Cyclization Products Derived from o-Benzoyl Malonanilates[1]

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2'-Benzoyl-2-aminomalonanilates such as **6** were prepared *via* the corresponding carbobenzoxy derivatives **3** or by reduction of the 2-nitro- or 2-isonitrosomalonanilates **16** and **17**. Depending on the substitution pattern, these amines cyclized to the benzodiazepine-3-carboxylates **7** or to the 3-amino-4-hydroxytetrahydroquinoline-2-one-3-carboxylates **5**. The latter derivatives were rearranged to the benzodiazepines **7** as was the aziridine **13**, a possible intermediate in this ring expansion. Reaction of 2'-benzoyl-2-bromomalonanilates **19** with ammonia, instead of leading to the expected amines, yielded the 3,4-epoxycarbostyrils **23** and the 3-phenyloxindoles **22**.

The malonanilates **3** (Scheme I) were prepared by acylating the benzophenones **1** with the monoester of 2-(benzyloxycarbonylamino)malonic acid and phosphorus pentachloride in a two-phase system of methylene chloride and aqueous sodium carbonate. These compounds cyclized with good stereoselectivity to the tetrahydroquinolones **4**[1c] in the presence of triethylamine. Cleavage of the carbobenzoxy group with hydrogen bromide in glacial acetic acid led to the corresponding amines **5** with no change of stereochemistry as indicated by nmr spectroscopy. The configurations assigned to compounds **4** and **5** were based on the following experiments. Acid-catalyzed cyclization of **3d** yielded, in addition to **4d**, the oxazolo derivative **12**, which upon cleavage with hydrogen bromide led to **11**, the diastereoisomer of **5d**. Compound **11**, in turn, reacted smoothly and almost quantitatively with phosgene in pyridine to yield **12**, indicating the cis configuration for the participating hydroxy and amino groups. The reaction of the stereoisomer **5d** with phosgene, under similar conditions, gave a complex mixture, chromatography of which yielded 34% of the oxazolone **9**, the diastereoisomer of **12**, and 25% of compound **10**. The ethyl carbamate was formed during the quenching of the phosgene reaction with ethanol, the carbamoyl chloride corresponding to **10** being most likely the precursor. Further support for the assigned stereochemistry rests on the observation that compound **11**, but not the diastereoisomer **5d**, could be converted to the aziridine **13**. This follows if we assume that the aziridine had formed by a trans elimination[2] from the intermediate bromo amine, which would be expected to result from an SN2 reaction of the cis amino alcohol **11** only.

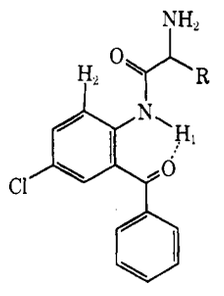
The diastereomeric amino alcohols **5d** and **11** were found to be thermally interconvertible. Refluxing either **5d** or **11** in toluene for 3 hr led to an equilibrium mixture containing the two isomers in a ratio of about 1:1. Treatment of these compounds with strong base, aqueous or anhydrous, yielded 3-aminocarbostyrils. Thus, compound **5d** was converted to the known 3-aminocarbostyril **8**.[3] Under acidic conditions, compounds **5** and **11** rearranged in high yields to the benzodiazepine-3-carboxylates **7**.[4]

This rearrangement was best effected by refluxing compounds **5** in an inert solvent such as toluene in the presence of a weak acid, *e.g.*, acetic acid. The stereoisomers **5d** and **11** showed no noticeable differences in their convertibility to the benzodiazepine **7d**. The aziridine **13** could also be transformed into the benzodiazepine **7d** under similar conditions. The acetyl derivative **14** was a by-product in this reaction, and for comparison it was prepared by acetylation of **13**. This finding suggests that the aziridine **13** is a likely intermediate in the conversion of **5** or **11** to the benzodiazepines. An alternate pathway would be ring opening of **5** or **11** to 2-aminomalonanilates such as **6** and recyclization to the seven-membered ring.

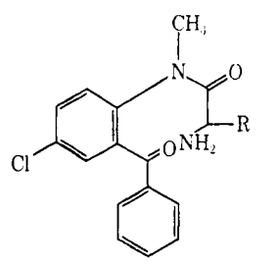
Removal of the protecting carbobenzoxy group from compounds **3** with hydrogen bromide in acetic acid led to the corresponding ammonium salts. The stability of the amines liberated from these salts was dependent on the substitution pattern. Three different cases designated A, B, and C in Scheme I were observed. In case A (R_1 = H; R_2 = Cl), the stable 2-aminomalonanilate **6** was obtained. It was cyclized to the benzodiazepine **7e** by heating in benzene in the presence of acetic acid. If both R_1 and R_2 were protons (case C) the main product was the tetrahydroquinolone **5a**, while, in case B (R_1 = CH_3; R_2 = H), the benzodiazepine **7c** was the major product.

While steric hindrance was most likely responsible for the lack of ring closure in case A, it is not obvious why a proton in place of a methyl group altered the course of cyclization. We suggest that it could be attributed to conformational differences due to hydrogen bonding. The existence of hydrogen bonding in acylated *o*-aminobenzophenones has been pointed out by Derieg and coworkers[5] on the basis of ir data and it is further supported by our nmr data.

Hydrogen bonding of the aniline proton to the car-



I



II

$H_1\delta$ ~11 ppm

$H_2\delta$ ~8.6 ppm

(1) (a) Address correspondence to Hoffmann-La Roche, Inc., Nutley, New Jersey 07110. (b) Presented in part at the Metrochem Meeting, San Juan, Puerto Rico, April 1971, and at the meeting of the Swiss Chemical Society, Lausanne, Switzerland, May 1971; *Chimia*, **25**, 247 (1971). (c) Related tetrahydroquinolones were described by C. Podseva, K. Vagi, and C. Solomon, *Can. J. Chem.*, **46**, 2263 (1968).

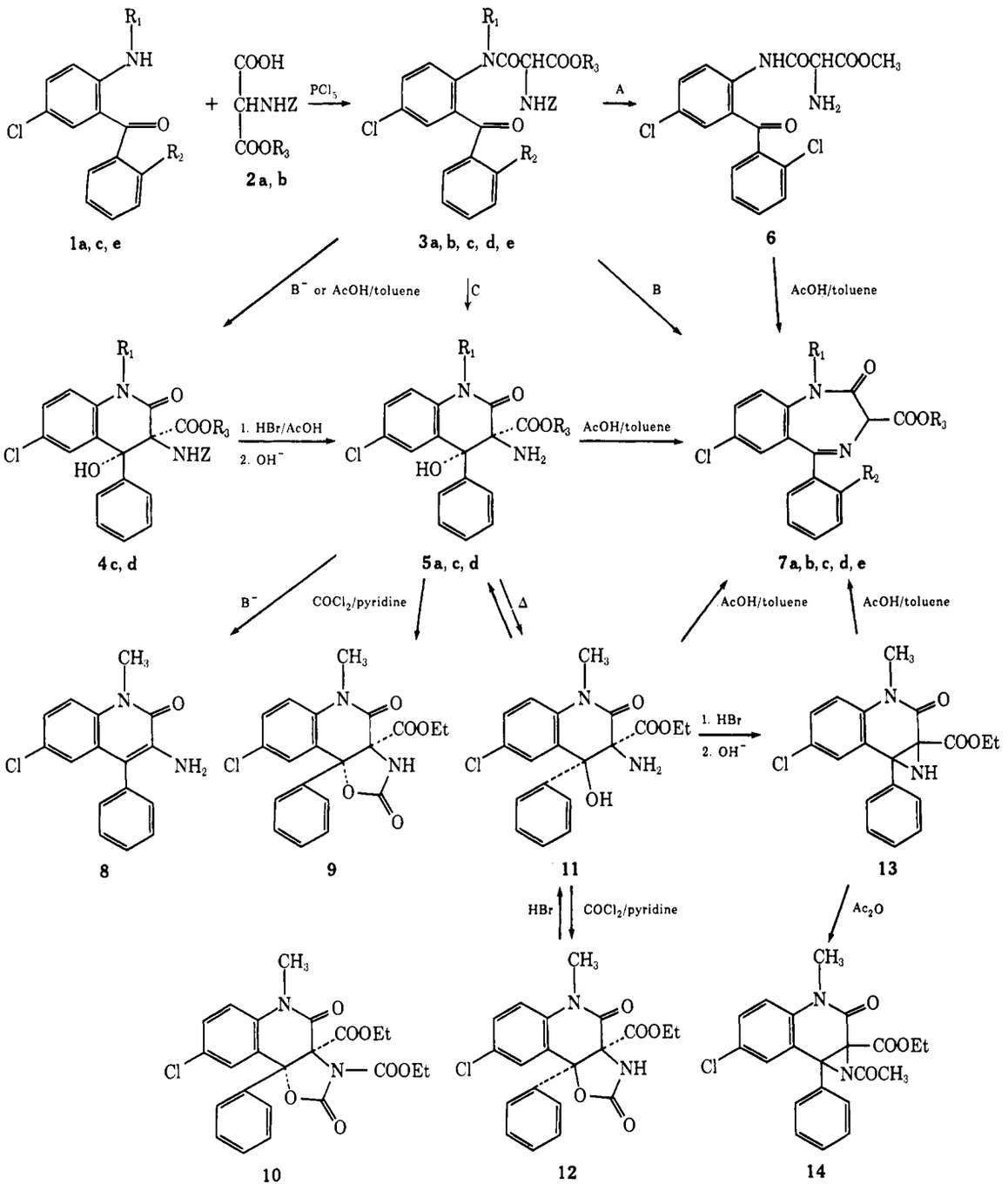
(2) A. Hassner and C. Heathercock, *Tetrahedron*, **20**, 1037 (1964).

