The Structure of the Reaction Product of *o*-Benzoylbenzoic Acid with Ethylenediamine

W. METLESICS, T. ANTON, AND L. H. STERNBACH

Department of Chemical Research, Research Division, Hoffmann-La Roche Inc., Nutley, New Jersey

Received January 21, 1967

The structure of the condensation product formed by heating *o*-benzoylbenzoic acid with ethylenediamine is shown to be the imidazoisoindolone II rather than the eight-membered heterocyclic compound I. Spectral data and unambiguous chemical proof for this conclusion are presented.

The condensation of *o*-benzoylbenzoic acid with ethylenediamine was described in a recent patent.[1] The structure of the product was claimed to be that of the 2,5-benzodiazocinone I.

It had been reported previously that similar condensations of phthalaldehydic acid with *o*-aminobenzylamine and α,α'-diamino-*o*-xylene[2a] as well as 2-amino-5-chloro-*p*-toluenesulfonamide[2b] gave condensed isoindolone derivatives rather than compounds containing many-membered heterocyclic rings. We therefore decided to investigate the structure of the product in question.

Ultraviolet absorption data should make it possible to distinguish between the structures I and II. Structure I contains a benzophenonimine grouping which on acidification should show a bathochromic shift and increased ultraviolet absorption. Structure II should give rise to an absorption similar to that of known 2,3-disubstituted phthalimidines[3] without much change on acidification.

The observed absorption of λ_{infl} 225 mμ (ϵ 16,000) and 260 mμ (ϵ 3800) which was not increased by lowering the pH to 1 indeed excludes the presence of a C=N group conjugated with the aromatic ring. Therefore, structure II was assigned to the product obtained by refluxing *o*-benzoylbenzoic acid in ethylenediamine.[4]

Chemical proof for structure II was obtained in the following manner. As expected, II was readily acetylated to III which, on catalytic hydrogenation, gave the phthalimidine derivative VII. This compound showed characteristics of a secondary amide. The same compound was obtained on hydrogenolysis of II and subsequent acetylation of the reaction product VI. Although structure I could also explain the uptake of 1 mole of hydrogen, it would be impossible to obtain identical acetyl derivatives on reversing the sequence of acetylation and hydrogenation. Hydrogenation of II gave a product which showed spectral properties compatible with structure VI. This compound was synthesized by heating 3-phenylphthalide X in ethylenediamine in analogy with a known procedure.[5]

Hydrolysis of II gave the 3-hydroxyphthalimidine V which showed compatible spectral properties[3] and, as expected,[6] gave VI on catalytic hydrogenation. Treatment of V with thionyl chloride in dimethylformamide resulted in cyclization to the imidazoisoindolone II which also supports structure II, since the recyclization of V could not be expected to give the benzodiazocine I. To remove any remaining doubt concerning structures of type II we have also recyclized IV to the N-acetyl derivative III.[7]

Compound V was also synthesized in analogy with the known procedure[3] and gave a hydrochloride which melted at 228–232° dec.[8]

Reduction of VI with lithium aluminum hydride gave the expected isoindoline derivative IX which was also obtained from VIII in analogy with the general method of preparing 2-substituted isoindolines.[9] (See Scheme I.)

Experimental Section[10]

1,2,3,9b-Tetrahydro-9b-phenyl-5H-imidazo[2.1-*a*]isoindol-5-one (II). A. From *o*-Benzoylbenzoic Acid.—This compound, melting at 148–150°, was prepared in 67% yield according to the patented procedure:[1,4] ν^{CHCl_3} 1700 cm^{-1} (C=O); $\lambda_{infl}^{i\text{-PrOH}}$ 225 mμ (ϵ 16,000), λ_{infl} 260 mμ (ϵ 3800); $\lambda_{infl}^{0.1\ N\ HCl}$ 225 mμ (ϵ 15,400), λ_{infl} 255 mμ (ϵ 4200), λ_{infl} 277 mμ (ϵ 1500); nmr peaks ($CDCl_3$) at δ 2.13 (1 H, singlet, NH, exchangeable with D_2O), 3.0–4.0 (4 H, multiplet, CH_2CH_2) 7.3–8.0 (9 H, multiplet).

