively. The structure of IVa was further supported by formation of aniline on saponification, and that of IVb by its solubility in 5% sodium hydroxide solution. Apparently IVa was converted by this alkaline solution to its sodium salt, but this salt was insoluble.

The structure of β-ketoamide IVa was confirmed by cyclodehydration with polyphosphoric acid to form 3,4-diphenylcarbostyril (Va) in 75% yield. Surprisingly, only a 6% yield of Va was obtained with concentrated sulfuric acid, which is satisfactory for the cyclization of acetoacetanilide to form 4-methylcarbostyril.[8]



Va Vb

Although hydroxyquinoline Vb may be in equilibrium with Va, the infrared spectrum of the product showed bands at 6 09 and 6.19 μ, indicative of the α,β-unsaturated δ-lactam group in Va,[9] but no band in the region for the free hydroxyl group of Vb.[10] The infrared spectrum of carbostyril itself, both in the solid state and in solution, shows analogous bands for the δ-lactam structure.[11]

The structure of β-ketoamide IVb was confirmed by independent synthesis involving treatment of α-benzoylphenylacetonitrile with boron fluoride in acetic acid.[7]

Next, an attempt was made to condense dipotassio salt Ia with benzophenone in liquid ammonia, but the starting materials were recovered even though the reaction mixture was neutralized inversely. However, such aldol type condensations were realized with both phenylacetanilide and phenylacetamide by employing

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(1) (a) Supported in part by the National Institutes of Health; (b) National Science Foundation Predoctoral Fellow (1958–1961).

(2) (a) C. R. Hauser and W. J. Chambers, *J. Am. Chem. Soc.*, **78**, 4942 (1956); (b) P. J. Hamrick and C. R. Hauser, *ibid.*, **82**, 1957 (1960); (c) R. B. Meyer and C. R. Hauser, *J. Org. Chem.*, **26**, 3183 (1961).

(3) (a) R. B. Meyer and C. R. Hauser, *ibid.*, **26**, 3696 (1961); (b) R. B. Meyer and C. R. Hauser, *ibid.*, **26**, 3187 (1961).

(4) H. Burton and C. W. Shoppee [*J. Chem. Soc.*, 546 (1937)] benzylated phenylacetonitrile and converted the resulting nitrile to II in unreported yield through the carboxylic acid.

(5) See L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 205.

(6) W. Wislecenus, H. Eichert, and M. Marquardt [*Ann.*, **436**, 88 (1924)] benzoylated phenylacetonitrile and converted the resulting nitrile to IVa in unreported yield through the ethyl ester.

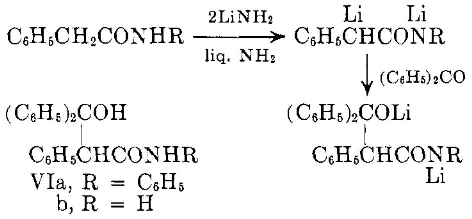
(7) C. R. Hauser and C. J. Eby [*J. Am. Chem. Soc.*, **79**, 725 (1957)] benzoylated phenylacetonitrile and the resulting α-benzoyl nitrile was converted to IVb by means of boron fluoride or polyphosphoric acid.

(8) W. M. Lauer and C. E. Kaslow, *Org. Syn.*, **24**, 68 (1944).

(9) See ref. 5, p. 213.

(10) See ref. 5, p. 96.

(11) Yu. N. Sheinker and Yu. I. Pomerantsev, *Zh. Fiz. Khim.*, **30**, 79 (1956); *Chem. Abstr.*, **50**, 14780i (1956).

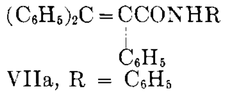


$$C_6H_5CH_2CONHR \xrightarrow[\text{liq. } NH_2]{2LiNH_2} C_6H_5\overset{Li}{C}HCO\overset{Li}{N}R \xrightarrow{(C_6H_5)_2CO} \underset{C_6H_5CHCON\underset{Li}{R}}{(C_6H_5)_2COLi} \rightarrow \underset{C_6H_5CHCONHR}{(C_6H_5)_2COH}$$

VIa, R = C_6H_5
b, R = H

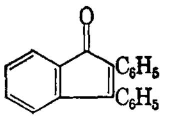
their dilithio salts, and β-hydroxyamides VIa,b were obtained in yields of 16 and 7%, respectively.