(3) R. I. Fryer, B. Brust, and L. H. Sternbach, *J. Chem. Soc.*, 3097 (1964).

(4) (a) J. Schmitt, P. Comoy, M. Suquet, G. Callet, J. LeMeur, and T. Clim, *Chim. Ther.*, **4**, 239 (1969); (b) Etabs. Clin-Byla S. A., French Patent 978,360 (June 15, 1964).

(5) M. E. Derieg, R. M. Schweininger, and R. Ian Fryer, *J. Org. Chem.*, **34**, 179 (1969).

SCHEME I



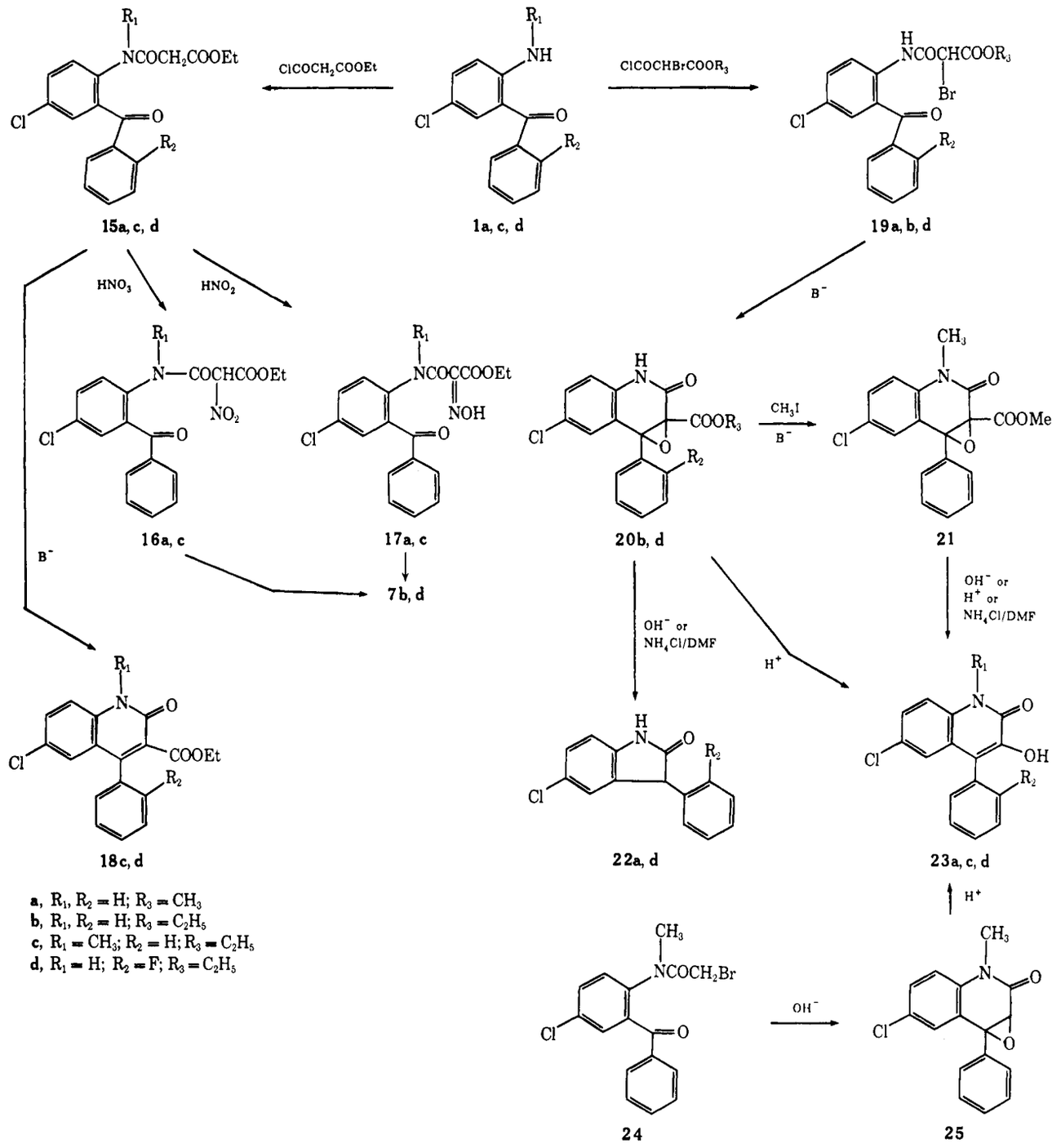
Z = $COOCH_2C_6H_5$
a, R_1 = H; R_2 = H; R_3 = CH_3
b, R_1, R_2 = H; R_3 = C_2H_5
c, R_1 = CH_3; R_2 = H; R_3 = CH_3
d, R_1 = CH_3; R_2 = H; R_3 = C_2H_5
e, R_1 = H; R_2 = Cl; R_3 = CH_3

bonyl oxygen of the benzophenone as illustrated in conformation I is responsible for its large chemical shift. The considerable deshielding of the proton ortho to the acylamino group also lends support for the dominance of conformation I. The N-methylated compounds represented by conformation II lack this deshielding of the ortho proton and often appear as a mixture of two rotamers in the nmr spectra.

Additional evidence for a stable conformation due to hydrogen bonding is the fact that the glycine derivative I (R = H) was obtained in crystalline form,[6] whereas the N-methylated derivative II (R = H) was never isolated; it cyclized spontaneously to the benzodiazepine. The same considerations may be valid for the 2-aminomalonanilates I and II (R = $COOR_3$), where formation of the six-membered ring dominates with compound I while the cyclization to

(6) A. Stempel and F. W. Landgraf, *J. Org. Chem.*, **27**, 4675 (1962).

SCHEME II



a, $R_1, R_2 = H; R_3 = CH_3$
b, $R_1, R_2 = H; R_3 = C_2H_5$
c, $R_1 = CH_3; R_2 = H; R_3 = C_2H_5$
d, $R_1 = H; R_2 = F; R_3 = C_2H_5$

the seven-membered ring is favored with the N-methylated compound II.

1,4-Benzodiazepine-3-carboxylates were also accessible in good overall yield by the sequence of reactions depicted in Scheme II.

Acylation of the aminobenzophenones **1** with malonic ester acid chloride yielded compounds **15**. Alkaline conditions had to be avoided in order to prevent cyclization of the products to the quinolones **18**. The malonanilates were nitrated or nitrosated in acetic acid to give either the nitro derivatives **16** or the oximes **17**. The nitromalonates **16** proved to be rather strong acids which were extractable from ether with sodium bicarbonate solution. Both the nitro derivatives **16** and the oximes **17** were reduced with zinc in acetic acid. The amines obtained in this way were cyclized directly, without isolation, to the benzodiazepines **7** by refluxing in benzene and acetic acid.

