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Development of a Commercially Viable Clonazepam Process

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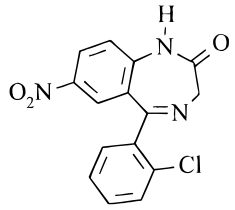
Abstract:

A commercial process to clonazepam (1) is described. An advanced chloro intermediate, 2-(2-chloroacetamido)-5-nitro-2′-chlorobenzophenone (6), is activated to the corresponding iodide 2-(2-iodoacetamido)-5-nitro-2′-chlorobenzophenone (7) via substitution with potassium iodide. Subsequent alkylation of ammonia with 7 yields the open form of clonazepam (8). The intermediate 8 is isolated as the hydrochloride salt 8b, cyclized to 1, and purified to yield United States Pharmacopoeia specification material. Formation of the known impurity 3-amino-4-(2-chlorophenyl)-6-nitro-2(1*H*)-quinolinone (9), as well as of the newly identified dimeric impurity *N*-[2-(2-chlorobenzoyl)-4-nitrophenyl]-2-{[[[2-(2-chlorobenzoyl)-4-nitrophenyl]carbamoyl]methyl]amino}acetamide (10), is minimized. The robust purification scheme readily removes both organic and inorganic impurities. This synergistic combination of pieces of several patented routes results in a process that is more viable than any previously described process.

Clonazepam (5-(2-chlorophenyl)-1,3-dihydro-7-nitro-2*H*-1,4-benzodiazepin-2-one, Clonopin, **1**) is an anticonvulsant of a larger class of antipsychotic compounds known as benzodiazepines.[1] Like many drugs, its patent protection is expiring, opening opportunities for generic firms to market it. There are several stepwise strategies to clonazepam and other benzodiazepines outlined in the literature.[2,3] Individually, none of these syntheses are industrially viable. We have found that, by combining portions of some of these syntheses with incremental process improvements, a robust industrial clonazepam process could be developed.



Clonazepam, 1

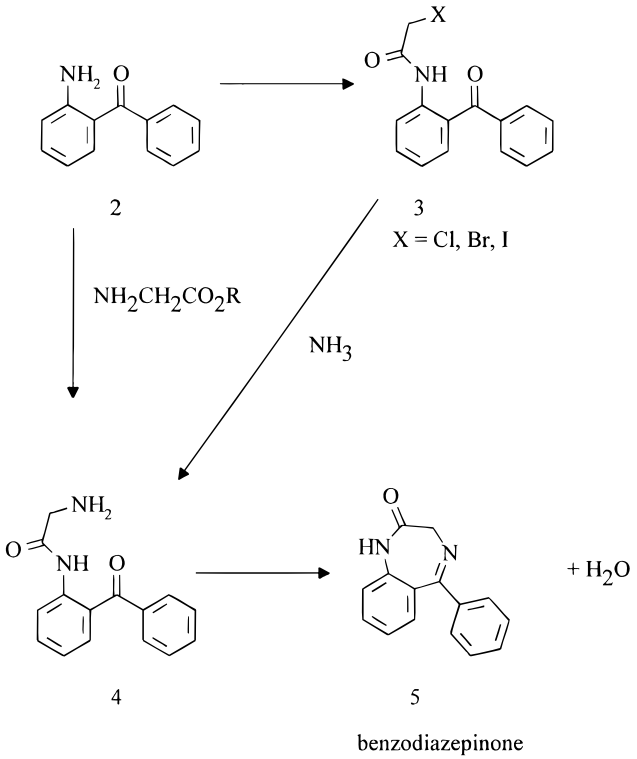


Figure 1. **General synthetic approach to benzodiazepines.**

A key component in synthesizing benzodiazepines is the construction of the benzodiazepinone nucleus. This is generally accomplished by ring closure via an internal imine formation from the corresponding α-(aminoacetamido)-benzophenone (**4**) (see Figure 1).[3c] The differences in benzodiazepine synthetic strategies lie basically on how one approaches the formation of **4**. It can be synthesized either via a stepwise formation of an α-(haloacetamido)benzophenone **3** followed by alkylation of ammonia[2] or by the direct condensation of the α-aminobenzophenone **2** with glycine esters.[3a] Clonazepam has been synthesized using both strategies, although the original synthesis involved the nitration of the parent chlorobenzodiazepine.[3b]

