Synthesis and Pharmacological Properties of Some Substituted 1,5-Benzodiazocin-2-ones

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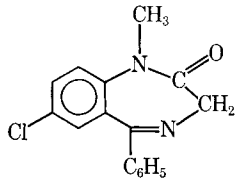
Abstract □ Some substituted 8-chloro-3,4-dihydro-6-phenyl-1,5-benzodiazocin-2-ones, which are structurally related to the anti-anxiety agent diazepam, have been synthesized and their central nervous system properties evaluated. Activity was observed for compounds bearing a methyl substituent at position one which was of a lower order of magnitude than that shown by diazepam.

Keyphrases □ 1,5-Benzodiazocin-2-ones, substituted—synthesis □ Pharmacological screening—1,5-benzodiazocin-2-ones □ UV spectrophotometry—identity □ IR spectrophotometry—identity □ NMR spectroscopy—identity

In view of the marked sedative, muscle relaxant, and anticonvulsant properties in animals of various compounds derived from the benzodiazepinone ring system (1), and the therapeutic utility of certain members of this class such as diazepam (I), it was of interest to determine the activities of structurally similar compounds in the benzodiazocine series.

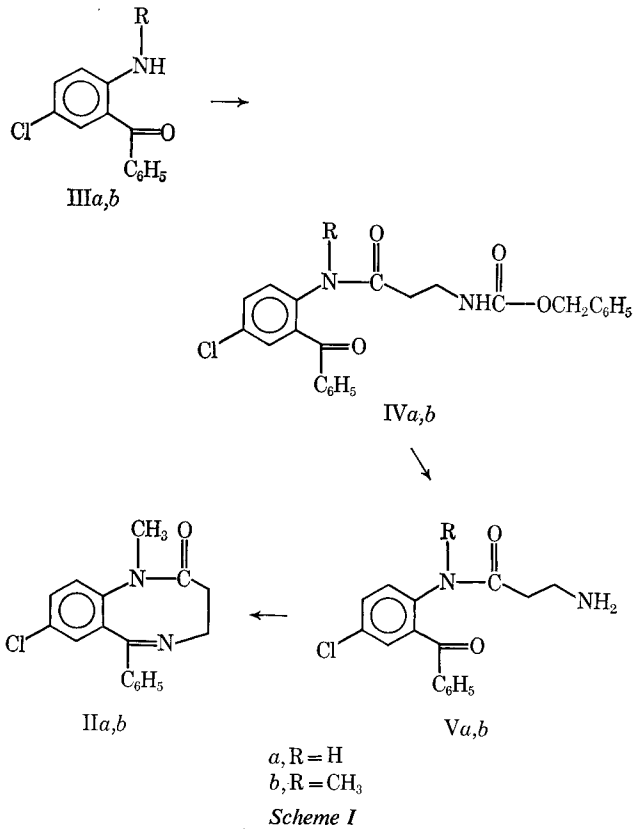


I

DISCUSSION

At the completion of the present investigations only one mention of benzodiazocines related in structure to diazepam had appeared in the literature, a recent patent (2) describing the synthesis of II*a* and reporting that the compound exhibited marked CNS-depressant activity.[1] The authors have prepared the *N*-methyl analog, II*b*, for pharmacological evaluation using the same synthetic pathway (Scheme I). The methylaminobenzophenone (III*b*) was condensed with the acid chloride of carbobenzoxy-β-alanine to form the amide IV*b*. The protective group was removed with hydrogen bromide in acetic acid and the resulting amine, V*b*, was cyclized in refluxing toluene, with azeotropic removal of water, to give II*b*.

Use of the phthalimido instead of the carbobenzoxy protecting group in an equivalent reaction sequence did not yield the desired benzodiazocine end product. Cleavage of VI*b* with hydrazine in alcohol was accompanied by oxidation, cyclization, and reaction with solvent (alcohol) to give the quinolone VII. Reaction of VI*a* with hydrazine afforded 2-amino-5-chlorobenzophenone (III*a*) as the only isolable product. Removal of the protecting group by treatment of VI*a* with refluxing dilute aqueous-alcoholic sodium hydroxide followed by dilute aqueous hydrochloric acid under reflux gave the aminomethylquinolone VIII*a*. The structure of