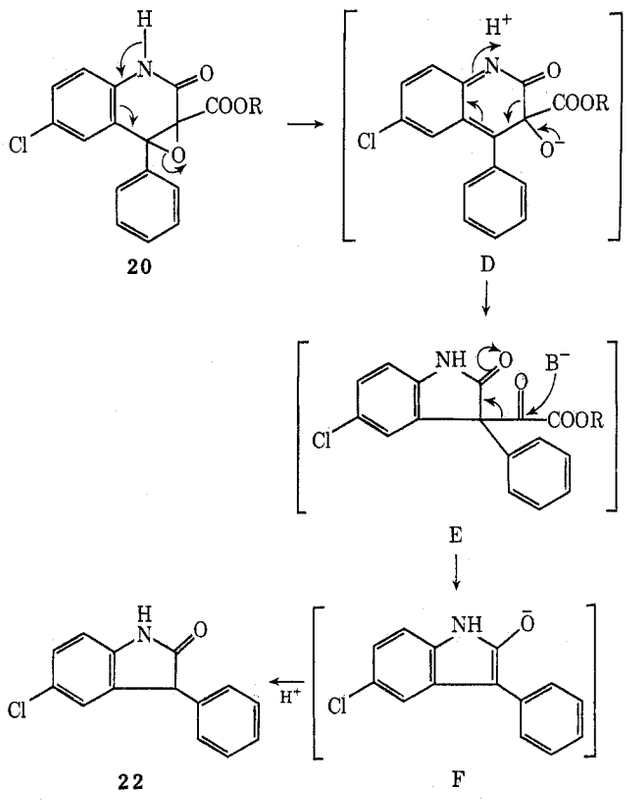
We also attempted the preparation of 1,4-benzodiazepine-3-carboxylates **7** by treating the bromides **19** with ammonia, a standard procedure for the synthesis of benzodiazepines. The bromomalonanilates **19** were obtained by acylation of the aminobenzophenones **1** with bromomalonic ester acid chloride. Displacement of the bromide with ammonia led, however, not to the desired amine, but to the epoxide **20** instead. Ammonia was apparently a strong enough base to generate the carbanion which attacked the

benzophenone carbonyl intramolecularly to form the epoxide *via* the intermediate bromohydrin.

In our search for a way to cleave the epoxide **20**, we heated it with ammonium chloride in dimethylformamide. Under these conditions, an almost quantitative conversion to the oxindole **22** was observed. The oxindole was also formed by treating the epoxide **20** with alkali. Strong acid, on the other hand, converted it to the carbostyril **23a**. When the N-methylated epoxide **21** was subjected to any of these conditions, no oxindole formation could be detected, and only the 3-hydroxycarbostyril **23c** was isolated. This same hydroxycarbostyril could be obtained *via* the epoxide **25** which was prepared in low yield from the bromoacetate **24**.

The interesting change in the path of epoxide cleavage due to the N-methyl group may be explained by the mechanism shown in Scheme III. Base is assumed to abstract the amide proton from compound **20**. Opening of the epoxide by the electron shifts as shown would lead to intermediate D. Reprotonation and ketol rearrangement would result in the ring-contracted β-dicarbonyl compound E. Decarbonylation of this intermediate leads to the enol form F, protonation of which yields the oxindole **22**. With the N-methylated compound **21**, the nucleophile cannot abstract a proton and must attack the carboxyl group. This will result in decarboxylation and conversion of the epoxide to the 3-hydroxycarbostyril **23c**.

SCHEME III



Experimental Section

Melting points were determined in a capillary melting point apparatus. The uv spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer; nmr spectra were recorded with a Varian A-60 or Varian T-60 instrument. Ir spectra were determined on a Beckman IR-9 spectrometer. Silica gel Merck (70–325 mesh) was used for chromatography.

Methyl 2′-Benzoyl-2-(benzyloxycarbonylamino)-4′-chloromalonanilate (3a).—Phosphorus pentachloride (12.5 g, 0.06 mol) was added to a suspension of 16 g (0.06 mol) of methyl 2-(benzyloxycarbonylamino)malonate (**2a**)[7] in 100 ml of methylene chloride cooled to −20°. After the solution was stirred for 30 min at −20 to −10°, 9.3 g (0.04 mol) of 2-amino-5-chlorobenzophenone was added to the solution. The temperature was allowed to reach 5–10°, when 100 ml of 10% aqueous sodium carbonate was added. The two-phase system was stirred vigorously for 30 min. The methylene chloride layer was separated, washed with sodium carbonate solution, dried over sodium sulfate, and evaporated. Crystallization of the residue from methanol yielded 17.5 g (91%) of product, mp 108–111°. The analytical sample was recrystallized from ether–hexane: mp 110–112°; nmr ($CDCl_3$) δ 3.82 (s, 3, OCH_3), 5.08 (d, 1, J = 7 Hz, –CHNH), 5.11 (s, 2, OCH_2), 6.06 (broad d, 1, J = 7 Hz, CHNH), 7.15–8.0 (m, 12, aromatic H), 8.52 (d, 1, J = 9 Hz, C_6, H), 11.25 (broad s, 1, NHCO).

Anal. Calcd for $C_{25}H_{21}ClN_2O_6$: C, 62.44; H, 4.40; N, 5.82. Found: C, 62.42; H, 4.37; N, 5.92.

The following compounds were prepared in the same way. They were not isolated in crystalline form, but used directly in further reactions: ethyl 2′-benzyl-2-(benzyloxycarbonylamino)-4′-chloromalonanilate (**3b**), ethyl 2′-benzoyl-2-(benzyloxycarbonylamino)-4′-chloro-*N*-methylmalonanilate (**3d**), and methyl 2′-benzoyl-2-(benzyloxycarbonylamino)-4′-chloro-*N*-methyl-malonanilate (**3c**).

Methyl 2-(Benzyloxycarbonylamino)-4′-chloro-2′-(2-chlorobenzoyl)malonanilate (3e).—Methyl 2-(benzyloxycarbonylamino)malonate (**2a**) (16 g) was treated as described above with 12.6 g of phosphorus pentachloride and 10.6 g (0.04 mol) of 2-amino-2′,5-dichlorobenzophenone[8] to yield 13.5 g (65%) of product, crystallized from methanol: mp 115–118°; nmr ($CDCl_3$) δ 3.86 (s, 3, OCH_3), 5.15 (s, 2, OCH_2), 5.16 (d, 1, J = 7 Hz, CHNH), 6.11 (broad d, 1, J = 7 Hz, CHNH), 7.1–7.8 (m, 11, aromatic H), 8.66 (d, 1, J = 9 Hz, C_6, H), 12.0 (broad s, 1, NHCO).

Anal. Calcd for $C_{25}H_{20}Cl_2N_2O_6$: C, 58.25; H, 3.91; N, 5.44. Found: C, 58.20; H, 4.00; N, 5.50.

Methyl 3-(Benzyloxycarbonylamino)-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (4c).—5-Chloro-2-methylaminobenzophenone (9.5 g) was acylated as described above with 16 g of methyl 2-(benzyloxycarbonylamino)malonate and 12.6 g of phosphorus pentachloride to yield 23.8 g of methyl 2′-benzoyl-2-(benzyloxycarbonylamino)-4′-chloro-*N*-methylmalonanilate (**3c**) as a light yellow resin which resisted all attempts at crystallization. This material was dissolved in 300 ml of anhydrous methanol containing 1 ml of triethylamine. After the solution was allowed to stand overnight, the crystals which separated were collected and washed with methanol to leave 18.2 g (92%) of product: mp 177–180°; nmr ($CDCl_3$) δ 3.50 (s, 3, NCH_3), 3.60 (s, 3, OCH_3), 5.07 (s, 2, OCH_2), 6.53 (broad s, 1, OH or NHCO), 6.95 (d, 1, J = 9 Hz, C_8 H), 7.05–7.5 (m, 12, 2 C_6H_5, OH, or NHCO, C_7 H), 7.68 (d, 1, J = 2.5 Hz, C_5 H).

Anal. Calcd for $C_{26}H_{23}ClN_2O_6$: C, 63.10; H, 4.68; N, 5.66. Found: C, 63.10; H, 4.68; N, 5.62.

Ethyl 3-(Benzyloxycarbonylamino)-6-chloro-4-hydroxy-1-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (4d). Method A. Base-Catalyzed Cyclization.—An ethanolic solution of crude ethyl 2′-benzoyl-2-(benzyloxycarbonylamino)-4′-chloro-*N*-methylmalonanilate (**3d**), prepared as was the corresponding methyl ester for **4c**, was treated with triethylamine. Crystallization from ethanol yielded the product, mp 165–168°.

Method B. Acid-Catalyzed Cyclization.—Crude ethyl 2′-benzoyl-2-(benzyloxycarbonylamino)-4′-chloro-*N*-methylmalonanilate (**3d**) (23 g) was refluxed for 3 days in a mixture of 200 ml of toluene and 100 ml of acetic acid. The solvents were evaporated under reduced pressure and the residue was partitioned between methylene chloride and 10% aqueous sodium carbonate solution. The organic phase was dried and evaporated. Chro-

(7) Mp 77–79°, prepared according to the procedure described by C. Gansser, *Bull. Soc. Chim. Fr.*, 1713 (1966), for the corresponding ethyl ester **2b**.