The literature syntheses were not found to be adequate for a scalable industrial process. They are typical laboratory procedures using process unfriendly solvents (benzene, dichloromethane), extractive workups, and tedious isolations. The critical aspect of product purity is not addressed. In effect, the literature clearly showed the necessary chemical steps, but no description of a robust commercial process to a marketable product was evident. The described process for the synthesis of clonazepam fills this void; it is scalable, uses readily available commercial solvents, requires relatively simple equipment, and produces high-quality product. It

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(1) Williams, M.; Holladay, M. W. In *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th ed.; Kroschwitz, J. I., Howe-Grant, M., Eds.; John Wiley and Sons: New York, 1994; Vol. 13, pp 1082−1100. *Pharmaceutical Chemicals in Perspective*; Reuben, B. C., Wittcoff, H. A., Eds.; John Wiley and Sons: New York, 1989. *American Hospital Formulary Service*; McEvoy, G. K., Ed.; American Society of Health-System Pharmacists: Bethesda, MD, 1995; pp 1504−1605. Sternbach, L. H. *J. Med. Chem.* **1979**, *22* (1), 1−7.

(2) Focella, A.; Rachlin, A. I. U.S. Patent 3 335 181, Aug 8, 1967; *Chem. Abstr.* **1968**, *68*, 69056.

(3) (a) Keller, O.; Steiger, N.; Sternbach, L. H. U.S. Patent 3 121 076, Feb 11, 1964; *Chem. Abstr.* **1963**, *58*, 10222d. (b) Sternbach, L. H.; Fryer, R. I.; Keller, O.; Metlesics, W.; Sach, G.; Steiger, N. *J. Med. Chem.* **1963**, *6*, 261−265. (c) Sternbach, L. H.; Fryer, R. I.; Metlesics, W.; Reeder, E.; Sach, G.; Saucy, G.; Stempel, A. *J. Org. Chem.* **1962**, *27*, 3788−3796. (d) Kariss, J.; Newmark, H. L. U.S. Patent 3 123 529, March 3, 1964; *Chem. Abstr.* **1964**, *60*, 12035e.

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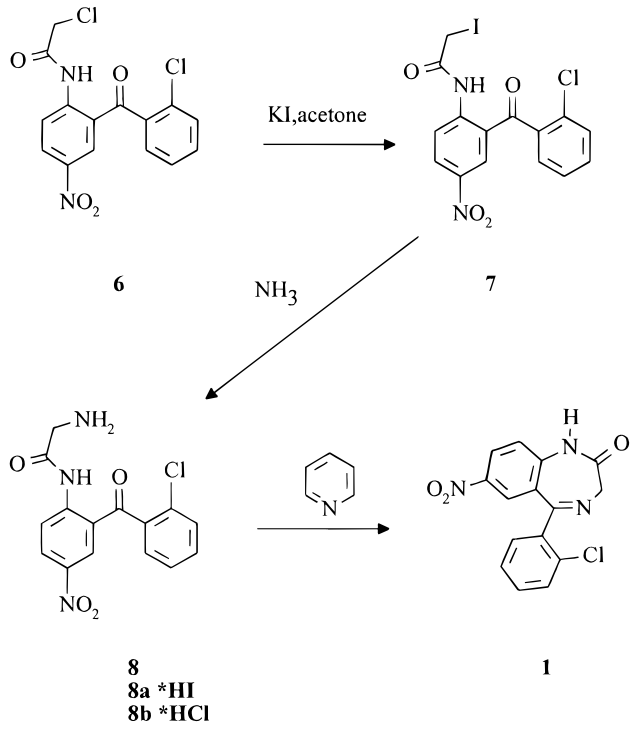
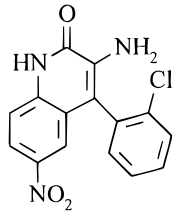


