The Schmidt reaction of anthraquinones

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Schmidt reaction (sodium azide/sulfuric acid) of 1,5- and of 1,8-dichloroanthraquinones gives, in each case, both of the theoretically possible lactams (2,3,5,6-dibenzoazepin-4,7-diones). Two of the four theoretically possible lactams have been identified from Schmidt reaction of 1- and 2-chloroanthraquinones respectively. Methods used include: (a) preferential hydrolysis of one lactam and identification of the isomeric aminoanthraquinone formed on cyclodehydration of the resulting amino acid; (b) identification of the isomeric aminoanthraquinone(s) formed on direct treatment of a lactam (or mixture of lactams) by sulfuric acid; (c) cleavage by potassium *tert*-butoxide of the amino acid formed by preferential hydrolysis of one lactam and identification of the resulting benzoic acid as its methyl ester.

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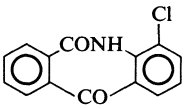
Les dichloro-1,5 et -1,8 anthraquinones soumises à la réaction de Schmidt (azoture de sodium/acide sulfurique) conduisent chacun aux deux lactames qui sont theoriquement possibles (dibenzo-2,3,5,6 azépinediones-4,7). On a identifié deux des quatres lactames pouvant provenir de la reaction de Schmidt sur les chloro-1 et chloro-2 anthraquinones respectivement. Les méthodes utilisées comprennent: (a) l'hydrolyse préférentielle d'un lactame et l'identification de l'aminoanthraquinone isomère formée par la cyclodeshydratation de l'acide amine formé; (b) l'identification des aminoanthraquinones isomères formées par la réaction directe du lactame (ou d'un melange de lactames) avec l'acide sulfurique; (c) l'utilisation du *tert*-butylate de potassium pour cliver l'acide aminé formé par l'hydrolyse préferentielle d'un lactame et l'identification de l'acide benzoique résultant sous forme d'ester méthylique.

[Traduit par le journal]

Substituted 2-aminobenzophenones are of interest as sources of various heterocyclic compounds, including acridones (1, 2). The reports of Caronna and Palazzo that five monosubstituted anthraquinones react with sodium azide in concentrated sulfuric acid (Schmidt reaction) to give in each case a single lactam (2,3,5,6-dibenzoazepin-4,7-dione) are thus of interest since these lactams can be hydrolyzed to the corresponding 2-aminobenzophenone-2′-carboxylic acid (3, 4). Structures were assigned to these lactams and were supported in three cases by hydrolysis and alternate cyclodehydration to the corresponding aminoanthraquinone. In particular, the lactams obtained from 1- and 2-chloroanthraquinones were formulated as **1** and **2** respectively.

Schmidt reaction of a number of alkyl-substituted 1,4-benzo- and naphthoquinones has similarly been reported to give single lactams (5). However, structures were incorrectly assigned and in the course of correction it was noted that lactam mixtures were produced in some reactions (6, 7). It was concluded that these Schmidt reactions proceeded primarily under steric control, with electronic effects exerting a minor influence. Preferential attack occurred at the more hindered, less basic carbonyl group, followed by preferential migration of the larger attached substituent with loss of nitrogen.



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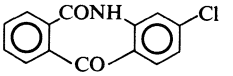

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Our objectives have been to verify, or otherwise, the course of the Schmidt reaction of 1- and 2-chloroanthraquinones, and to extend the study to 1,8- and 1,5-dichloroanthraquinones.

Schmidt reaction of 1-chloroanthraquinone gave a lactam product in high yield. It was, however, immediately apparent from thin-layer chromatography (tlc) and mass spectrometry that this product was a mixture of two or more lactams (four being theoretically possible) with closely related R_f values. It was in fact possible by careful chromatography to separate two lactam fractions which for discussion we designate as lactam **A** (mp 178–180°C) and, in slightly larger quantity, lactam **B** (mp 227–229°C). This separation could, in effect, also be achieved by partial hydrolysis of the crude mixture using 2% ethanolic potassium hydroxide when lactam **A** was preferentially hydrolyzed. The amino acid thus produced (from lactam **A**) was heated with sulfuric acid to effect cyclization to the corresponding anthraquinone (3, 4). This gave a material (ca. 20%) which was separated by chromatography into 1-amino-2-chloroanthraquinone and lactam **A**, alternate products of cyclization of 2-amino-3-chlorobenzophenone-2′-carboxylic acid.