(8) L. H. Sternbach, E. Reeder, O. Keller, and W. Metlesics, *J. Org. Chem.*, **26**, 4488 (1961).

matography of the residue on 500 g of silica gel with methylene chloride yielded 13 g (56%) of product, mp 165–168°.

Anal. Calcd for $C_{27}H_{25}ClN_2O_6$: C, 63.72; H, 4.95; N, 6.96. Found: C, 63.56; H, 5.09; N, 7.12.

Methyl 3-Amino-6-chloro-4-hydroxy-2-oxo-4-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (5a).—A mixture of 4.8 g (0.01 mol) of methyl 2′-benzoyl-2-(benzyloxycarbonylamino)-4′-chloromalonanilate, 30 ml of methylene chloride, 30 ml of acetic acid, and 20 ml of acetic acid containing 30% hydrogen bromide was allowed to stand at room temperature for 20 hr. After evaporation under reduced pressure, the residue was dissolved in methylene chloride and the amorphous hydrobromide of methyl 2-amino-2′-benzoyl-4′-chloromalonanilate was precipitated with ether: nmr ($CDCl_3$) δ 3.80 (s, 3, OCH_3), 5.67 (s, 1, CH), 7.2–8.0 (m, 7, aromatic H), 8.33 (d, 1, J = 9 Hz, C_6, H), 8.65 (broad s, 3, NH_3^+), 11.15 (s, 1, NHCO).

The amorphous salt was partitioned between methylene chloride and 10% aqueous sodium carbonate solution. The organic layer was separated, dried, and evaporated. Crystallization of the residue from ether yielded 2.7 g (78%) of product, mp 168–170° after recrystallization from methylene chloride–ether: nmr ($CDCl_3$) δ 2.15 (very broad s, 2, NH_2), 3.55 (s, 3, OCH_3), 5.8 (broad s, 1, OH), 6.73 (d, 1, J = 9 Hz, C_8 H), 6.95 (d, 1, J = 2.5 Hz, C_5 H), 7.3 (q, 1, J_{AB} = 9, J_{AX} = 2.5 Hz, C_7 H), 7.36 (s, 5, C_6H_5), 9.1 (broad s, 1, NHCO).

Anal. Calcd for $C_{17}H_{15}ClN_2O_4$: C, 58.88; H, 4.36; N, 8.08. Found: C, 59.03; H, 4.39; N, 8.00.

Methyl 3-Amino-6-chloro-4-hydroxy-1-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (5c).—A mixture of 10 g of methyl 3-(benzyloxycarbonylamino)-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline-2-one-3-carboxylate (4c), 50 ml of methylene chloride, 50 ml of acetic acid and 40 ml of acetic acid containing 30% hydrogen bromide was allowed to stand at room temperature for 16 hr. The solvents were removed under reduced pressure and the crystalline residue, after being slurried with ether, was collected to yield 8.5 g (96%) of hydrogen bromide salt, mp 143–148° dec. This salt was partitioned between methylene chloride and 10% aqueous sodium carbonate solution and the organic layer was dried and evaporated. The residue was crystallized from ether to yield 6.5 g (89%) of product: mp 125–128°; nmr ($CDCl_3$) δ 2.14 (broad s, 2, NH_2), 3.43 (s, 3, NCH_3), 3.62 (s, 3, OCH_3), 5.08 (s, 1, OH), 7.0 (d, 1 J = 9 Hz, C_8 H), 7.3 (s, 5, C_6H_5), 7.34 (q, 1, J_{AB} = 9, J_{AK} = 2.5 Hz, C_7 H), 7.62 (d, 1, J = 2.5 Hz, C_5 H).

Anal. Calcd for $C_{18}H_{17}ClN_2O_4$: C, 59.92; H, 4.75; N, 7.76. Found: C, 60.11; H, 4.74; N, 7.77.

Ethyl 3-Amino-6-chloro-4-hydroxy-1-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (5d).—Cleavage of ethyl 3-(benzyloxycarbonylamino)-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (4d) with hydrogen bromide as described in the previous experiment yielded the product in 70% yield: mp 98–100° crystallized from ether–hexane; nmr ($CDCl_3$) δ 1.0 (t, 3, J = 7 Hz, CH_3) 2.13 (broad s, 2, NH_2), 3.42 (s, 3, NCH_3), 4.05 (ABX_3 system, 16 lines in 100-MHz spectrum, 2, OCH_2CH_3), 5.10 (s, 1, OH), 6.96 (d, 1, J = 9 Hz, C_8 H), 7.3 (q, 1, J_{AB} = 9, J_{AX} = 2.5 Hz, C_7 H), 7.25 (s, 5, C_6H_5), 7.45 (d, 1, J = 2.5 Hz, C_5 H).

Anal. Calcd for $C_{19}H_{19}ClN_2O_4$: C, 60.88; H, 5.11; N, 7.48. Found: C, 61.30; H, 5.09; N, 7.37.

Ethyl 3-Amino-6-chloro-4-hydroxy-1-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (11). Method A. By Cleavage of Compound 12.—A solution of 3.6 g of ethyl 8-chloro-5-methyl-2,4-dioxo-9b-phenyl-2,3,5,9b-tetrahydrooxazolo[4,5-*c*]-quinoline-3a-carboxylate (12) in 140 ml of glacial acetic acid containing 30% hydrogen bromide and 35 ml of water was allowed to stand at room temperature for 3 days. The mixture was poured into ice and aqueous sodium carbonate solution and the base was extracted with ether. The extracts were washed with water, dried, and evaporated. Chromatography of the residue on silica gel using methylene chloride, followed by crystallization of the clean fractions from ether–petroleum ether (bp 30–60°), yielded 1.3 g (38%) of product: mp 110–112°; nmr ($CDCl_3$) δ 0.98 (t, 3, J = 7 Hz, CH_3), 2.37 (broad s, 2, NH_2), 3.52 (s, 3, NCH_3), 3.96 (q, 2, J = 7 Hz, OCH_2), 5.60 (broad s, 1, OH), 6.98 (d, 1, J = 2.5 Hz, C_5 H), 7.06 (d, 1, J = 9 Hz, C_8 H), 7.35 (s, 5, C_6H_5), 7.36 (q, 1, J_{AB} = 9, J_{AX} = 2.5 Hz, C_7 H).

Anal. Calcd for $C_{19}H_{19}ClN_2O_4$: C, 60.88; H, 5.11; N, 7.48. Found: C, 61.03; H, 5.13; N, 7.35.

Method B. By Thermal Isomerization of 5d.—A solution of 11.5 g of ethyl 3-amino-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (5d) in 200 ml of toluene was refluxed for 3 hr. The solvent was removed under reduced pressure and the residue was chromatographed over 300 g of silica gel using 5% ethyl acetate in methylene chloride. In addition to 5 g of starting material, 4 g (35%) of the isomeric product, mp 110–112°, was obtained.

Methyl 2-Amino-4′-chloro-2′-(2-chlorobenzoyl)malonanilate (6).—A mixture of 5.15 g of methyl 2-(benzyloxycarbonylamino)-4′-chloro-2′-(2-chlorobenzoyl)malonanilate (3e), 30 ml of methylene chloride, 30 ml of glacial acetic acid, and 20 ml of glacial acetic acid containing 30% hydrogen bromide was allowed to stand at room temperature for 4 hr. After evaporation of the solvents under reduced pressure, the residue was partitioned between water and ether. The water phase was washed with ether and was made alkaline with aqueous sodium carbonate solution. The precipitated base was extracted with methylene chloride. The dried extracts were evaporated and the residue was crystallized from ether to yield 2.75 g (72%) of product: mp 106–109°; ir (KBr) 3400, 3340, 3210 (CONH, NH_2), 1740 ($COOCH_3$), 1690 (NHCO), 1650 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.17 (broad s, 2, NH_2), 3.87 (s, 3, OCH_3), 4.47 (s, 1, CH), 7.2–7.8 (m, 6, aromatic H), 8.8 (d, 1, J = 9 Hz, C_6, H), 12.4 (broad s, 1, NHCO).

Anal. Calcd for $C_{17}H_{14}Cl_2N_2O_4$: C, 53.56; H, 3.70; N, 7.35. Found: C, 53.46; H, 3.79; N, 7.31.