Figure 2. **Synthesis of clonazepam.**

includes, as a key step, the activation of the chloro compound **6** to the corresponding iodide, 2-(2-iodoacetamido)-5-nitro-2′-chlorobenzophenone **7** (see Figure 2). Alkylation of ammonia with (**7**) yields the open form of clonazepam, 2-(2-aminoacetamido)-5-nitro-2′-chlorobenzophenone (**8**). The intermediate **8** is isolated as the amine HCl salt **8b**, cyclized to **1**, and purified to yield USP grade material.

Our goal was to develop a commercially viable process that would yield United States Pharmacopoeia (USP) grade clonazepam within a short development cycle. As part of this strategy an unusually advanced intermediate, 2-(2-chloroacetamido)-5-nitro-2′-chlorobenzophenone (**6**), was located and identified as the starting material for this process. Intermediate **6** is a highly specific and costly intermediate. This high-value starting point weighted economic evaluations of processing steps heavily in favor of processing that would maximize conversion and selectivity. However, due to time constraints, process optimization was stopped when process ecomomics were deemed favorable.

The synthesis of **8** from **6** could be carried out via either of two approaches: direct substitution with ammonia, or an equivalent, or conversion through an additional intermediate. Literature suggests that the conversion of analogous compounds can be carried out in methanolic ammonia, ammonia and methylene chloride, or liquid ammonia.[3c] The bromo analog of **6**, 2-(2-bromoacetamido)-5-nitro-2′-chlorobenzophenone, is described to react with ammonia to yield the hydrobromide salt of **8** in a mixture of methylene chloride and ethyl acetate (EtOAc).[2] Use of halogenated solvents is discouraged due to environmental and industrial hygiene concerns. However, the use of EtOAc looked promising as a starting point for development. Compound **6** was not very reactive under alkylation conditions (ammonia-saturated ethyl acetate at ambient temperature and pressure), and significant side reactions took place, notably formation of carbostyril (3-amino-4-(2-chlorophenyl)-6-nitro-2(1*H*)-quinolinone, **9**), a difficult to remove impurity.[4] This is the impurity recognized in the USP.[5] Addition of KI to accelerate the reaction showed some promise, but carbostyril formation was still a problem. The direct alkylation of ammonia with **6** did not look promising.



Carbostyril, 9

The utility of ammonia equivalents was evaluated as well. The ammonia substitute hexamethylenetetramine (HMTA) yields the corresponding amino compound after hydrolysis of the intermediary HMTA adduct.[6] Synthesis of **1** from a bromo compound using HMTA is known.[3] Unfortunately, HMTA was not reactive enough with **6**, even in the presence of KI, to yield significant amounts of adduct. Further, when some HMTA adduct was formed, the cleavage to **8** or **1** was not clean. Urea, another ammonia equivalent, indicated only a modest conversion of **6** to **1**, with several side products formed. Due to safety considerations and handling issues, substitution with sodium azide as an ammonia equivalent was not considered for the commercial process. In effect, neither HMTA nor urea seemed to offer a clean route to **1** or **8** directly from **6**.