III*a*,*b*

IV*a*,*b*

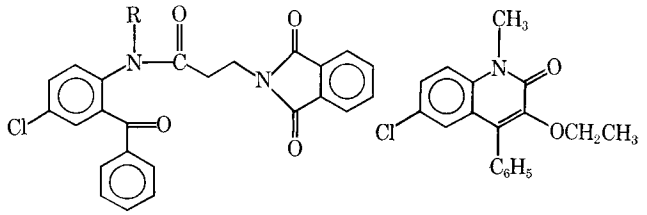
II*a*,*b*

V*a*,*b*

a, R = H
b, R = CH_3

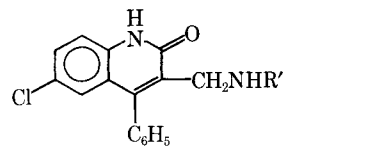
Scheme I

VIII*a* was confirmed by acetylation of the primary amine function to give VIII*b*. When a similar hydrolytic sequence was carried out on VI*b*, the corresponding aminomethylquinolone was not obtained.



VI*a*, R = H
VI*b*, R = CH_3

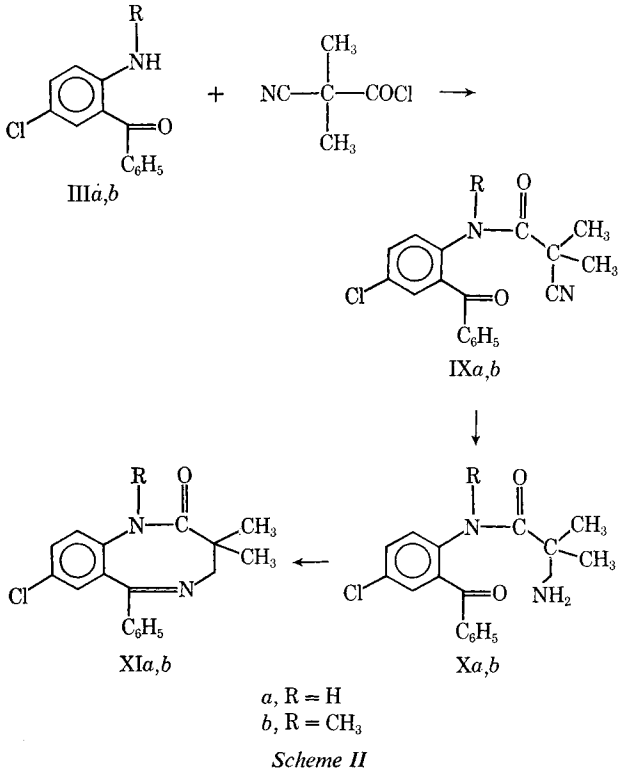
VII



VIII*a*, R′ = H
VIII*b*, R′ = $COCH_3$

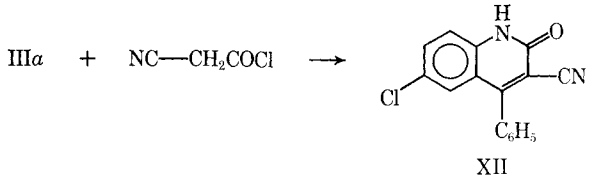
The 3,3-dimethyl analogs XI*a*,*b* of II*a*,*b* were prepared by another route (Scheme II) which utilized dimethylcyanoacetyl chloride to form the amides IX*a*,*b*. Upon reduction, X*a* was obtained and was cyclized to XI*a* in refluxing toluene with azeotropic removal of water; on the other hand, X*b* spontaneously cyclized to XI*b*. In an

[1] After this manuscript was submitted for publication, M. E. Derieg, R. M. Schweininger, and R. I. Fryer, *J. Org. Chem.*, 34, 179(1969) and M. Denzer and H. Ott, *ibid*, 34, 183(1969) both reported that this compound is in fact a dimer of II*a*. The synthesis of II*b* was also reported in these papers but no pharmacological data were given.



Scheme II

attempt to synthesize II*a* by this route only the quinolone XII was obtained.



Pharmacology[2]—The benzodiazocines prepared in this investigation were tested in the mouse screen as described by Irwin (3) and the antipentylenetetrazole test (4). The *N*-methyl compound, II*b*, caused weak CNS depression and XI*b* as the maleate salt had slight antipentylenetetrazole activity at 30 mg./kg. Compound XI*a* did not show any significant activity.