Ethyl 8-Chloro-5-methyl-2,4-dioxo-9b-phenyl-2,3,4,9b-tetrahydrooxazolo[4,5-*c*]quinoline-3a-carboxylate (12). Method A.—Crude ethyl 2′-benzoyl-2-(benzoloxycarbonylamino)-4′-chloro-*N*-methylmalonanilate (3d) (23 g) was refluxed for 3 days in 200 ml of toluene and 100 ml of acetic acid. The solvents were evaporated under reduced pressure and the residue was partitioned between methylene chloride and 10% aqueous sodium carbonate solution. The organic phase was dried and evaporated. The residue was chromatographed over 500 g of silica gel using methylene chloride. After elution of 13 g of ethyl 3-(benzyloxycarbonylamino)-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (4d), 6.5 g of 12 was eluted and crystallized from ethanol: mp 218–220°; nmr ($CDCl_3$) δ 0.85 (t, 3, J = 7 Hz, CH_3), 3.53 (2, 3, NCH_3), 3.69 (m, 2, OCH_2), 6.6 (broad s, 1, NH), 7.13 (d, 1, J = 9 Hz, C_6 H), 7.20 (d, 1, J = 2.5 Hz, C_9 H), 7.2–7.6 (m, 6, rest of aromatic protons).

Anal. Calcd for $C_{20}H_{17}ClN_2O_5$: C, 59.93; H, 4.28; Cl, 8.84. Found: C, 59.97; H, 4.43; Cl, 8.68.

Method B.—Ethyl 3-amino-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (11) (0.5 g) was dissolved in 7 ml of pyridine, and 3 ml of a 20% solution of phosgene in chloroform was added with ice cooling. The mixture was allowed to stand at 0° for 2 hr and was then partitioned between methylene chloride and 2 *N* hydrochloric acid. The organic layer was dried, filtered, and evaporated. Crystallization of the residue from ethanol yielded 0.4 g (75%) of product, identical with the material obtained in A.

Ethyl 8-Chloro-5-methyl-2,4-dioxo-9b-phenyl-2,3,5,9b-tetrahydrooxazolo[4,5-*c*]quinoline-3a-carboxylate (9) and Diethyl 8-Chloro-5-methyl-2,4-dioxo-9b-phenyl-2,3,5,9b-tetrahydrooxazolo-[4,5-*c*]quinoline-3,3a-dicarboxylate (10).—A 27% solution of phosgene in chloroform (6 ml) was added to a solution of 3 g of ethyl 3-amino-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (5d) in 30 ml of anhydrous pyridine and 12 ml of chloroform. The mixture was stirred at 0° for 75 min, when ethanol was added and stirring was continued for an additional 15 min. The reaction mixture was partitioned between methylene chloride and 2 *N* hydrochloric acid. The organic layer was washed with 2 *N* hydrochloric acid and water, dried, and evaporated. The residue was chromatographed on 200 g of silica gel using 10% ethyl acetate in methylene chloride. Crystallization from ether yielded 1.1 g (34%) of 9: mp 155–157°; nmr ($CDCl_3$) δ 0.96 (t, 3, J = 7 Hz, CH_3), 3.17 (s, 3, NCH_3), 4.00 (q, 2, J = 7 Hz, OCH_2), 6.72 (s, 1, NH), 6.95 (d, 1, J = 9 Hz, C_6 H), 7.1–7.6 (m, 6, aromatic H), 7.65 (d, 1, J = 2.5 Hz, C_9 H).

Anal. Calcd for $C_{20}H_{17}ClN_2O_5$: C, 59.93; H, 4.28; N, 6.99. Found: C, 59.70; H, 4.27; N, 6.80.

The second product which was eluted was crystallized from ether to yield 0.8 g (25%) of 10, mp 206–208° dec.

Anal. Calcd for $C_{23}H_{21}ClN_2O_7$: C, 58.42; H, 4.48; N, 5.92. Found: C, 58.12; H, 4.44; N, 5.74.

Ethyl 6-Chloro-3-methyl-2-oxo-7b-phenyl-1,2,3,7b-tetrahydro-1a*H*-azirino[2,3-*c*]quinoline-1a-carboxylate (13).—A solution of 16 g of ethyl 3-amino-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**11**) in 120 ml of glacial acetic acid containing 30% of hydrogen bromide was allowed to stand at room temperature for 24 hr. The solvent was evaporated under reduced pressure and the residue was partitioned between methylene chloride and ice-cold sodium carbonate solution. The methylene chloride layer was washed with water, dried, and evaporated. Crystallization of the residue from ether–petroleum ether yielded 11.2 g (73%) of product: mp 188–190°; nmr ($CDCl_3$) δ 0.92 (t, 3, J = 7 Hz, CH_3), 3.52 (s, 3, NCH_3), 3.97 (q, 2, J = 7 Hz, OCH_2), 6.96 (d, 1, J = 2.5 Hz, C_7 H), 7.03 (d, 1, J = 9 Hz, C_4 H), 7.2–7.9 (m, 6, aromatic H), NH very broad between 2 and 3 ppm.

Anal. Calcd for $C_{19}H_{17}ClN_2O_3$: C, 63.96; H, 4.80; N, 7.85. Found: C, 63.43; H, 4.69; N, 7.65.

Ethyl 1-Acetyl-6-chloro-3-methyl-2-oxo-7b-phenyl-1,2,3,7b-tetrahydro-1a*H*-azirino[2,3-*c*]quinoline-1a-carboxylate (14).—One drop of perchloric acid was added to a suspension of 0.1 g of ethyl 6-chloro-3-methyl-7b-phenyl-1,2,3,7b-tetrahydro-1a*H*-azirino[2,3-*c*]quinolin-2-one-1a-carboxylate in 1 ml of acetic anhydride. After stirring for 5 hr at room temperature the reaction mixture was partitioned between ice-cold 10% sodium carbonate solution and methylene chloride. The organic phase was washed, dried, and evaporated. Crystallization from ether yielded 60 mg (54%) of product, mp 228–230°.

Anal. Calcd for $C_{21}H_{19}ClN_2O_4$: C, 63.24; H, 4.80; N, 7.02; Cl, 8.89. Found: C, 63.26; H, 4.85; N, 7.01; Cl, 8.90.

3-Amino-6-chloro-1-methyl-4-phenylcarbostyril (8).[3]—Sodium methoxide (0.3 g, 5.5 mmol) was added to a solution of 1 g (3.7 mmol) of methyl 3-amino-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**5c**) in 20 ml of methanol. The solution was allowed to stand at room temperature for 20 hr. It was then neutralized with acetic acid and partitioned between methylene chloride and aqueous sodium carbonate solution. The organic phase was separated, dried, and evaporated. Crystallization from ether yielded 0.65 g (85%) of product, mp 130–133°.

Methyl 7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one-3-carboxylate (7a).[4]—A mixture of 1 g of methyl 3-amino-6-chloro-4-hydroxy-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**5a**), 20 ml of benzene, and 2 ml of acetic acid was refluxed for 4 hr. The solvents were evaporated and the residue was crystallized from methylene chloride–methanol to yield 0.72 g (76%) of product, mp 217–219°.

Ethyl 7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one-3-carboxylate (7b).[4] **Method A.**—Zinc dust (2 g) was added to a solution of 2 g of ethyl 2′-benzoyl-4′-chloromesoxalanilate-2-oxime (**17a**) in 40 ml of methylene chloride and, within 5 min, 4 ml of acetic acid was added dropwise with stirring. The mixture was stirred for 1 hr at room temperature and then filtered. The filtrate was evaporated, dissolved in 20 ml of benzene and 2 ml of acetic acid, and refluxed for 2 hr. The solution was extracted with 10% sodium carbonate solution, dried, and evaporated. Crystallization of the residue from ethanol yielded 1.1 g (60%) of product, mp 232–234°.

Method B.—Fuming nitric acid (98%) (30 ml) was added to a solution of 34.6 g of ethyl 2′-benzoyl 4′-chloromalonanilate (**15a**) in 250 ml of acetic acid. After sitting at room temperature for 2.5 hr, the mixture was diluted with 1 l. of water. The precipitated resin was collected, washed with water, and dissolved in ether. The ether phase was extracted several times with saturated sodium bicarbonate solution. The extracts were washed with ether and acidified with hydrochloric acid. The precipitated product was extracted with methylene chloride. The extracts were dried over sodium sulfate and evaporated to leave 26.5 g (68%) of ethyl 2′-benzoyl-4′-chloro-2-nitromalonanilate (**16a**) as a yellow resin. A solution of 2 g of this product in 50 ml of methylene chloride was treated with 2 ml of acetic acid and 2 g of zinc dust. After a vigorous reaction, the mixture was stirred for an additional 10 min and filtered. The filtrate was evaporated, dissolved in 70 ml benzene and 2 ml of acetic acid, and refluxed for 2 hr. The mixture was washed with saturated sodium bicarbonate solution, dried over sodium sulfate, and evaporated. Crystallization of the residue from ethanol yielded 0.8 g (45%) of product, mp 228–230°.