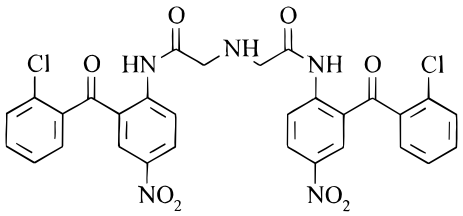
The less direct route was pursued to activate **6** prior to substitution with ammonia. The reaction of corresponding bromo and iodo compounds with ammonia was disclosed,[2,7] with examples of the bromo compound. Transformation of **6** to a bromide analogue by reaction with KBr in acetone went in only 20% yield. Using classical Finkelstein conditions,[3c,8] the conversion of **6** to the iodide **7** went very well, with isolated yields of >90%. Although KI is more expensive than KBr, their respective contribution to the overall cost of producing **1** was insignificant. Further development could have likely improved the bromide substitution reaction, but there was no incentive from a process perspective to do that. In addition, **7** has solubility properties that were readily taken advantage of; it is soluble in hot acetone and almost insoluble in cold. Hence, when the reaction is over, the entire reaction is hot filtered to remove KCl and other insolubles. Upon cooling, **7** precipitates almost quantitatively. The isolation is desirable as it acts as both purification and process simplification. It effectively removes nearly all of the inorganic contaminants without an aqueous workup and eliminates the requisite solvent exchange for the next step. Water was found to have

(4) Bahr, F.; Usbeck, H. *Pharmazie* **1981**, *36* (10), 668−671.
(5) *The United States Pharmacopeia XXII*; United States Pharmacopeial Convention: Rockville, MD, 1990; p 330.
(6) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley-Interscience: New York, 1992; p 413. Blazevic, N.;, Kolbah, D.; Belin, B.; Sunjic, V.; Kajfez, F. *Synthesis* **1979**, 161−176.
(7) Keller, O.; Steiger, N.; Sternbach, L. H. U.S. Patent 3 121 114, Feb 11, 1964; *Chem. Abstr.* **1964**, *61*, 13332b.
(8) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley-Interscience: New York, 1992; pp 430−431.

no effect in this reaction up to concentrations of 1 wt % in the acetone. In fact, the filter cake of **7** was much whiter when water was present, possibly owing to better removal of unreacted KI. However, water has a detrimental effect in the subsequent chemistry and it improves the solubility of KCl. Hence, the reaction of **6** to **7** was carried out under the lowest water conditions possible.

The more reactive **7** is readily converted to the amine **8** via direct alkylation of ammonia in EtOAc. EtOAc is unique as a solvent in that it dissolves enough ammonia to carry out the reaction but not so much as to get side reactions.[2] In ethanol, where ammonia saturates at 10 wt %, alkylation yields primarily the carbostyril **9**. In toluene, where ammonia saturates at approximately 0.6 wt %, the conversion was less than 3% under the same conditions. The reaction is carried out at ambient temperature and pressure; increased temperature promotes the formation of **9**. A small amount of a dimeric impurity (**10**, *N*-[2-(2-chlorobenzoyl)-4-nitrophenyl]-2-{[[[2-(2-chlorobenzoyl)-4-nitrophenyl]carbamoyl]-methyl]amino}acetamide)) arises in this step as well. Presumably it is formed from **8** reacting with **7** under alkaline conditions.[9]

After the alkylation is through, excess ammonia is purged out with a nitrogen subsurface sparge, followed by refluxing under vacuum at approximately 30 °C. The initial product is the hydroiodide salt **8a**, which begins to precipitate at this point. The hydroiodide is not very stable and has a reasonable solubility in cold ethyl acetate. Conversion to the hydrochloride is desirable for both isolation and stability. Addition of hydrogen chloride gas precipitates the hydrochloride salt **8b** in an overall yield of more than 60%. The hydrochloride is stable even as a wet cake for more than 24 h; the hydroiodide wet cake discolors and degrades upon standing. However, the hydrochloride sometimes precipitates as agglomerates or forms a large ball, making it difficult to stir or isolate. A small amount of water improves the solids, making them crystalline and easily filtered. The amount of water needed is sufficient such that concentrated hydrochloric acid can be used as the HCl source. This simplifies the process away from handling anhydrous HCl. Too much water causes aqueous and organic phases to form and drastically reduces the isolated yield of **8b**. Fortunately, the window for water addition is sufficiently wide to make it readily scaled up.