EXPERIMENTAL[3]

2-(β-Carbobenzoxyalanyl-N-methylamido)-5-chlorobenzophenone (IVb)—Phosphorus pentachloride (10.6 g., 0.05 mole) was added to a stirred mixture of carbobenzoxy-β-alanine (5) (9.1 g., 0.04 mole) in anhydrous ether (175 ml.) cooled in an ice bath. The mixture was stirred with cooling for 1.5 hr. and then decanted from the insoluble material into a solution of 5-chloro-2-methylaminobenzophenone (6) (9.3 g., 0.038 mole) in $CHCl_3$ (55 ml.) and stirred for 1 hr. The solution was washed with water and saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and the solvent evaporated to give a yellow oil (15 g., 90%) which was used directly in the next step; $\lambda_{max.}^{CHCl_3}$ 2.90 (N—H), 5.80, 5.98, 6.05 (sh)μ (amide, urethane, C=O).

8-Chloro-3,4-dihydro-1-methyl-6-phenyl-1,5-benzodiazocin-2(1H)-one (IIb)—Compound IV*b* (5.4 g., 0.012 mole) was treated with 30% hydrogen bromide (13 ml.) in acetic acid for 1 hr. at room temperature. Ether was added, but no material precipitated; concentrated ammonia was added and the ether was evaporated. The mixture was extracted with toluene (65 ml.) and the resulting solution refluxed using a water separator for 2 days. The toluene was evaporated, the residue was dissolved in acetone, treated with charcoal, and upon addition of hexane, product (1.1 g., 30%) was obtained, m.p. 167–168°; $\lambda_{max.}$ 243 mμ (ε 17,300); $\lambda_{max.}$ 6.01 (amide), 6.17 μ (C=N); NMR ($CDCl_3$), δ = 3.13 (N—CH_3, 3H, singlet), 2.60–4.50 (N-CH_2-CH_2, 4H, multiplets) p.p.m.

Anal.—Calcd. for $C_{17}H_{15}ClN_2O$: C, 68.33; H, 5.06; N, 9.38. Found: C, 68.55; H, 4.95; N, 9.14.

2-(N-Methyl-β-phthalimidopropionamido)-5-chlorobenzophenone (VIb)—β-Phthalimidopropionic acid (7) (9.2 g., 0.042 mole) in benzene (300 ml.) was treated with oxalyl chloride (5.9 g., 0.046 mole). The mixture was stirred for 0.5 hr. at room temperature and then under reflux for 0.5 hr. After cooling 5-chloro-2-methylaminobenzophenone (6) (8.6 g., 0.035 mole) in benzene (130 ml.) was added and the mixture stirred for 0.5 hr. at room temperature and then for 2 hr. under reflux. The benzene was evaporated and the residue dissolved in $CHCl_3$; this solution was extracted twice with 10% Na_2CO_3, once with water, dried (Na_2SO_4), and evaporated to an oil. Attempted crystallization from benzene-hexane led to recovery of III*b* (1.3 g.). The solvents were evaporated to yield a viscous oil (13.1 g.) which was used in subsequent experiments. The analytical sample was prepared by slow crystallization from acetone-ether, m.p. 159°; $\lambda_{max.}$ 218 mμ (ε 67,500); $\lambda_{max.}$ 5.60, 5.73, 5.80 (imide, amide), 5.98 μ (C=O).

Anal.—Calcd. for $C_{25}H_{19}ClN_2O_4$: C, 67.19; H, 4.28; N, 6.27. Found: C, 66.87; H, 4.32; N, 6.18.