Methyl 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one-3-carboxylate (7c). Method A.—A mixture of 0.5 g of methyl 3-amino-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**5c**), 20 ml of benzene, and 2 ml of acetic acid was refluxed for 3 hr. The residue, obtained upon evaporation to dryness, was recrystallized from methylene chloride–methanol to yield 0.43 g (91%) of product, mp 224–226°.

Anal. Calcd for $C_{18}H_{15}ClN_2O_3$: C, 63.07; H, 4.41; N, 8.17. Found: C, 63.25; H, 4.49; N, 8.05.

Method B.—Glacial acetic acid (40 ml) containing 30% of hydrogen bromide was added to a solution of 5 g of crude methyl 2′-benzoyl-2-(benzyloxycarbonylamino)-4′-chloro-*N*-methylmalonanilate (**3c**). After standing at room temperature for 4 hr, the solvent was removed under reduced pressure and the residue was partitioned between methylene chloride and 10% aqueous sodium carbonate solution. The organic layer was dried and evaporated. Crystallization of the residue from methylene chloride–methanol yielded 2.7 g (77%) of product, mp 224–226°.

Ethyl 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one-3-carboxylate (7d).[4] **Method A.**—A mixture of 3.74 g of ethyl 3-amino-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**5d**), 50 ml of toluene, and 5 ml of acetic acid was refluxed for 2 hr. The usual work-up and crystallization from ethanol yielded 2.6 g (73%) of product **7d**, mp 196–199°.

Method B.—Ethyl 3-amino-6-chloro-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**11**) (2 g) yielded, under the same conditions, 1.6 g (84%) of product **7d**.

Method C.—A mixture of 0.4 g of ethyl 6-chloro-3-methyl-7b-phenyl-1,2,3,7b-tetrahydro-1a*H*-azirino[2,3-*c*]quinazolin-2-one-1a-carboxylate (**13**), 20 ml of toluene, and 5 ml of acetic acid was refluxed for 5 hr. The residue obtained after the usual work-up was chromatographed over 20 g of silica gel using 10% ethyl acetate in methylene chloride. After elution of 0.1 g (22%) of ethyl 1-acetyl-6-chloro-3-methyl-7b-phenyl-1,2,3,7b-tetrahydro-1a*H*-azirino[2,3-*c*]quinolin-2-one-1a-carboxylate (**14**), 0.2 g (50%) of **7d**, mp 196–199°, was obtained.

Method D.—Zinc dust (2 g) was added to a solution of 2 g of ethyl 2′-benzoyl-4′-chloro-*N*-methylmesoxalanilate 2-oxime (**17c**) in 40 ml of methylene chloride, and 4 ml of acetic acid was added dropwise with stirring within 5 min. After the addition, stirring was continued for 20 min. The filtered reaction mixture was evaporated and the residue was refluxed for 2 hr in 20 ml of benzene and 2 ml of acetic acid. The solution was washed with 10% aqueous sodium carbonate, dried over sodium sulfate, and evaporated. Crystallization of the residue from ethanol–ether yielded 0.5 g (27%) of **7d**, mp 196–199°.

Method E.—Fuming nitric acid (98%) (30 ml) was added to a solution of 36 g of ethyl 2′-benzoyl-4′-chloro-*N*-methylmalonanilate (**15c**) in 250 ml of acetic acid. After standing for 2 hr at room temperature, the mixture was poured into 1 l. of water. The precipitated resin was collected, washed with water, and dissolved in benzene. The benzene solution was washed with water, dried, and evaporated to leave 34.5 g (85%) of crude ethyl 2′-benzoyl-4′-chloro-2-nitro-*N*-methylmalonanilate (**16c**), which was reduced as follows. To a solution of 2 g of the crude **16c** in 50 ml of methylene chloride and 2 ml of acetic acid, 2 g of zinc dust was added with stirring. After the exothermic reaction, stirring was continued for an additional 10 min. The residue obtained after filtration and evaporation of the reaction mixture was partitioned between benzene and 2 *N* hydrochloric acid. The benzene layer was extracted twice with 2 *N* hydrochloric acid. The extracts were combined, washed with ether, and made alkaline by addition of 10% aqueous sodium carbonate solution. The precipitated base was extracted with methylene chloride and the extracts were dried and evaporated. The residue was refluxed in 20 ml of benzene containing 2 ml of acetic acid for 2 hr. The cold mixture was washed with 10% aqueous sodium carbonate, dried, and evaporated. The residue was crystallized from ethanol to yield 0.5 g (48% overall) of **7d**, mp 196–199°.

Methyl 7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one-3-carboxylate (7e).—A mixture of 0.5 g of methyl 2-amino-2′-(2-chlorobenzoyl)-4′-chloromalonanilate (**6**), 20 ml of benzene, and 2 ml of acetic acid was refluxed for 3 hr. After evaporation, the residue was crystallized from methanol–ether to yield 0.33 g (70%) of product: mp 216–219°; nmr ($CDCl_3$) δ 3.94 (s, 3, OCH_3), 4.72 (s, 1, CH), 7.0–7.8 (m, 7, aromatic H), 9.55 (broad s, 1, NHCO).

Anal. Calcd for $C_{17}H_{12}Cl_2N_2O_3$: C, 56.22; H, 3.33; N, 7.71. Found: C, 56.02; H, 3.18; N, 7.73.

Ethyl 2′-Benzoyl-4′-chloromalonanilate (15a).—A solution of 23 g (0.1 mol) of 2-amino-5-chlorobenzophenone in 200 ml of methylene chloride was overlaid with 100 ml of saturated sodium bicarbonate solution. At 0–5°, 19.3 g (0.115 mol) of 2-carboethoxyacetyl chloride was added dropwise with vigorous stirring. After complete addition, stirring was continued for 10 min. The methylene chloride solution was separated, washed with bicarbonate solution, dried, and evaporated. The residue was crystallized from ether–hexane by cooling to −10° to yield 22 g (64%): mp 54–55°; nmr ($CDCl_3$) δ 1.30 (t, 3, J = 7 Hz, CH_2CH_3), 3.50 (s, 2, CH_2), 4.28 (q, 2, J = 7 Hz, OCH_2CH_3), 7.2–8.0 (m, 7, aromatic H), 8.55 (d, 1, J = 9 Hz, C_6 H), 11.04 (broad s, 1, NHCO); ir (KBr) 3260 (NH), 1720 (COOEt), 1690 (NHCO), and 1650 cm^{-1} (C=O).

Anal. Calcd for $C_{18}H_{16}ClNO_4$: C, 62.52; H, 4.66; N, 4.05. Found: C, 62.37; H, 4.62; N, 3.77.

Ethyl 2′-Benzoyl-4′-chloro-*N*-methylmalonanilate (15c).—2-Carboethoxyacetyl chloride (39.2 g, 0.235 mol) was added to a solution of 49.2 g (0.2 mol) of 5-chloro-2-methylaminobenzophenone in 400 ml of methylene chloride cooled to 0°. After 20 min, 400 ml of saturated sodium bicarbonate solution was added within 15 min at 0–5° with vigorous stirring. The organic layer was separated, dried, and evaporated. Crystallization of the residue from ether–hexane yielded 64.3 g (89.5%) of colorless crystals: mp 98–100°; ir (KBr) 1745 (COOEt), 1680 (NHCO), and 1660 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.22 (t, 3, J = 7 Hz, CH_2CH_3), 3.05 and 3.30 (s, 3, NCH_3), rotamers), 3.24 (s, 2, CH_2), 4.11 and 4.13 (q, 2, OCH_2CH_3, rotamers), 7.2–8.0 (m, 8, aromatic protons).

Anal. Calcd for $C_{19}H_{18}ClNO_4$: C, 63.43; H, 5.04; N, 3.89. Found: C, 63.18; H, 5.00; N, 3.84.

Ethyl 4′-chloro-2′-(2-fluorobenzoyl)malonanilate (15d) was obtained as above by treating 25 g (0.1 mol) of 2-amino-5-chloro-2′-fluorobenzophenone[9] with 18 g (1.2 mol) of 2-carboethoxyacetyl chloride. The product was crystallized from ether–hexane: mp 74–77°; ir ($CHCl_3$) 3300, 1745, 1700, 1655 cm^{-1}.

Anal. Calcd for $C_{18}H_{15}ClFNO_4$: C, 59.43; H, 4.16; N, 3.85. Found: C, 59.36; H, 4.02; N, 4.00.