Structures VIa,b were established by analyses and by dehydrations with sulfuric acid to form α,β-unsaturated amides VIIa,b[12] in yields of 74 and 85%, respectively. These products were cyclized to give 2,3-diphenylindenone (VIII)[13] in yields of 93 and 80%, respectively. In the cyclization of VIIa the by-product aniline was obtained in 80% yield.



$$(C_6H_5)_2C{=}\underset{C_6H_5}{C}CONHR$$

VIIa, R = C_6H_5
b, R = H

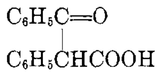


VIII

Finally, phenylacetic acid was benzoylated through its dipotassio salt (IX) to form β-keto acid X, which was isolated as its decarboxylation product, desoxybenzoin (22%).[14]

$$C_6H_5\overset{K}{C}HCOOK$$

IX



$$C_6H_5\overset{C_6H_5C=O}{C}HCOOH$$

X

Discussion

These six new condensations complement six earlier ones[2,3] so that phenylacetanilide, phenylacetamide, and phenylacetic acid each have been shown now to undergo the four important types of condensations—alkylation, aroylation, carbonyl addition, and conjugate addition. These reactions furnish useful methods for the synthesis of the four types of derivatives of these active hydrogen compounds. Although certain of the present yields were low, they could probably be improved, and even the low yields are offset somewhat by the directness and convenience of the methods.

Experimental[15]

Dipotassio Salts Ia,b.—To a stirred solution of 0.1 mole of potassium amide in 600 ml. of liquid ammonia was added, from an Erlenmeyer flask through Gooch tubing, 0.05 mole of solid phenylacetanilide. After stirring for 30 min., the resulting bright yellow suspension was assumed to contain 0.05 mole of dipotassio salt Ia.

Similarly, 0.05 mole of dipotassio salt Ib was prepared as a yellow-brown suspension from 0.05 mole of phenylacetamide and 0.1 mole of potassium amide in 600 ml. of liquid ammonia.

Benzylation of Dipotassio Salt Ia.—To the stirred suspension of 0.05 mole of Ia was added, during 5 min., 6.96 g. (0.055 mole) of benzyl chloride in 50 ml. of dry ether. The reaction mixture was stirred for 30 min., and 0.1 mole of solid ammonium chloride was added. The liquid ammonia was evaporated as ether was added. After adding 100 g. of crushed ice, the resulting mixture was stirred to dissolve inorganic salts. The precipitate that remained was collected and washed with small portions of ether and 95% ethanol to give 10.19 g. of 2,3-diphenylpropionanilide (II), m.p. 168–168.5°, lit.[4] m.p. 166°. An additional 3.09 g. of II was isolated from the ethereal layer of the filtrate to give a total yield of 88%.

Independent synthesis of II was effected by converting 2.26 g. (0.01 mole) of 2,3-diphenylpropionic acid[2a] to its acid chloride and treating the crude acid chloride with 1.86 g. (0.02 mole) of aniline. There was obtained, after recrystallization from 95% ethanol, 2.4 g. (80%) of II, m.p. 168–169°, not depressed on admixture with a sample of II prepared by benzylation of Ia. The infrared spectra of the two samples were identical.

Benzoylation of Dipotassio Salt Ia to Form IVa.—To a stirred suspension of 0.05 mole each of Ia and potassium amide in 600 ml. of liquid ammonia was added 13.62 g. (0.1 mole) of methyl benzoate in 50 ml. of dry ether. After 2 hr., the ammonia of the yellow-green reaction mixture was replaced by ether. A mixture of 150 g. of crushed ice and 25 ml. of 12 N hydrochloric acid was added. The resulting precipitate was fractionally crystallized from 95% ethanol to give, first, 3.65 g. (23%) of α-benzoylphenylacetanilide (IVa), m.p. 164–165°, and, second, 2.15 g. of recovered phenylacetanilide, m.p. 108–112°. After another recrystallization, IVa melted at 168–169°, lit.[6] m.p. 168°. The product produced a deep green color with ethanolic ferric chloride solution. More (2.11 g., total recovery 39%) phenylacetanilide was isolated from the ethereal layer of the original ether–water filtrate. After another recrystallization, it had m.p- 116–117°, not depressed on admixture with an authentic sample.