Dimer, **10**

The isolated yield of **8b** is impacted by the chilling time. The crystallization is rather slow, requiring a minimum of 8 h to fully precipitate out the product. The isolation is important as it acts as a purification as well. Simply removing the solvent by distillation or solvent exchange and going directly into the ring closure yields **1** of inferior quality which cannot be sufficiently purified.

Cyclization of the appropriate amines to the corresponding benzodiazepines is described in many places.[2,3,7,10] This cyclization has also been facilitated over activated silica.[11] In our process, the isolated hydrochloride **5** was cyclized by heating in a solution of ethanol and pyridine to give **1**, similar to descriptions in the literature. The same cyclization followed by a recrystallization from a chloroform/EtOH mixture has been described previously.[2] The pyridine in the reaction serves a dual purpose in the cyclization. It scavenges residual HCl that carries through from the previous step and it reacts with liberated HCl that is generated as the cyclization reaction proceeds. Literature suggests that the cyclization reaction can be run neat in pyridine.[3a,7] In our hands cyclization of **8b** in pyridine changes the selectivity of the product to carbostyril **9**. The cyclization reaction requires 3−5 h of reflux under ambient pressure to achieve completion. While **1** is still dissolved in the ethanol pyridine mixture, the solution is carbon treated. After removal of the carbon, the solution is concentrated by distillation of 50% of the solvent.

This concentration step improves the recovery of **1**. The balance between concentrating the solute and losing material to increased solubility in pyridine must be optimized. As ethanol is distilled, the pyridine concentration in the pot residue increases. Higher pyridine concentrations in EtOH result in higher solubility of the clonazepam. The solubility of clonazepam in EtOH at 78 °C is 3%; the addition of pyridine to a concentration of as little as 3% in ethanol increases the solubility of clonazepam to between 5 and 6.5%. Excessive distillation of ethanol results in lower recoveries of the clonazepam.

The bulk of the crystallization occurs during the distillation step. The solution is then cooled to approximately 6 °C to increase recovery and then filtered. The crude clonazepam is then washed with water to displace the mother liquor and to remove potassium and ammonium salts. The crude product is then recrystallized from ethanol. The previously described chloroform/ethanol mixture[2] was found to be unnecessary, and chloroform (chlorinated solvents, *vide supra*) was removed from the crystallization system. The filtered crystals are washed again with water to ensure adequate removal of inorganic salts, followed by ethanol to facilitate drying. Yields from the starting material **6** range from 35 to 43%.

Our goal was to develop a commercially viable process that would yield USP grade clonazepam within the shortest possible development cycle. Using a combination of existing literature steps and process descriptions as a template, an efficient and economical process for clonazepam was devised. The process economics are weighted heavily toward the starting material, driving the process toward maximizing yields; however, development eventually reaches a point of diminishing returns, and a process must be taken to the plant as soon as economics are favorable. In addition, the

(9) Bock, M. G.; DiPardo, R. M.; Evans, B. E.; Rittle, K. E.; Veber, D. F.; Freidinger, R. M.; Hirshfield, J.; Springer, J. P. *J. Org. Chem.* **1987**, *52*, 3232−3239.

(10) Kariss, J., Newmark, H. L. U.S. Patent 3 116 203, Dec 31, 1963; *Chem. Abstr.* **1964**, *60*, 5529a.

(11) Hoffmann-La Roche & Co. GB 1 385 610, Feb 26, 1975; *Chem. Abstr.* **1974**, *80*, 108590.

described process minimizes the levels of both **9**, a compound closely scrutinized by the USP, and the new dimeric impurity **10** to well below the 0.1% levels currently recommended for manufacture of pharmaceuticals.[12]

Experimental Section

2-(2-Chloroacetamido)-5-nitro-2′-chlorobenzophenone (**6**) of ≥96% purity was obtained from Shanghai KJ Corporation (China). All other chemicals were obtained from the usual commercial suppliers. HPLC analyses were done on a Hewlett Packard 1090 chromatograph, using a Phenomenex Ultracarb ODS(20) column (250 × 4.6 mm) and an acetonitrile/water mobile phase. The water component was acidified with H_3PO_4 to a pH of 2.5. The gradient ran from approximately 20% CH_3CN to 80% CH_3CN over 25 min. ^{1}H- and ^{13}C-NMR were run on a Bruker model ARX-400 MHz instrument.