Ethyl 6-Chloro-1,2-dihydro-4-(2-fluorophenyl)quinolin-2-one-3-carboxylate (18d).—Potassium *tert*-butoxide (1 g, 9 mmol) was added to a solution of 18.2 g (0.05 mol) of ethyl 4′-chloro-2′-(2-fluorobenzoyl)malonanilate in 200 ml of ethanol. After stirring at room temperature for 2 hr, the mixture was diluted with water. The precipitated product was filtered and recrystallized from ethanol–methylene chloride to yield 12.1 g (70%) of product: mp 245–247°; uv (2-PrOH) λ_{max} 237–238 mμ (ε 44,300), 271–272 (7120), sh 280 (6650), infl 533 (4700), 337–338 (6280), infl 360 (5350); ir ($CHCl_3$) 1735, 1660 cm^{-1}.

Anal. Calcd for $C_{18}H_{13}ClFNO_3$: C, 62.53; H, 3.79; N, 4.05. Found: C, 62.26; N, 3.83; N, 3.98.

Ethyl 6-Chloro-1,2-dihydro-1-methyl-4-phenylquinolin-2-one-3-carboxylate (18c).—By the same procedure a mixture of 18 g (0.05 mol) of ethyl 2′-benzoyl-4′-chloro-*N*-methylmalonanilate, 200 ml of ethanol, and 1 g of potassium *tert*-butoxide gave 15.3 g of **18c**: mp 127–128°; nmr ($CDCl_3$) δ 0.97 (t, 3, J = 7 Hz, CH_3), 3.75 (s, 3, NCH_3), 4.05 (q, 2, J = 7 Hz, OCH_2), 7.1–7.7 (m, 8, aromatic H).

Anal. Calcd for $C_{19}H_{16}ClNO_3$: C, 66.77; H, 4.72; N, 4.10. Found: C, 66.60; H, 4.40; N, 4.03.

Ethyl 2′-Benzoyl-4′-chloromesoxalanilate 2-Oxime (17a).—A solution of 50 g of sodium nitrite in 100 ml of water was added dropwise to a solution of 34.6 g (0.1 mol) of ethyl 2′-benzoyl-4′-chloromalonanilate (**15a**) in 250 ml of acetic acid. The mixture was stirred for 90 min at room temperature. The precipitated crystals were separated, washed with water, and dried *in vacuo* to leave 33 g of product, mp 98–105°. The filtrate was diluted with water to yield a second crop, 3.5 g (total yield 97%).

The product was a mixture of two isomeric oximes which could be separated by chromatography on silica gel using 20% ethyl acetate in methylene chloride. The isomer eluted first crystallized from ethanol: mp 115–117°; ir (KBr) 3450, 3150, 1720, and 1650 cm^{-1}; nmr ($CDCl_3$) δ 1.35 (t, 3, J = 7 Hz, CH_3), 4.42 (q, 2, J = 7 Hz, OCH_2), 7.2–7.9 (m, 7, aromatic H), 8.64 (d, 1, J = 9 Hz, C_6 H), 10.4 (s, 1, OH), 11.55 (broad s, 1, NHCO).

Anal. Calcd for $C_{18}H_{15}ClN_2O_3$: C, 57.69; H, 4.03; N, 7.47; Cl, 9.46. Found: C, 57.68; H, 3.91; N, 7.51; Cl, 9.51.

(9) L. H. Sternbach, R. I. Fryer, W. Metlesics, G. Sach, and A. Stempel, *J. Org. Chem.*, **27**, 3781 (1962).

The second isomer eluted had mp 131–132°; nmr ($CDCl_3$) δ 1.40 (t, 3, J = 7 Hz, CH_3), 4.46 (q, 2, J = 7 Hz, OCH_2), 7.4–8.0 (m, 7, aromatic H), 8.38 (d, 1, J = 9 Hz, C_6, H), 12.0 (broad s, NH or OH), 16.2 (broad s, 1, NH or OH).

Ethyl 2′-Benzoyl-4′-chloro-*N*-methylmesoxalanilate 2-Oxime (17c).—A solution of 25 g of sodium nitrite in 50 ml of water was added to a solution of 18 g (0.05 mol) of ethyl 2′-benzoyl-4′-chloro-*N*-methylmalonanilate (**15c**) in 125 ml of acetic acid. Concentrated sulfuric acid (10 ml) was added dropwise to the stirred solution and after stirring for 2 hr at room temperature, the product was precipitated by addition of water to yield 7 g (36%) of crystalline oxime, mp 196–198°. The analytical sample was recrystallized from benzene–ethyl acetate: mp 203–205°; mixture of two isomers in solution; nmr (DMSO) δ 1.12 and 1.15 (t, 3, CH_3), 3.14 and 3.20 (s, 3, NCH_3), 3.86 and 4.13 (q, 2, J = 7 Hz, OCH_2), 7.3–8.0 (m, 8, aromatic H), 12.9 (s, 1, OH).

Anal. Calcd for $C_{19}H_{17}ClN_2O_5$: C, 58.70; H, 4.41; N, 7.21; Cl, 9.12. Found: C, 58.33; H, 4.31; N, 7.09; Cl, 9.46.

Ethyl 2-Bromo-4′-chloro-2′-(2-fluorobenzoyl)malonanilate (19d).—2-Bromo-2-carboethoxyacetyl chloride[10] (25 g, 0.11 mol) was added to a solution of 25 g (0.1 mol) of 2-amino-5-chloro-2′-fluorobenzophenone in 200 ml of methylene chloride. After stirring at room temperature, the mixture was poured into 200 ml of saturated sodium bicarbonate solution. The methylene chloride layer was washed with water, dried, and evaporated. Crystallization of the residue from ethanol yielded 31 g (70%) of product: mp 81–83°; ir ($CHCl_3$) 3250, 1750, 1690, 1650 cm^{-1}.

Anal. Calcd for $C_{18}H_{14}BrClFNO_4$: C, 48.83; H, 3.19; N, 3.16. Found: C, 48.90; H, 3.19; N, 3.06.

Methyl 2′-Benzoyl-2-bromo-4′-chloromalonanilate (19a).—In the same way, reaction of 24 g (0.11 mol) of 2-bromo-2-carbomethoxyacetyl chloride with 23 g (0.1 mol) of 2-amino-5-chlorobenzophenone yielded 29 g (71%) of product, mp 92–93°, crystallized from methylene chloride–hexane: nmr ($CDCl_3$) δ 3.86 (s, 3, OCH_3), 4.90 (s, 1, CH), 7.3–8.0 (m, 7, aromatic H), 8.55 (d, 1, J = 9 Hz, C_6, H), 11.5 (broad s, 1, NHCO).

Anal. Calcd for $C_{17}H_{13}BrClNO_4$: N, 3.41; Br, 19.46; Cl, 8.63. Found: N, 3.57; Br, 19.83; Cl, 8.80.

Methyl 6-Chloro-3,4-epoxy-1,2,3,4-tetrahydro-4-phenylquinolin-2-one-3-carboxylate (20a).—A solution of 4.1 g of methyl 2′-benzoyl-2-bromo-4′-chloromalonanilate (**19a**) in 20 ml of methylene chloride was added to 20 ml of liquid ammonia. After the addition, the reaction mixture was allowed to warm gradually to room temperature, while being stirred for 1 hr. The methylene chloride solution was washed with water, dried, and evaporated. The residue was crystallized from methylene chloride–hexane to yield 3 g (91%): nmr δ 3.54 (s, 3, OCH_3), 7.04 (d, 1, J = 9 Hz, C_8 H), 7.07 (d, 1, J = 2.5 Hz, C_5 H), 7.2–7.9 (m, 6, aromatic H), 10.3 (broad s, 1 NH).

Anal. Calcd for $C_{17}H_{12}ClNO_4$: C, 61.92; H, 3.67; H, 4.25. Found: C, 62.07; H, 3.63; N, 4.25.

Ethyl 6-chloro-3,4-epoxy-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (20b) was obtained in the same manner by causing crude ethyl 2′-benzoyl-2-bromo-4′-chloromalonanilate (**19b**) to react with liquid ammonia: mp 192–193°; ir (KBr) 3210, 1770, 1750, and 1690 cm^{-1}.

Anal. Calcd for $C_{18}H_{14}ClNO_4$: C, 62.89; H, 4.11; N, 4.07. Found: C, 62.77; H, 4.00; N, 4.09.

Ethyl 6-Chloro-3,4-epoxy-4-(2-fluorophenyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (20d).—A solution (50 ml) of 2.3 g of sodium in 100 ml of ethanol was added to a solution of 22 g (0.05 mol) of ethyl 2-bromo-4′-chloro-2′-(2-fluorobenzoyl)-malonanilate (**19d**) in 200 ml of benzene. The mixture was stirred for 10 min, neutralized with acetic acid, and washed with water. The benzene layer was separated, dried, and evaporated. Crystallization of the residue from ether yielded 14 g (78%) of product: mp 223–226° after recrystallization from ethanol; ir ($CHCl_3$) 3375, 3250, 1750, and 1695 cm^{-1}.