Hydrolysis of IVa (0.50 g.) was effected with 20 ml. of 25% aqueous potassium hydroxide (refluxed 16 hr.). There was obtained 0.09 g. (60%) of aniline, identified by vapor phase chromatographic analysis. Only a trace amount of impurity was present.

Cyclization of IVa (0.50 g.) was accomplished with 25 ml. of polyphosphoric acid (stirred 30 min. at 130° and 1.5 hr. at room temperature). After adding crushed ice, the reaction mixture was poured into 100 g. of ice–water. The resulting precipitate was collected and recrystallized from 95% ethanol to give 0.35 g. (75%) of 3,4-diphenylcarbostyril (Va), m.p. 305–307°, 309–310° after two additional recrystallizations.

Anal. Calcd. for $C_{21}H_{15}NO$: C, 84.82; H, 5.09; N, 4.71. Found: C, 85.15; H, 5.04; N, 4.67.

Benzoylation of Dipotassio Salt Ib to Form IVb.—This reaction was effected essentially as described for the benzoylation of Ia. After 30 min., the ammonia of the yellow-green reaction mixture was replaced by ether. The resulting ethereal suspension was acidified with 200 ml. of 5% hydrochloric acid to precipitate 5.2 g. of α-benzoylphenylacetamide (IVb), m.p. 165–168°, 174–176° after two recrystallizations from 95% ethanol; lit.[7] m.p. 172–174°. An additional 0.7 g. of IVb was isolated from the ethereal layer of the filtrate to give a total yield of 50%. The product produced a deep purple color with ethanolic ferric chloride solution.

Independent synthesis of IVb was accomplished from phenylacetonitrile and methyl benzoate through α-benzoylphenylacetonitrile, which was treated with boron fluoride in acetic acid as described previously.[7] The product had m.p. 175–176°, not depressed on admixture with a sample of IVb prepared by the benzoylation of Ib. The infrared spectra of the two samples were identical.

Condensation of Dilithiophenylacetanilide with Benzophenone to Form VIa.—To a stirred suspension of 0.04 mole of dilithiophenylacetanilide (prepared from 0.08 mole of lithium amide in 600 ml. of liquid ammonia) was added 7.29 g. (0.04 mole) of benzophenone in 100 ml. of ether. The original yellow-green color changed to dark gray within 5 min. After stirring for 15 min., the reaction mixture was poured into a stirred solution of 10.7 g. of ammonium chloride in 200 ml. of liquid ammonia. The resulting mixture was returned to the original flask, and the ammonia was replaced by ether. The ethereal suspension was stirred with 100 ml. of 10% hydrochloric acid. The ether layer was combined with an ethereal extract of the aqueous layer and washed with water. The ethereal solution was dried over anhy-

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[12] Previously phenylacetonitrile had been treated with dichlorodiphenylmethane and the resulting nitrile was hydrolyzed to form VIIb in unreported yield [G. Heyl and V. Meyer, *Ber.*, **28**, 1798 (1895)].

[13] See B. W. Rockett and C. R. Hauser, *J. Am. Chem. Soc.*, in press; G. Heyl and V. Meyer, *Ber.*, **28**, 2776 (1895).

[14] Previously phenylacetic acid had been benzoylated through the Ivanov reagent to form X, which was isolated as desoxybenzoin (75%) [D. Ivanov and N. J. Nicolov, *Bull. soc. chim. France*, [4] **51**, 1331 (1932)].