B. From V.—To a solution of 2.68 g (0.01 mole) of V in 50 ml of dimethylformamide was slowly added 0.75 ml of thionyl chloride. The clear solution was refluxed for 5 hr and concentrated *in vacuo*. The residue was basified with an aqueous solution of sodium bicarbonate and extracted with ethyl acetate to give 0.8 g (32%) of II.

Hydrochloride of II.—Compound II (0.8 g) was dissolved in a mixture of 5 ml of methylene chloride and 3 ml of methanol and a solution of hydrogen chloride in ether was added. The crystalline precipitate was collected and recrystallized from a mixture of methanol and ether to give white prisms melting at 260–262° dec: ν^{KBr} 1733 cm^{-1} (C=O).

(1) American Home Products Corp., Netherlands Patent 6,403,794 (Oct 12, 1964).

(2) (a) E. F. M. Stephenson, *J. Chem. Soc.*, 2354 (1954), and earlier papers; (b) S. C. Bell, P. H. L. Wei, and S. J. Childress, *J. Org. Chem.*, **29**, 3206 (1964).

(3) W. Graf, E. Girod, E. Schmid, and W. G. Stoll, *Helv. Chim. Acta*, **42**, 1085 (1959). The authors describe the ultraviolet absorption of 2-ethyl-3-hydroxy-3-phenylphthalimidine (A) and similar compounds as λ_{max}^{MeOH} <220 mμ. In addition, we found a broad maximum at 255 mμ (ϵ 3700) for A which is the expected value for the benzenoid absorption in that area.

(4) While this work was in progress a patent was issued to J. R. Geigy A. G. [Belgian Patent 659,530 (Aug. 10, 1965); *Chem. Abstr.*, **64**, 6664 (1966)] in which this reaction was described and structure II was assigned to the reaction product. See also American Home Products Corp., Belgian Patent 679,508 (Oct 14, 1966).

(5) S. Ohki, *J. Pharm. Soc. Japan*, **70**, 92 (1950); *Chem. Abstr.*, **44**, 5867*h* (1950). See also C. F. Huebner, U. S. Patent 2,957,872 (Oct 1960); *Chem. Abstr.*, **55**, 16489*b* (1961).

(6) The reduction of 2-dialkylaminoalkyl-3-hydroxy-3-phenylphthalimidines to the corresponding compounds of type VI has been described by O. Bub, German Patent 1,135,461 (Aug 1962); *Chem. Abstr.*, **58**, 1412*d* (1963).