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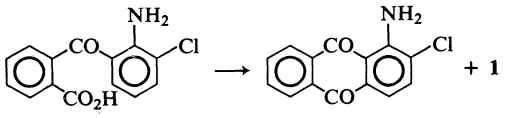
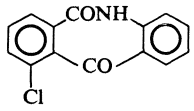


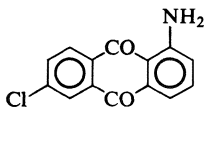
These are evidently derived from **1** as reported previously (4).

Lactam **B** was hydrolyzed using 25% aqueous potassium hydroxide. Cyclization of the resulting amino acid using sulfuric acid gave a material (ca. 30%) which on chromatography gave an aminoanthraquinone fraction and lactam **B**. The former was tentatively identified as (impure) 1,8-aminochloroanthraquinone since a mixture mp with the alternative 1,5-isomer showed depression; tlc and mass spectral characteristics were not sufficiently definitive to corroborate this identification. With this proviso, lactam **B** may be formulated as:



LACTAM B

The case of 2-chloroanthraquinone also presents the possibility of four isomeric lactams being produced, of which **2** is one. Schmidt reaction gave a lactam mixture in good yield. The product showed simply a broad spot on tlc and, while assumed to be a mixture, did not lend itself to chromatographic separation or to attempts at preferential hydrolysis. In an attempt to identify (some of) the lactams present, this mixture was submitted to direct treatment with sulfuric acid (8). This gave a complex mixture (tlc) containing none of the starting lactams. Chromatography gave, in order of elution, compounds **3**, **4**, and **5**, each of which was identified by comparison with authentic samples; recovery was ca. 50%. Compound **5** is evidently an artifact arising from hydrolytic displacement of chlorine either before or after formation of **4**. These compounds would have lactam **6** as precursor and compound **3** would similarly be derived from lactam **7**. Caronna and Palazzo's lactam **2** or the fourth possible isomer may have been present in the crude lactam mixture, but we obtained no evidence on this point.



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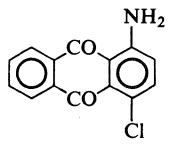

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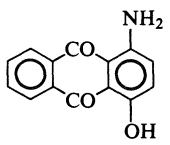

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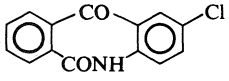

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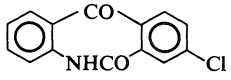

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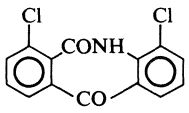
The cases of 1,8- and 1,5-dichloroanthraquinones are in principle more tractable in that each of the quinones can yield at most two lactams. Schmidt reaction of 1,8-dichloroanthraquinone gave a mixture of two isomeric lactams (tlc) in good yield. Partial hydrolysis of this mixture with 2% ethanolic potassium hydroxide gave the (unhydrolyzed) lactam of slightly lower R_f value and, after acidification, an amino acid derived from the other lactam. The lactam mixture was treated directly with sulfuric acid (8) and the product was chromatographed giving 1-amino-2,5-dichloroanthraquinone together with the lactam of lower R_f value. A separate experiment confirmed that the lactam of lower R_f value was only slightly affected under these reaction conditions. The quinone was evidently derived from **8** (lactam of higher R_f) since **9** (lactam of lower R_f) could not give a quinone without substituent displacement. The lactam of lower R_f was hydrolyzed separately using 25% aqueous potassium hydroxide and the resulting amino acid was treated with sulfuric acid. Reversion to the lactam occurred, consistent with its formulation as **9**; interestingly, formation of 3-chlorophthalic anhydride as a minor product was observed. The amino acid from **8**, similarly treated, gave the aforementioned quinone, together with **8** and 3-chlorophthalic anhydride (tlc, mass spectrum).