[15] Melting points were taken on a Mel-Temp capillary melting point apparatus and are uncorrected. Infrared spectra were determined with a Perkin-Elmer Model 137 or 237 Infracord by the potassium bromide pellet method. Elemental analyses were by Galbraith Microanalytica Laboratories, Knoxville, Tenn.

drous magnesium sulfate and most of the solvent was removed. The resulting precipitate was collected and boiled with 100 ml. of 95% ethanol. The remaining solid was collected to give 3-hydroxy-2,3,3-triphenylpropionanilide (VIa). The ethanol was removed from the filtrate, and the residue was treated twice more with successively smaller amounts of ethanol in the same manner, to leave in each case VIa; the total yield was 2.54 g. (16%), m.p. 193–193.5°, after two recrystallizations from 95% ethanol. Its infrared spectrum showed principal bands at 2.92, 3.31, 6.09, and 6.27 μ.

Anal. Calcd. for $C_{27}H_{23}NO_2$: C, 82.42; H, 5.89; N, 3.56. Found: C, 82.26; H, 5.74; N, 3.54.

The final ethanol extract was cooled to precipitate (two crops) 4.89 g. (58%) of recovered phenylacetanilide, m.p. and m.m.p. 116–117°.

The solvent was removed from the original ethereal filtrate, and the residue was dissolved in 500 ml. of boiling petroleum ether (b.p. 30–60°). The volume of the solution was reduced, and the red oil that precipitated was discarded. The solution was cooled to precipitate 4.33 g. (60%) of recovered benzophenone, m.p. 47–48°, after recrystallization from petroleum ether. A mixture melting point with an authentic sample showed no depression.

When the experiment was repeated employing a 2-hr. condensation period, the yield of VIa was 5%.

Dehydration of VIa to Form VIIa.—To 10 ml. of stirred concentrated sulfuric acid at 0° was added, in small portions, 0.50 g. of VIa. After almost all of the solid had dissolved, the reaction mixture was poured into 30 g. of ice–water. The resulting milky white suspension was extracted with 200 ml. of ether. The ethereal extract was washed successively with water and saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Most of the solvent was removed, and the resulting precipitate was collected to give 0.35 g. (74%) of 2,3-diphenylcinnamanilide (VIIa), m.p. 216–217°, 218.5° after two recrystallizations from anhydrous ether. Its infrared spectrum showed principal bands at 2.95, 6.10, and 6.28 μ.

Anal. Calcd. for $C_{27}H_{21}O$: C, 86.37; H, 5.64; N, 3.73. Found: C, 86.48; H, 5.60; N, 3.54.

Cyclization of VIIa (0.20 g.) was effected in a mixture of 13 ml. of glacial acetic acid, 4 ml. of concentrated sulfuric acid, and 3 ml. of water (refluxed 17 hr.). The reaction mixture was diluted with water and extracted with ether. The ethereal extract was dried over anhydrous magnesium sulfate, and most of the solvent was removed. The resulting precipitate was collected to give 0.14 g. (93%) of 2,3-diphenylindenone (VIII, red prisms), m.p. 150–153°, 152–154° after recrystallization from 95% ethanol, lit.[13] m.p. 152–153°. A mixture melting point with an authentic sample of VIII[13] showed no depression and the infrared spectra of the two samples were identical.

Condensation of Dilithiophenylacetamide with Benzophenone to Form VIb.—This reaction was effected and the reaction mixture was worked up essentially as described above for dilithiophenylacetanilide employing 0.1 mole each of dilithiophenylacetamide and benzophenone. There was obtained 2.1 g. (7%) of 3-hydroxy-2,3,3-triphenylpropionamide (VIb), m.p. 188–189°, 189–189.5° after recrystallization from 95% ethanol. Its infrared spectrum showed principal bands at 2.99 and 6.06 μ.

Anal. Calcd. for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.42. Found: C, 79.66; H, 6.02; N, 4.60.

There was recovered 88% of the starting phenylacetamide and 81% of the benzophenone.

Dehydration of VIb to Form VIIb.—This reaction was effected essentially as described for the dehydration of VIa. The reaction mixture was poured onto crushed ice, and the resulting precipitate was collected and recrystallized from 95% ethanol to give (two crops) 0.40 g. (85%) of 2,3-diphenylcinnamamide (VIIb), m.p. 223–226°, 232–232.5° after two additional recrystallizations, lit.[12] m.p. 223°. Its infrared spectrum showed principal bands at 3.00, 3.23, and 6.13 μ.