2-(2-Iodoacetamido)-5-Nitro-2′-chlorobenzophenone (7). 2-(2-Chloroacetamido)-5-nitro-2′-chlorobenzophenone (**6**, 1 kg, 2.83 mol) was charged to a jacketed glass reactor equipped with a mechanical stirrer, thermowell, and condenser. Potassium iodide (0.68 kg, 4.1 mol) was charged to the same reactor. The reactor was purged with nitrogen, followed by charging of acetone (11.6 kg). The reaction mixture was brought to reflux for 3 h. The potassium chloride salts were then filtered out while the solution was still above 55 °C. Acetone (1.1 kg), at ambient temperature, was used to wash the salt cake. The acetone filtrates were combined in a simple distillation setup, and the volume of the total solution was reduced 50% by distillation at atmospheric pressure. The pot residue was cooled to 5 °C and held at this temperature for 2 h. The crystals were filtered from the reaction mixture and washed with 6 °C acetone (1.1 kg). Compound **7** was not dried but used immediately in the next process step. A typical isolated yield is 90%. ^{13}C-NMR (100.6 MHz, DMSO-d_6): δ 0.43 (CH_2−I), 122.3, 126.0, 127.0, 127.4, 128.9, 130.3, 130.7 (2), 132.9, 136.1, 142.2, 143.5, 168.7 (amido C═O), 193.8 (C═O). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.98 (s, CH_2−I).

2-(2-Aminoacetamido)-5-nitro-2′-chlorobenzophenone Hydrochloride (8b).[2] Compound **7** from the previous step was charged to a glass reactor equipped with a condenser, mechanical stirrer, thermowell, and gas sparging tube. The outlet of the condenser was connected to a 5% acetic acid (aqueous) scrubber. The reactor was purged with nitrogen followed by charging of ethyl acetate (25 kg). The temperature of the kettle was adjusted to 25 °C, and ammonia gas (0.4−0.5 kg, 25−30 mol) was bubbled through the reactor over a 3.5 h period. The bulk of unreacted ammonia was then displaced from the reaction mixture by bubbling nitrogen through the medium for 1 h. Vacuum, 25 in. gauge, was applied to the kettle for 16 h to flash off the remaining ammonia from the solution. During this degassing, the reaction temperature was maintained at about 30 °C, essentially refluxing the ethyl acetate under vacuum. After the degassing was complete, the reactor was brought to atmospheric pressure, and hydrochloric acid (37%, 0.57 kg, 5.8 mol) was then added to the reaction mixture. The reaction temperature was not allowed to exceed 30 °C during the hydrochloric acid addition step. Water (0.57 kg) was added to the reaction mixture, followed by cooling to 6 °C for 9 h. Compound **8b** was then filtered from the mixture. Ethyl acetate (0.8 kg) that had been cooled to 5 °C was used to wash the intermediate. This wash step was repeated. Compound **8b** was not dried but used immediately in the next process step. Typical isolated yields are 60%, based on the charge of **7**. ^{13}C-NMR (100.6 MHz, DMSO-d_6): δ 41.2 (CH_2−N), 123.3, 126.3, 127.4, 128.1, 128.6, 130.5, 131.4, 133.2, 135.7, 142.1, 142.8, 166.1 (amido C═O), 192.9 (C═O).). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.82 (s, CH_2−N).