6-Chloro-3-ethoxy-1-methyl-4-phenyl-2(1H)-quinolone (VII)—A solution of VI*b* (9.0 g., 0.02 mole) and hydrazine hydrate (3.0 g., 0.06 mole) in 95% ethanol (400 ml.) was refluxed for 2.5 hr. and then concentrated to about half volume. On cooling a gelatinous precipitate formed. The mixture was acidified with 5% HCl, heated to 75°, and cooled. A small amount of solid material was removed by filtration and the aqueous solution was extracted with CH_2Cl_2. The organic layer was washed with 5% NaOH followed by water, dried (Na_2SO_4), and the solvent evaporated to give an oil (3.6 g.). This oil was placed in a thimble and extracted for 20 hr. with hexane (500 ml.). Evaporation of the hexane left an oil (3.0 g.) which was chromatographed on silica gel[4] (250 g.). The column was eluted with benzene (200-ml. fractions) and Fractions 5–14 furnished product (1.1 g.) which was recrystallized from benzene-hexane (charcoal) to yield VII (0.7 g.) m.p. 87°; $\lambda_{max.}$ 241, 302 mμ (ε 36,400, 15,100); $\lambda_{max.}$ 5.80 (sh), 5.88 μ (amide); NMR (CCl_4), δ = 1.00 (C-CH_3, 3H, triplet, J = 7 cps.), 4.03 (N-CH_3, 3H, singlet), 4.09 (O-CH_2, quartet, J = 7 cps.) p.p.m.

Anal.—Calcd. for $C_{18}H_{16}ClNO_2$: C, 68.92; H, 5.14; Cl, 11.30; N, 4.46. Found: C, 69.29; H, 5.28; Cl, 11.38; N, 4.28.

2-(β-Phthalimidopropionamido)-5-chlorobenzophenone (VIa)—A procedure analogous to that described for the preparation of VI*b* was employed. From III*a* (11.5 g., 0.05 mole) and 2-phthalimidopropionyl chloride (7) (12 g., 0.05 mole) there was obtained VI*a* (14.1 g., 65%) (crystallized from ethanol), m.p. 146–148°. The analytical sample was prepared by recrystallizing again from ethanol, m.p. 149°; $\lambda_{max.}$ 232 mμ (ε 37,600); $\lambda_{max.}$ 5.60, 5.78, 5.83 (imide, amide), 6.10 μ (C=O).

Anal.—Calcd. for $C_{24}H_{17}ClN_2O_4$: C, 66.58; H, 3.96; Cl, 8.19; N, 6.47. Found: C, 67.01; H, 3.87; Cl, 8.47; N, 6.25.

3-Aminomethyl-6-chloro-4-phenyl-2(1H)-quinolone (VIIIa)—A solution of VI*a* (5.0 g., 0.012 mole) in ethanol (500 ml.) and 1 *N* NaOH (25 ml.) was refluxed for 2 hr. The ethanol was evaporated, water (25 ml.) and 1 *N* HCl (50 ml.) were added and the resulting precipitate was collected, added to water (500 ml.) and 1 *N* HCl (25 ml.) and the mixture refluxed for 4 hr. After cooling, the solution was filtered, the filtrate basified with 1 *N* NaOH and the resulting precipitate was collected and dried to give VIII*a* (1.3 g., 20%), m.p. 260°. The analytical sample was obtained by recrystallizing twice from methanol-water, m.p. 240°; $\lambda_{max.}$ 238 mμ (ε 43,200); $\lambda_{max.}$ 2.95, 3.02 (NH_2), 6.06 μ (amide).

Anal.—Calcd. for $C_{16}H_{13}ClN_2O$: C, 67.50; H, 4.60; Cl, 12.46; N, 9.84. Found: C, 67.27; H, 4.70; Cl, 12.40; N, 9.54.

3-Acetamidomethyl-6-chloro-4-phenyl-2(1H)-quinolone (VIIIb)—A solution of VIII*a* (0.3 g., 0.0011 mole) and acetic anhydride (0.13 g., 0.0013 mole) in benzene (150 ml.) was refluxed for 5 hr., cooled and

[2] The authors are indebted to Dr. Robert Taber, Biological Research Division, Schering Corp., for these data.

[3] Melting points were determined in a Thomas-Hoover capillary melting-point apparatus and are corrected. UV absorption spectra were determined in methanol solution and IR absorption spectra as mineral oil mulls (Nujol) except where indicated otherwise. The NMR spectra were recorded on a Varian Associates A-60 spectrometer at 60 Mc.p.s. with Me_4Si as internal standard.

[4] Grade 923, Davison Chemical, Baltimore, Md.

filtered to give VIII*b* (0.3 g.), m.p. 276°; $\lambda_{max.}$ 239 mμ (ε 45,700); $\lambda_{max.}$ 5.96, 6.08 μ (amide).