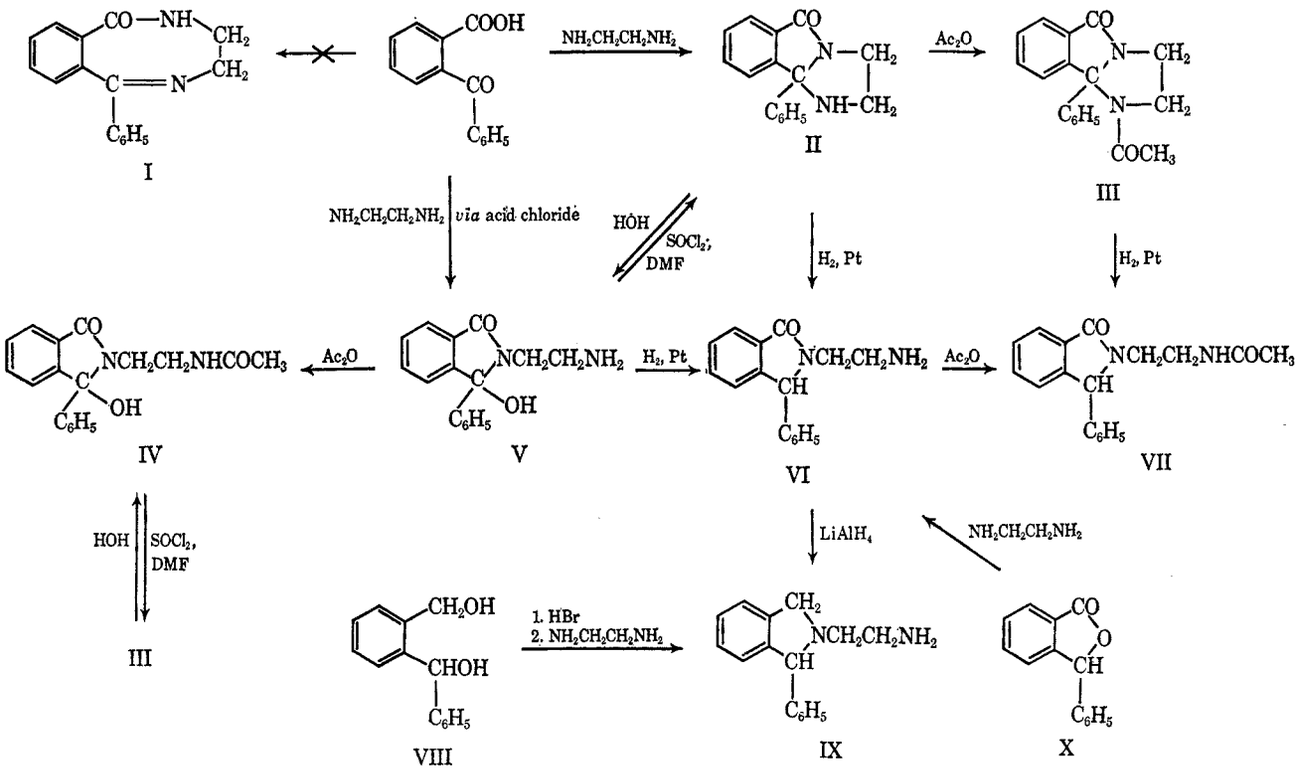
(7) This experiment designed to ascertain structure III was suggested by the referee, since there is the theoretical possibility that the keto form of V (see ref 3) could condense to give the eight-membered heterocyclic compound I.

(8) This compound was described by P. Truitt, L. R. Brammer, and L. T. Creagh [*J. Med. Chem.*, **8**, 731 (1965)] with mp 261–263°. *Anal.* Calcd: N, 9.19. Found: N, 9.20. It is suggested that these authors actually prepared the hydrochloride of II (*Anal.* Calcd: N, 9.77.) for which we found mp 260–262° dec.

(9) M. Scholtz, *Chem. Ber.*, **31**, 627 (1898).

(10) All melting points are corrected. The infrared spectra were determined with a Beckman IR-9 spectrophotometer, the ultraviolet spectra with a Carey Model 14 spectrophotometer, and the nmr spectra with a Varian A-60 instrument. Identity of compounds was proved by mixture melting point and comparison of infrared spectra.

SCHEME I



Anal. Calcd for $C_{16}H_{14}N_2O \cdot HCl$: C, 67.03; H, 5.27; Cl, 12.37. Found: C, 67.27; H, 5.23; Cl, 12.29.

1-Acetyl-1,2,3,9b-tetrahydro-9b-phenyl-5H-imidazo[2,1-*a*]-isoindol-5-one (III). A. From II.—A solution of 10 g of II and 3 drops of boron trifluoride etherate in 35 ml of acetic anhydride was heated for 5 min on a steam bath, then kept at 25° for 20 hr. The solution was poured into ice water and the crystalline precipitate was collected on a filter. White prisms (10 g, 85%) melting at 173–175° were obtained after recrystallization from a mixture of methylene chloride and methanol: ν^{CHCl_3} 1710, 1665 cm^{-1} (C=O); $\lambda_{infl}^{i\text{-PrOH}}$ 275 mμ (ϵ 2000).

Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52. Found: C, 73.74; H, 5.39.

B. From IV.—To a solution of 1.55 g of IV in 25 ml of dimethylformamide was slowly added 0.4 ml of thionyl chloride. The mixture was refluxed for 1.5 hr and concentrated *in vacuo* to a brown oil which was partitioned between aqueous sodium bicarbonate solution and ethyl acetate. The organic extract was concentrated and gave a partly crystalline residue which after recrystallization from a mixture of tetrahydrofuran and petroleum ether gave 0.3 g of white prisms melting at 170–173°.

2-(2-Acetamidoethyl)-3-hydroxy-3-phenylphthalimidine (IV). A. From III.—A solution of 3 g of III in a mixture of 10 ml of acetic acid and 30 ml of water was refluxed for 30 min. On cooling a crystalline precipitate was obtained which after washing with ether gave 2.6 g (82%) of white prisms melting at 184–188° dec.

B. From V.—A solution of 3 g of V in 25 ml of acetic anhydride was stirred for 1 hr. A precipitate was collected and after recrystallization from a mixture of chloroform and ether gave 2 g (58%) of white prisms melting at 186–189° dec: ν^{CHCl_3} 1690 cm^{-1} (2C=O), $\lambda_{max}^{i\text{-PrOH}}$ 253 mμ (ϵ 4000).

Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85. Found: C, 69.67; H, 5.74.

2-(2-Aminoethyl)-3-hydroxy-3-phenylphthalimidine (V). A. From II.—A solution of 30 g (0.12 mole) of II in a mixture of 75 ml of acetic acid and 150 ml of water was refluxed for 30 min. The solution was concentrated *in vacuo* to 75 ml. After addition of 150 ml of methanol the solution was basified with 100 ml of concentrated ammonia. The crystalline precipitate was collected on a filter and washed with ethanol. Recrystallization from methanol gave white prisms (18.0 g, 56%) melting at 175–176°: ν^{CHCl_3} 1693 cm^{-1} (C=O); $\lambda_{max}^{i\text{-PrOH}}$ 253 mμ (ϵ 3800), λ_{infl} 279 mμ (ϵ 1300), 297 mμ (ϵ 900).

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; O, 11.93. Found: C, 71.64; H, 6.01; O, 12.14.

B. From *o*-Benzoylbenzoic Acid.—A solution of 22.6 g (0.1 mole) of *o*-benzoylbenzoic acid in 30 ml of thionyl chloride was refluxed for 30 min. The thionyl chloride was removed *in vacuo*, the residue was dissolved in 150 ml of chloroform, and this solution was added to 33 ml of ethylenediamine. The temperature was kept below 50° by external cooling. The solution was washed, dried, and concentrated. The residue crystallized and after recrystallization from methanol gave 12 g (45%) of V.

Hydrochloride of V.—To a solution of 1 g of V, in methanol, was added a solution of hydrogen chloride in ethanol. Ether was added and the crystalline precipitate was collected. Recrystallization from methanol gave white prisms melting at 228–232° dec: ν^{KBr} 1713 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{16}N_2O_2 \cdot HCl$: C, 63.05; H, 5.62; Cl, 11.63. Found: C, 63.15; H, 5.73; Cl, 11.66.