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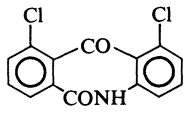

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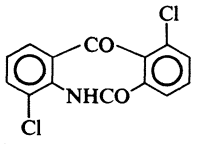
Implicit in methods of identifying these difficultly separable isomeric lactams by direct treatment with sulfuric acid or by preferential hydrolysis to an amino acid followed by treatment with sulfuric acid is the assumption that only direct cyclization to a quinone, where possible, occurs; i.e. there is no electrophilic displacement (or migration) of chlorine, nor do quinones arise by dismutation/recombination reactions. There are additional practical

problems of low yields and the absence of reference quinones for comparison as well as similarities in properties of isomeric quinones. For the Schmidt reaction of 1,5-dichloroanthraquinone, we have therefore developed an alternative approach. This reaction gave a mixture of two isomeric lactams, **10** and **11**, with closely related R_f values. The lactam



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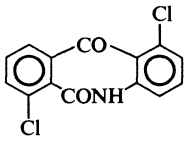

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of higher R_f was preferentially hydrolyzed on treatment of the mixture with 2% ethanolic potassium hydroxide. The amino acid thus obtained is a substituted benzophenone and should thus be amenable to base cleavage to substituted benzoic (or phthalic) acids. Since cleavage of 2-chloro- and 2-carboxybenzophenones has been found to occur mainly on the side of the carbonyl group closer to the substituent (9), examination of cleavage product(s) should permit identification of the amino acid and hence of the precursory lactam. The amino acid in question was successfully cleaved by potassium *tert*-butoxide in 1,2-dimethoxyethane and the acid(s) isolated were converted to the methyl ester(s). Examination of the methyl ester(s) by gas–liquid chromatography (glc), using methyl 2- and 3-chlorobenzoates as standards, revealed the presence of the latter but none of the former ester. This is consistent only with the formulation of the preferentially hydrolyzed lactam as **10** and the other lactam as **11**. This method is reasonably convenient and likely to be useful in cases where the requisite anthraquinones are not available as standards for application of the earlier procedures for assigning lactam structures (3, 4, 8).

The synthetic usefulness of the Schmidt reaction of substituted anthraquinones is thus marred by the production of difficultly separable isomers rather than single lactams as previously reported (3, 4). Isomer production is a feature in common with the Schmidt reaction of some 1,4-benzo- and naphthoquinones (6, 7).

Experimental

The ir spectra are quoted for KBr discs. The ^{1}H nmr spectra were obtained on a Bruker WP-60FT spectrometer (60 MHz; tetramethylsilane as internal standard). Mass spectra were determined with an AEI MS-30 double-beam spectrometer; *m/e* values are reported for the lowest isotopic species (relative intensities in parentheses).

The tlc and plate chromatography were performed on silica gel; glc was carried out on an F and M Laboratory Chromatograph Model 700 using a six-foot column of diethylene glycol succinate on Chromosorb (80–100 mesh); column temperature 150°C, flow rate 40 mL/min.

Purity of all samples was checked before use. Commercial 1-amino-5-chloroanthraquinone was purified by plate chromatography, followed by sublimation, and had mp 221°C (lit. (10) mp 215–217°C); 1-amino-8-chloroanthraquinone was a prepared sample and had mp 225–229°C (lit. (10) mp 225–227°C), but was not quite pure.

Schmidt reaction of 1-chloroanthraquinone

To a stirred solution of the quinone (11.0 g) in concentrated H_2SO_4 (160 mL) was added NaN_3 (9.75 g) in portions so as to maintain a reaction temperature of 40–50°C. Stirring was continued at 40–50°C for 4 h and the mixture was then poured into water to give an off-white solid (10.6 g), mp 185–190°C, consisting apparently of two or more isomeric compounds (tlc, mass spectrum) similar in R_f value.

A sample (1.0 g) of the crude product was chromatographed (silica gel, benzene). Elution gave lactam **A** (i.e. **1**) as a colorless solid (325 mg), mp 178–180°C (after crystallization from aqueous Me_2SO); ir: 3185, 1670 and 1655 cm^{-1}; ^{1}H nmr (Me_2SO-d_6) δ: 10.09–10.04 (br s, 1H, exchangeable with D_2O); mass spectrum *m/e*: 257 (M^+, 75), 256 (M − H, 100), 229 (M − CO, 75), 222(M − Cl, 5), 201 (M − 2CO, 17), 166 (M − 2CO − Cl, 25), 139 (166 − HCN, 15). *Anal.* calcd. for $C_{14}H_8ClNO_2$: C 65.26, H 3.13, Cl 13.76, N 5.44; found: C 64.90, H 3.21, Cl 13.46, N 5.57.