Clonazepam (1). The intermediate **8b** from the previous step was charged to a glass reactor equipped with a condenser, mechanical stirrer, and thermowell. The reactor was purged with nitrogen and charged with ethanol (8.9 kg), followed by pyridine (0.33 kg, 4.2 mol). The reaction mixture was heated to reflux and stirred under that condition for 3.5 h. Pulverized activated carbon (0.06 kg) was added and the slurry stirred for an additional 15 min. The carbon was hot filtered while the solution temperature was kept above 58 °C. Ethanol (0.63 kg) was used to wash the carbon cake. The combined filtrates were charged into a simple distillation setup, and ethanol (5.2 kg) was then flashed from the reaction mixture. The pot residue was then cooled to 3 °C and stirred at that temperature for 0.5 h. The crude clonazepam was then filtered and washed with 5 °C ethanol (0.72 kg) followed by water (3.4 kg). The washed cake was then charged to a glass reactor equipped with a condenser, agitator, and thermowell. The vessel was then purged with nitrogen, and ethanol (14.9 kg) was added. The solution was heated to reflux and the crude clonazepam dissolved. The solution was then cooled over a 2 h period to 3 °C. The crystallized suspension was held at 3 °C for 0.5 h and then filtered. The clonazepam cake was washed with water (1.43 kg) followed by 5 °C ethanol (0.6 kg). The crystals were then dried at 50−60 °C *in vacuo* for 6 h to give USP grade clonazepam **1** (359 g, 1.14 mol, 40% yield from **6**). ^{13}C-NMR (100.6 MHz, DMSO-d_6): δ 57.0 (CH_2), 122.1, 124.8, 126.3, 126.9, 127.4, 129.7, 131.4, 131.4, 131.8, 137.9, 141.6, 144.2, 167.8, 169.2. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 4.30 (s, CH_2).

Hydrochloride Salt of *N*-[2-(2-Chlorobenzoyl)-4-nitrophenyl]-2-{[[[2-(2-chlorobenzoyl)-4-nitrophenyl]carbamoyl]methyl]amino}acetamide (10). 2-(2-Aminoacetamido)-5-nitro-2′-chlorobenzophenone hydrochloride (**8b**, 35 g, 95 mmol), chloroform (500 mL), and water (500 mL) were combined, and the pH was adjusted to 11.9 with 40% NaOH. The aqueous layer was separated and washed with chloroform (250 mL). The combined organic layers were dried over K_2CO_3, and the solvent was removed under reduced pressure to yield **8** as a brown solid (28.1 g, 84 mmol).

This solid was combined with toluene (500 mL), $CHCl_3$ (50 mL), aqueous $NaHCO_3$ (saturated, 250 mL), and **7** (17.5 g, 39 mmol). The reaction mixture was brought to reflux overnight. After cooling, the entire reaction mixture was filtered and the solids (mostly **1**) were discarded. The

(12) *Fed. Regist.* **1996**, *61*, 372−376. Department of Health and Human Services, Food and Drug Administration [Docket No. 94D-0325] "International Conference on Harmonization; Guidelines on Impurities in New Drug Substances; Availability".

aqueous layer was separated off and discarded. The toluene layer was washed with water (2 × 200 mL) and dried over K_2CO_3. After the K_2CO_3 was filtered off, HCl(g) was slowly bubbled through the solution until saturation was reached. The solution was sparged with nitrogen for 30 min, cooled in an ice bath, and filtered. After washing with toluene (50 mL), the solids were dried *in vacuo* at 50 °C. The hydrochloride salt of impurity **10** was isolated as a white solid (8.2 g, 12 mmol, 31% yield based on **7**). ^{13}C-NMR (100.6 MHz, DMSO-d_6): δ 48.5 (CH_2−N), 123.5, 126.3, 127.4, 128.2, 128.5, 130.5, 131.1, 131.3, 133.2, 135.8, 142.1, 142.9, 165.4 (amido C═O), 192.9 (C═O).

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Supporting Information Available

^{1}H and ^{13}C NMR spectra and mass spectra of **7** (3 pages). See any current masthead page for ordering and Internet access instructions.

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