2-(2-Aminoethyl)-3-phenylphthalimidine (VI). A. From II.—A solution of 25 g (0.1 mole) of II, in 150 ml of acetic acid containing 2.5 g of hydrogen chloride was shaken under 1 atm of hydrogen at 25° using 0.5 g of platinum oxide as catalyst. In the course of 7 hr, 3000 ml of hydrogen (theory 2500 ml) was absorbed and the rate of uptake had slowed considerably. The solution was poured into ice water, basified with ammonia, and extracted with methylene chloride. The organic phase was dried and concentrated. The residue crystallized with ether and after recrystallization from a mixture of methylene chloride and petroleum ether gave 17 g (67%) of white prisms melting at 90–93°: ν^{CHCl_3} 1685 cm^{-1} (C=O); $\lambda_{max}^{i\text{-PrOH}}$ 247 mμ, (ϵ 6000), 279 mμ (ϵ 1900); nmr ($CDCl_3$)[11] δ 1.08 (singlet, NH_2) ~3.8 (H_A), 2.6–3.2 (H_B + 2Hc, ABC_2 multiplet, $CH_AH_BCH_CH_CNH_2$), 5.50 (singlet, CH), and 6.9–7.9 (multiplet, nine aromatic protons).

Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39. Found: C, 75.81; H, 6.32.

B. From V.—A solution of 2.7 g of V in 50 ml of acetic acid and 7 ml of concentrated hydrochloric acid was shaken under 1 atm of hydrogen at 25° using 0.2 g of platinum oxide as catalyst. After uptake of 200 ml of hydrogen the mixture was filtered, basified, and extracted with ether. White prisms melting at 89–91° were identified as VI.

(11) 2-Alkyl-substituted 3-phenylphthalimidines show characteristic nmr spectra. The sequence $>NC(H_AH_B)C(H_CH_C)$ gives rise to two multiplets with an intensity ratio of 1:3. This is caused by a large difference (*ca.* 1 ppm) in chemical shifts between H_A and H_B. This unusually large difference for geminal protons has been reported for 2-benzyl-3-phenylphthalimidine ($\Delta\delta$ (H_AH_B) = 1.75 ppm) by A. H. Lewin, J. Lipowitz and T. Cohen, *Tetrahedron Letters*, 1241 (1965).

C. From X.—A solution of 21 g (0.1 mole) of 3-phenylphthalide[12] X and 5 g of pyridine hydrochloride in 67 ml of ethylenediamine was heated at 200° in a steel autoclave for 13 hr. The solution was concentrated *in vacuo* and the residue was dissolved in methylene chloride. The solution was washed with water, dried, and concentrated. The residue crystallized on addition of ether and, after washing with ether, gave 16.5 g (65%) of crude VI melting at 83–90°.

2-(2-Acetamidoethyl)-3-phenylphthalimidine (VII). A. From III.—A solution of 2.5 g of III in 100 ml of acetic acid containing 2.5 g of hydrogen chloride was shaken under 1-atm pressure and 25° in an atmosphere of hydrogen using 0.4 g of platinum oxide as catalyst. The uptake of hydrogen had slowed after 5 hr (total consumption 400 ml, theory 300 ml) and the solution was poured into ice water, basified with sodium hydroxide, and extracted with ether. White prisms melting at 162–164° were obtained after recrystallization from a mixture of methylene chloride and petroleum ether: ν^{CHCl_3} 3450 cm^{-1} (NH); ν^{CHCl_3} 1680, 1535 cm^{-1} (C=O); $\lambda_{max}^{i\text{-PrOH}}$ 245 mμ (ε 5800), 279 mμ (ε 1600).

Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; O, 10.87. Found: C, 73.72; H, 6.17; O, 10.74.

B. From VI.—Compound VI (1 g) was added to 5 ml of acetic anhydride and kept at 25° for 20 hr. The solution was poured into ice water and the crystalline precipitate was collected on a filter. White prisms (VII, 0.7 g) melting at 162–164° were obtained after recrystallization from a mixture of methylene chloride and petroleum ether (bp 30–60°).