Further elution gave lactam **B** as a colorless solid (500 mg), mp 227–229°C (after crystallization from aqueous Me_2SO); ir: 3180, 1670, and 1655 cm^{-1}; ^{1}H nmr (Me_2SO-d_6) δ: 11.2 (br s, 1H, exchangeable with D_2O); mass spectrum *m/e*: 257 (M^+, 90), 256 (100), 229 (70), 222 (33), 201 (38), 166 (45), 139 (23). *Anal.* calcd. for $C_{14}H_8ClNO_2$: C 65.26, H 3.13, Cl 13.76, N 5.44; found: C 65.21, H 3.14, Cl 13.84, N 5.54.

Hydrolysis of the foregoing lactams

(a) A sample of the crude lactam mixture (5.0 g) from the previous experiment was boiled with 2% ethanolic KOH solution (100 mL) for 15 min. When cool, the solution was filtered and the filtrate was poured into water. The precipitated solid was crystallized from aqueous Me_2SO to give the unhydrolyzed lactam **B** (2.45 g), mp 225–227°C, identical with the reference sample (mixture mp, tlc, ir spectrum).

The ethanolic filtrate from the hydrolysis was carefully acidified (concentrated H_2SO_4). Next day, the precipitated solid was collected and crystallized from aqueous ethanol to give 2-amino-3-chlorobenzophenone-2′-carboxylic acid (1.1 g), mp 180–181°C (lit. (11) mp 188°C); ir: 3465, 3345, 1690, and 1650 cm^{-1}; mass spectrum *m/e*: 275 (M^+). *Anal.* calcd. for $C_{14}H_{10}ClNO_3$: C 60.99, H 3.66, Cl 12.86, N 5.08; found: C 60.94, H 3.67, Cl 12.73, N 5.09.

(b) The lactam **B** (1.3 g, mp 225–227°C) was boiled with 25% aqueous KOH solution (60 mL) for 15 min and the solution was then filtered. When cool, the solution was carefully acidified (concentrated H_2SO_4) and left to stand overnight. The precipitated solid was collected, dried, and crystallized from benzene to give 2-amino-6′-chlorobenzophenone-2′-carboxylic acid (450 mg), mp 152–153°C; ir: 3460, 3345, 1720, and 1690 cm^{-1}; mass spectrum *m/e*: 275 (M^+). *Anal.* calcd. for $C_{14}H_{10}ClNO_3$: C 60.99, H 3.66, Cl 12.86, N 5.08; found: C 60.97, H 3.74, Cl 12.81, N 5.08.

Treatment of the foregoing amino acids with concentrated sulfuric acid

(a) A solution of 2-amino-3-chlorobenzophenone-2′-carboxylic acid (400 mg, mp 181–183°C) in concentrated H_2SO_4 (2.0 g) was slowly heated to 140–145°C and this reaction temperature was maintained for 6 h. When cool, the mixture was poured into ice-cold water. The precipitated solid (75 mg, mp 175–177°C),

which apparently contained two components (tlc), was chromatographed on silica gel using benzene/petroleum ether as eluant. An orange solid (50 mg) was collected which crystallized from benzene/petroleum ether to give orange needles of 1-amino-2-chloroanthraquinone, mp 192–193°C (lit. (4) mp 197–198°C), identical with an authentic sample (mixture mp, tlc, mass spectrum); mass spectrum *m/e*: 257 (M^+).

Further elution (benzene) gave lactam **A** (**1**) (15 mg), mp 175–177°C, after crystallization from aqueous Me_2SO, identical with the reference sample (mixture mp tlc, ir spectrum).

(b) A solution of 2-amino-6′-chlorobenzophenone-2′-carboxylic acid (250 mg, mp 151–153°C) in concentrated H_2SO_4 (3.0 g) was heated slowly to 160–165°C and this temperature was maintained for 7 h. Isolated as in (a) above, the product (70 mg), which apparently contained two components (tlc), was chromatographed on silica gel (benzene/petroleum ether). This gave a brownish red solid (35 mg) which was crystallized twice from benzene to give red needles, mp 212–217°C, slightly contaminated with lactam **B** (mp 227–230°C); a mixture mp with 1,5-aminochloroanthraquinone was 189–210°C.

Further elution (benzene) gave lactam **B** (30 mg), mp 225–227°C after crystallization from aqueous Me_2SO, identical with the reference sample (mixture mp, tlc, ir, and mass spectra).

Schmidt reaction of 2-chloroanthraquinone

2-Chloroanthraquinone (16.5 g) was treated as for the 1-isomer above to give a crude product (14.8 g) consisting of two or more components with almost identical R_f values. The mass spectrum suggested the presence of isomeric lactams (*m/e* 257; M^+). Attempts at chromatographic separation were unsuccessful as were attempts at preferential hydrolysis which gave presumably a mixture of amino acids with similar R_f values.