Anal. Calcd for $C_{18}H_{13}ClFNO_4$: C, 59.76; H, 3.62; N, 3.87. Found: C, 59.80; H, 3.42; N, 3.88.

Methyl 6-Chloro-3,4-epoxy-1-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (21).—Potassium *tert*-butoxide (2.7 g, 0.024 mol) was added to a solution of 6.6 g (0.02 mol) of methyl 6-chloro-3,4-epoxy-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**20a**) in 50 ml of dimethylformamide cooled to −10°. After stirring for 5 min, 3.4 g (0.024 mol) of methyl

(10) H. Staudinger and H. Becker, *Ber.*, **50**, 1016 (1917).

iodide was added and the reaction mixture was allowed to reach room temperature. The product was precipitated by pouring into ice water. It was collected, washed with water, and dissolved in methylene chloride. The solution was dried and evaporated and the residue was crystallized from methanol to yield 5.5 g (80%) of **21**, mp 143–145°.

Anal. Calcd for $C_{18}H_{14}ClNO_4$: C, 62.89; H, 4.11; N, 4.07. Found: C, 63.10; H, 4.24; N, 3.77.

6-Chloro-3-hydroxy-4-phenylcarbostyril (23a).—Methyl 6-chloro-3,4-epoxy-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**20a**) (3.3 g) was added with stirring to 30 ml of concentrated sulfuric acid. Evolution of carbon dioxide ceased within 15 min. The clear solution was poured into ice water and the precipitated product was collected, washed with water, and dissolved in methylene chloride. The solution was dried and evaporated. Crystallization of the residue from ethyl acetate–methanol yielded 2.05 g (75%) of **23a**: mp 255–258°; uv (2-PrOH) λ_{max} 231–232 mμ (ε 47,400), 287 (7750), infl 313 (7150), 325 (10,200), 338 (8100); ir (KBr) 3375 and 1640 cm^{-1}.

Anal. Calcd for $C_{15}H_{10}ClNO_2$: C, 66.31; H, 3.71; N, 5.16. Found: C, 66.54; H, 3.89; N, 5.02.

6-Chloro-4-(2-fluorophenyl)-3-hydroxycarbostyril (23d) was obtained in 93% yield by treating 12 g of ethyl 6-chloro-3,4-epoxy-4-(2-fluorophenyl)-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**20d**) with 50 ml of concentrated sulfuric acid as described in the previous example: mp 255–257°; ir ($CHCl_3$) 3400, 3150, 1660 cm^{-1}.

Anal. Calcd for $C_{15}H_9ClFNO_2$: C, 62.19; H, 3.13; N, 4.84. Found: C, 62.49; H, 2.96; N, 4.77.

6-Chloro-3-hydroxy-1-methyl-4-phenylcarbostyril (23c). Method A.—A mixture of 3.43 g (0.01 mol) of methyl 6-choro-3,4-epoxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**21**), 1 g (0.018 mol) of ammonium chloride, and 30 ml of dimethylformamide was refluxed for 2 hr. The cooled mixture was poured into water. The precipitate was collected, washed with water, and dissolved in methylene chloride. The solution was dried and evaporated. The crystalline residue was slurried with methylene chloride–ether to yield 2.4 g (84%) of **23c**. The analytical sample was recrystallized from methylene chloride–ethyl acetate: mp 252–253; uv (2-PrOH) λ_{max} 232 mμ (ε 48,500), 290 (8300), sh 315 (7100), 321–322 (9700), 339 (7500); ir (KBr) 3250 and 1620 cm^{-1}.

Anal. Calcd for $C_{16}H_{12}ClNO_2$: C, 67.26; H, 4.23; N, 4.90. Found: C, 67.54; H, 4.24; N, 4.77.

The same compound was obtained by treating **21** with either concentrated sulfuric acid or aqueous alkali.

Method B.—6-Chloro-3,4-epoxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one (**25**) (1 g) was added to 5 ml of concentrated sulfuric acid. After solution was complete, the reaction mixture was poured into ice water and the precipitate was extracted with methylene chloride. The dried extracts were evaporated and the residue was recrystallized from methylene chloride–ethyl acetate to yield 0.85 g (85%) of **23c**, mp 250–253°.

6-Chloro-3,4-epoxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one (25).—A solution of 3 g (0.075 mol) of sodium hydroxide in 30 ml of water was added to a solution of 18.5 g (0.05 mol) of 2-bromo-2′-benzoyl-4′-chloro-*N*-methylacetanilide in 100 ml of dimethylformamide. The mixture, which was stirred at room temperature for 30 min. crystallized on seeding and cooling in ice water. Seeds were obtained by chromatography of crude material on silica gel using methylene chloride and crystallization of the clean fractions from methanol–ether. The separated crystals were collected, washed with methanol–water, and recrystallized twice from acetone–methanol to yield 5.1 g (35%) of **25**: mp 123–124°; ir (KBr) 1650 cm^{-1}; uv (2-PrOH) λ_{max} 266–267 mμ (ε 12,280), infl 300 (2900); nmr ($CDCl_3$) δ 3.41 (s, 3, CH_3), 3.75 (s, 1, CH), 6.8–7.6 (m, 8, aromatic H).

Anal. Calcd for $C_{16}H_{12}ClNO_2$: C, 67.26; H, 4.23; N, 4.90. Found: C, 67.30; H, 4.24; N, 4.98.

5-Chloro-3-phenyloxindole (22a).[11]—A mixture of 2 g (6 mmol) of methyl 6-chloro-3,4-epoxy-4-phenyl-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**20a**), 1 g (18 mmol) of ammonium chloride, and 20 ml of dimethylformamide was refluxed for 20 min. The product was precipitated by the addition of water to the cooled reaction mixture. It was collected, washed with water, and recrystallized from methanol–water to give 1.4 g (94%) of 5-chloro-3-phenyloxindole, mp 190–192°.

5-Chloro-3-(2-fluorophenyl)oxindole (22d).—A mixture of 1.8 g (5 mmol) of ethyl 6-chloro-3,4-epoxy-4-(2-fluorophenyl)-1,2,3,4-tetrahydroquinolin-2-one-3-carboxylate (**20d**), 1 g of ammonium chloride, and 30 ml of dimethylformamide was refluxed for 30 min. The product was crystallized by the addition of water to the cooled reaction mixture. It was collected, washed with water, and recrystallized from methanol to yield 1.17 g (90%) of **22d**: mp 188–190°; uv (2-PrOH) λ_{max} 255–256 mμ (ε 14,020), 293 (1640); ir ($CHCl_3$) 3450, 3200, and 1720 cm^{-1}; nmr ($CDCl_3$) δ 4.9 (s, 1, CH), 6.8 (d, 1, J = 9 Hz, C_7 H) 6.9–7.4 (m, 6, aromatic H), 9.3 (broad s, 1, NHCO).

Anal. Calcd for $C_{14}H_9ClFNO$: C, 64.27; H, 3.47; N, 5.35. Found: C, 64.38; H, 3.47; N, 5.34.

Registry No.—**3a**, 29177-48-8; **3e**, 37393-55-8; **4c**, 37393-91-2; **4d**, 37393-92-3; **5a**, 37393-93-4; **5c**, 37393-94-5; **5d**, 37393-95-6; **6**, 37393-56-9; **7a**, 5606-56-4; **7b**, 5606-55-3; **7c**, 29301-14-2; **7d**, 5606-57-5; **7e**, 37393-61-6; **8**, 5220-02-0; **9**, 37393-96-7; **10**, 37393-97-8; **11**, 37393-98-9; **12**, 37393-99-0; **13**, 37393-63-8; **14**, 37393-64-9; **15a**, 29177-68-2; **15c**, 29177-70-6; **15d**, 37393-67-2; *syn*-**17a**, 29230-24-5; *anti*-**17a**, 29312-54-7; *syn*-**17c**, 37394-02-8; *anti*-**17c**, 37394-03-9; **18c**, 37393-68-3; **18d**, 37393-69-4; **19a**, 37393-70-7; **19d**, 37393-71-8; **20a**, 37393-72-9; **20b**, 37393-73-0; **20d**, 37393-74-1; **21**, 37393-75-2; **22a**, 15815-97-1; **22d**, 37393-77-4; **23a**, 17259-81-3; **23c**, 37393-79-6; **23d**, 37393-80-9; **25**, 37393-81-0; methyl 2-amino-2′-benzoyl-4′-chloromalonanilate hydrobromide, 37393-82-1.

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