2-(2-Aminoethyl)-1-phenylisoindoline (IX). A. From VI.—To a suspension of 7.5 g (0.2 mole) of lithium aluminum hydride in 750 ml of boiling ether was added 8 g (0.032 mole) of VI. After refluxing for 17 hr 38 ml of water was added slowly; the mixture was stirred for 30 min and filtered. The solution was concentrated to a brown oil and dissolved in ethanol, and an ethanolic solution of picric acid was added. Yellow crystals precipitated which were collected on a filter. The base was liberated with sodium hydroxide, extracted into ether and transferred into a bulb tube. Distillation at a bath temperature of 120–130° (0.1 mm) gave 2.5 g (33%) of a colorless oil which crystallized on scratching. White, waxy prisms melting at *ca.* 53° were obtained: $\lambda_{max}^{i\text{-PrOH}}$ 252 mμ (ε 710), 258 (805), 264 (900), 272 (740); nmr ($CDCl_3$) δ 1.07 (singlet, NH_2), 2.68 (multiplet, CH_2CH_2), 3.65 (H_A), 4.40 (H_B), 4.68 (H_C, J_{AB} = 12 cps, J_{AC} = 3 cps, J_{BC} = 2 cps, $Ar_2CH_CNRCH_AH_BAr$),[13] 6.5–7.5 (multiplet, nine aromatic protons).

Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.38; H, 7.86; N, 11.76.

B. From VIII.[14]—To a solution of 127 g (0.59 mole) of VIII in 900 ml of benzene, 80 g of anhydrous magnesium sulfate was added and the mixture was cooled in an ice bath. Hydrogen bromide was bubbled into the stirred solution until saturation (about 30 min). During this time the temperature of the solution was kept at 15–18°. The ice bath was removed and the temperature was allowed to rise to 35° in the course of 1 hr. The mixture was heated for 1 hr longer at 40–45° on a steam bath. During the entire reaction hydrogen bromide was passed into the solution to keep it saturated. The mixture was filtered and the solution was concentrated *in vacuo* to give 178.7 g of a red oil which was dissolved in 200 ml of benzene and added to 342 g (5.7 mole) of ethylenediamine in the course of 15 min. During the addition the mixture was stirred and cooled to maintain a temperature of *ca.* 40°. The mixture was stirred at 25° for 70 min. Two layers were obtained and separated. The benzene layer was washed with water and concentrated *in vacuo*. The residual oil was dissolved in 250 ml of ether. This solution was extracted with two 300-ml portions of cold 1 *N* hydrochloric acid. The acidic aqueous phase was basified with aqueous sodium hydroxide and extracted with 350 ml of ether. The ethereal solution was washed with 250 ml of water, dried, and concentrated. The residue was 75.1 g (53% over-all VIII → IX) of an amber oil which crystallized on scratching.

Dihydrochloride of IX.—The base obtained above was dissolved in methanol and excess ethereal hydrogen chloride was added. The crystalline precipitate was collected and recrystallized from a mixture of methanol, tetrahydrofuran, and ether to give white needles melting at 215–220° dec.

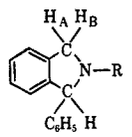
Anal. Calcd for $C_{16}H_{18}N_2 \cdot 2HCl$: Cl, 22.78. Found: Cl, 22.53.

Registry No.—II, 5810-66-2; hydrochloride of II, 5810-67-3; III, 13449-92-8; IV, 13449-93-9; V, 13449-94-0; hydrochloride of V, 3532-79-4; VI, 13449-96-2; VII, 13449-93-3; IX, 13449-98-4; dihydrochloride of IX, 13449-99-5.

Acknowledgment.—We are indebted to Dr. V. Toome, Mr. S. Traiman, and Dr. F. Vane for spectroscopic measurements and interpretation, and to Dr. Al Steyermark and his staff for microanalyses. We wish to thank Professor G. Büchi for valuable discussions.

(12) F. Ullmann, *Ann. Chem.*, **291**, 23 (1896).

(13) The nmr spectra of 2-substituted isoindolines show nonequivalent benzylic protons which are coupled across the five-membered ring. The relative positions of H_A and H_B *vs.* H_C remain undetermined.



(14) W. A. Bonner, *J. Am. Chem. Soc.*, **85**, 439 (1963).