A sample of the crude lactam mixture (6.0 g) was heated with concentrated H_2SO_4 (90 g) at 160–170°C for 6 h. When cool, the mixture was poured into ice-cold water and the purple solid (1.7 g) was filtered off, and dried.

A sample (900 mg) of the purple solid, shown by tlc to be a complex mixture, was chromatographed on silica gel using benzene/petroleum ether (1:3) as eluant. First eluted was 1-amino-6-chloroanthraquinone **3** (40 mg) as a red solid, mp 206–208°C (from nitrobenzene) (lit. (12) mp 210–211°C), identical with an authentic sample (mixture mp, tlc, mass spectrum); mass spectrum *m/e*: 257 (M^+). Continued elution with benzene/petroleum ether (1:1) gave 1-amino-4-chloroanthraquinone **4** (70 mg), mp 182–184°C (from toluene) (lit. (13) mp 179–180°C), identical with an authentic sample (mixture mp, tlc, mass spectrum); mass spectrum *m/e*: 257 (M^+). Finally, benzene eluted 1-amino-4-hydroxyanthraquinone **5** (315 mg) which crystallized from benzene/petroleum ether as violet needles, mp 210–212°C (lit. (14) mp 215°C), identical with an authentic sample (mixture mp, tlc, mass spectrum); ^1H nmr ($CDCl_3$) δ: 13.55 (s, 1H, -OH); mass spectrum *m/e*: 239 (M^+).

Schmidt reaction of 1,8-dichloroanthraquinone

Treatment of 1,8-dichloroanthraquinone (13.8 g) as above gave an off-white solid (12.9 g), mp 230–233°C, which apparently contained two isomeric lactams, **8** and **9** (tlc).

A sample of the lactam mixture (2.5 g) was heated with concentrated H_2SO_4 (35 g) at 140–145°C for 7 h. A portion (1.0 g) of the resulting brown solid, which was apparently a mixture of two components (tlc), was chromatographed on silica using toluene/petroleum ether (1:1) as eluant to give 1-amino-2,5-dichloroanthraquinone as orange-red needles (100 mg), mp 182–183°C (from toluene); mass spectrum *m/e*: 291 (M^+, 100), 263 (20), 239 (7), 237 (10), 200 (15), 173 (12), 164 (24), 127 (12), and 88 (12). *Anal.* calcd. for $C_{14}H_7Cl_2NO_2$: C 57.73, H 2.40, Cl 24.05, N 4.81; found: C 57.48, H 2.40, Cl 23.84, N 4.70.

Further elution gave lactam **9** (650 mg), mp 306–308°C, identical (mixture mp, ir spectrum, tlc) with the lactam of corresponding mp described below. A sample of this lactam (200 mg), similarly treated with H_2SO_4, was recovered (140 mg) in slightly impure form, a trace of a second compound being indicated by tlc.

Hydrolysis of the foregoing lactams (8 and 9)

(a) The crude lactam mixture (5.8 g) was boiled with 2% ethanolic KOH solution (65 mL) for 15 min, and unhydrolyzed material was collected as before. Crystallization from aqueous Me_2SO gave lactam **9** (2.1 g), mp 306–308°C (homogeneous by tlc). An analytical sample had mp 313–315°C (from ethanol); mass spectrum *m/e*: 291 (M^+, 100), 290 (53), 263 (93), 256 (81), 235 (24), 228 (14), 200 (41), 173 (16), and 164 (43). *Anal.* calcd. for $C_{14}H_7Cl_2NO_2$: C 57.56, H 2.42, N 4.80; found: C 57.51, H 2.47, N 4.83.

The hydrolysis filtrate was carefully acidified (H_2SO_4). Next day, the yellow solid (1.45 g) was collected and crystallized from ethanol to give 2-amino-3,3′-dichlorobenzophenone-2′-carboxylic acid, mp 170–171°C; mass spectrum *m/e*: 309 (M^+). *Anal.* calcd. for $C_{14}H_9Cl_2NO_3$: C 54.22, H 2.92, Cl 22.86, N 4.52; found: C 54.37, H 2.94, Cl 23.09, N 4.45.