Anal. Calcd. for $C_{21}H_{17}NO$: C, 84.25; H, 5.73; N, 4.68. Found: C, 84.02; H, 5.62; N, 4.68.

Cyclization of VIIb (0.10 g.) was effected as described for that of VIIa to give 0.07 g. (80%) of red 2,3-diphenylindenone (VIII), m.p. 152–154°, not depressed on admixture with an authentic sample of VIII.[13] The infrared spectra of the two samples were identical.

Benzoylation of Dipotassiophenyl Acetate.—To a stirred suspension of 0.1 mole each of dipotassiophenyl acetate and potassium amide was added 0.2 mole of methyl benzoate in 100 ml. of dry ether. After 1.5 hr., the ammonia was replaced by ether. The resulting ethereal suspension was poured into 10% hydrochloric acid. The solvent was removed from the ethereal layer, and the residue was fractionally distilled *in vacuo* to give 13.6 g. (50%) of recovered methyl benzoate, b.p. 80° at 8.6 mm., and 19.7 g. of material, b.p. 138–165° at 8.6 mm. The latter fraction, which solidified, was shaken with 5% sodium hydroxide. The insoluble material was collected to give 4.4 g. (22%) of desoxybenzoin, identified by the mixture melting point method. The alkaline filtrate was acidified to precipitate 9.7 g. (71%) of recovered phenylacetic acid.

An Inositol Analog Containing One Sulfur Atom (Mercaptocyclohexanepentol). Synthesis and Nuclear Magnetic Resonance Characterization of Derivatives[1,2]

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Reaction of 1,2-anhydro-*cis*-inositol diketal with benzyl mercaptan gave a benzylmercaptopentol diketal, which was reduced to the mercaptopentol diketal. Hydrolysis of the latter gave *meso*-6-mercapto-6-deoxy-*epi*-inositol, m.p. 180° (hexaacetate, 182°). Desulfurization produced *cis*-cyclohexanepentol, confirming the configuration. The mercaptopentol diketal on acetonation gave the triisopropylidene derivative (oxathiolane), which contains a new tetracyclic ring system. The same diketal on acetylation gave an *O*,*S*-diacetate, which also can be prepared directly from the anhydro diketal by reaction with thiolacetic acid. Acidic hydrolysis of the diketal diacetate gives the mercaptopentol. N.m.r. and infrared spectra were used to characterize the new compounds prepared.

The synthesis and n.m.r. characterization of the first sulfur analogs of inositol were recently reported.[3c] These analogs were dimercapto derivatives (I) of cyclohexanetetrol (dideoxyinositol). We now have extended this investigation to the mercapto derivatives (II) of cyclohexanepentol (deoxyinositol or quercitol).

The new analogs containing a single sulfur atom are of interest for their possible inositol or anti-inositol

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(1) Presented by G. E. McCasland to the Symposium on Thio Derivatives of Carbohydrates at the 145th National Meeting of the American Chemical Society, New York, N. Y., September, 1963.

(2) Paper XVII on Cyclitol Stereochemistry by G. E. McCasland and co-workers; for preceding paper, see *J. Am. Chem. Soc.*, **85**, 2866 (1963).

(3) (a) G. E. McCasland, S. Furuta, L. F. Johnson, and J. N. Shoolery *J. Am. Chem. Soc.*, **83**, 2335 (1961); (b) **83**, 4243 (1961); (c) (with A. Furst), *J. Org. Chem.*, **28**, 456 (1963); (d) **28**, 894 (1963); (e) H. Eagle and G. E. McCasland, *Biochemistry*, **2**, 1125 (1963); (f) G. E. McCasland, S. Furuta, L. F. Johnson, and J. N. Shoolery, *J. Am. Chem. Soc.*, submitted for publication; (g) G. E. McCasland, S. Furuta, and A. Furst, *ibid.*, **85**, 2866 (1963).