(b) Lactam **9** (700 mg, mp 306–308°C) was boiled with 25% aqueous KOH solution (30 mL) for 30 min and the solution was then filtered. When cool, the solution was carefully acidified (H_2SO_4). The gummy solid was collected, dried, and crystallized from benzene to yield yellow flakes of 2-amino-6,6′-dichlorobenzophenone-2′-carboxylic acid (450 mg), mp 179–180°C; mass spectrum *m/e*: 309 (M^+). *Anal.* calcd. for $C_{14}H_9Cl_2NO_3$: C 54.22, H 2.92, Cl 22.86, N 4.52; found: C 54.18, H 2.99, Cl 22.81; N 4.50.

Treatment of the foregoing amino acids with concentrated sulfuric acid

(a) The amino acid (70 mg, mp 170–171°C) derived from **8** was heated in concentrated H_2SO_4 (1.5 g) at 140–145°C for 6 h. This gave a brown solid (40 mg) consisting (tlc and mass spectra) of 1-amino-2,5-dichloroanthraquinone, 3-chlorophthalic anhydride, and lactam **8**.

(b) The amino acid (100 mg, mp 179–180°C) derived from **9** when similarly treated gave a near colourless solid (30 mg), shown (tlc and mass spectra) to consist of 3-chlorophthalic anhydride and lactam **9**. Chromatographic separation followed by sublimation gave the anhydride (6 mg), mp 126–127°C (lit (15) mp 126°C); ir: 1810 and 1750 (C=O) cm^{-1}; mass spectrum *m/e*: 182 (M^+).

Schmidt reaction of 1,5-dichloroanthraquinone

Treatment of 1,5-dichloroanthraquinone (8.5 g) as above gave a creamy-white powder (8.78 g) which apparently contained two isomeric lactams, **10** and **11** (tlc).

The lactam mixture (8.78 g) was boiled with 2% ethanolic KOH solution (100 mL) as before and unhydrolyzed material was filtered off. The filtrate was carefully acidified (H_2SO_4). The resulting gum was extracted with ethanol (35 mL), a small amount of insoluble solid being combined (tlc) with the unhydrolyzed material collected previously. The ethanolic solution was diluted with water and the resulting yellow solid was collected and crystallized from aqueous ethanol to give 2-amino-2′,3-dichlorobenzophenone-6′-carboxylic acid (3.2 g) as yellow spikes, mp 182–184°C; mass spectrum *m/e*: 309 (M^+). *Anal.* calcd. for $C_{14}H_9Cl_2NO_3$: C 54.22, H 2.92, Cl 22.86; found: C 54.13, H 2.96, Cl 23.07.

Crystallization of the unhydrolyzed lactam fraction from ethanol gave **11** (4.2 g) as white prisms, mp 321–322°C; mass spectrum *m/e*: 291 (M^+, 84), 290 (82), 263 (100), 256 (88), 235 (62), 200 (88), 173 (33), and 164 (85). *Anal.* calcd. for $C_{14}H_7Cl_2NO_2$: C 57.56, H 2.42, Cl 24.27; found: C 57.63, H 2.38, Cl 24.05.

Cleavage of 2-amino-2',3-dichlorobenzophenone-6'-carboxylic acid

The amino acid (1.6 g, mp 182–184°C) was added to a mixture made by adding water (0.28 g, 16 mmol) to a rapidly stirred solution of potassium *tert*-butoxide (5.8 g) in 1,2-dimethoxyethane (50 mL) under nitrogen. The mixture was stirred at 20°C for 3 h and then poured into water (250 mL). The solution was washed with ether (washings discarded), acidified (concentrated H_2SO_4), and then extracted with ether (3 × 50 mL). The combined ether extracts were washed with saturated aqueous $KHCO_3$ solution (2 × 50 mL). The bicarbonate washings were carefully acidified (concentrated HCl) and extracted with ether (2 × 50 mL). The ether solution was washed with water, dried (Na_2SO_4), and the solvent evaporated to give a light yellow residue (1.3 g). This mixture was esterified by refluxing in methanol (25 mL) and concentrated H_2SO_4 (2 mL) for 3 h. The mixture was then poured into water and extracted with ether. The ether was washed with saturated aqueous $KHCO_3$ solution (to remove any unreacted acid), then with water, and dried (Na_2SO_4).

The ethereal solution was then concentrated and the residue analyzed by glc. This showed the presence of methyl 3-chlorobenzoate (by comparison with an authentic sample).

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