Anal.—Calcd. for $C_{18}H_{15}ClN_2O_2$: C, 66.16; H, 4.63; N, 8.57. Found: C, 66.51; H, 4.68; N, 8.39.

5-Chloro-2-dimethylcyanoacetamidobenzophenone (IXa)—Dimethylcyanoacetic acid (8) (5.0 g., 0.044 mole) and oxalyl chloride (5.6 g., 0.044 mole) were stirred in benzene (125 ml.) at room temperature for 1 hr. The solution was then refluxed with stirring for 2 hr., cooled, and III*a* (9.9 g., 0.044 mole) in benzene (125 ml.) added with stirring. The mixture was then refluxed for 3 hr., filtered, and the filtrate evaporated to dryness. The residue was dissolved in $CHCl_3$ and the solution was washed twice with aqueous $NaHCO_3$ followed by water, dried (Na_2SO_4), and the solvent evaporated affording IX*a* (11.4 g., 79%), m.p. 102–104°. Recrystallization twice from methanol gave the analytical sample, m.p. 103°, $\lambda_{max.}$ 238 mμ (ε 20,000), $\lambda_{max.}$ 4.44 (CN), 5.80, 5.87 (amide), 6.09 μ (C=O).

Anal.—Calcd. for $C_{18}H_{15}ClN_2O_2$: C, 66.15; H, 4.64; N, 8.57. Found: C, 66.53; H, 4.73; N, 8.47.

5-Chloro-2-(α,α-dimethyl-N-methylcyanoacetamido)benzophenone (IXb)—From dimethylcyanoacetic acid (8) (5.0 g., 0.044 mole) and III*b* (6) (10.9 g., 0.044 mole) using the procedure described for the preparation of IX*a*, there was obtained IX*b* (7.5 g.), m.p. 86–87°. The analytical sample was obtained by recrystallizing twice from methanol, m.p. 92–93°; $\lambda_{max.}$ 253 mμ (ε 14,800); $\lambda_{max.}$ 4.44 (CN), 5.97 (amide), 6.02 μ (C=O).

Anal.—Calcd. for $C_{19}H_{17}ClN_2O_2$: C, 66.95; H, 5.04; N, 8.22. Found: C, 66.55; H, 5.08; N, 8.17.

8-Chloro-3,4-dihydro-3,3-dimethyl-6-phenyl-1,5-benzodiazocin-2(1H)-one (XIa)—Compound IX*a* (5.5 g., 0.017 mole) was dissolved in methanol (150 ml.) and hydrogenated at room temperature and a pressure of 3.5 kg./cm.^{2} in the presence of an active nickel catalyst[5] for 48 hr. The oil remaining after filtering off the catalyst and evaporating the solvent was chromatographed on silica gel[4] (100 g.) using benzene as eluant (three 900-ml. fractions) followed by increasing percentages of $CHCl_3$ in benzene and finally $CHCl_3$. A total of 15 fractions was collected; the first 3 yielded 0.45 g. of starting material and the remainder were combined to yield X*a* (4.8 g.) as an oil. Compound X*a* (2.0 g.) was dissolved in dilute HCl and mixed with aqueous picric acid solution. The resulting picrate was collected, dried, and recrystallized from ethanol-benzene to give the pure picrate 2.2 g., m.p. 202°; $\lambda_{max.}$ 238, 350 mμ (ε 38,200, 18,000); $\lambda_{max.}$ 6.00 (amide), 6.10 μ (C=O); NMR (d_6-DMSO), δ = 1.02 (H_3C-C-CH_3, 6H, singlet), 2.78 (CH_2, 2H, singlet) p.p.m.

Anal.—Calcd. for $C_{24}H_{22}ClN_3O_9$: C, 51.48; H, 3.96; N, 12.51. Found: C, 51.84; H, 3.95; N, 12.72.

The picrate salt (0.5 g.) in ethanol was placed on a column of 30 ml. of ion-exchange resin[6] in ethanol and the column was eluted with ethanol. Upon evaporation of the solvent, the free base was obtained which set to a glass. The NMR spectrum unequivocally established the structure as X*a*; NMR ($CDCl_3$), δ = 1.02 (H_3C-C-CH_3, 6H, singlet), 2.78 (CH_2, 2H, singlet) p.p.m.

The oil X*a* (4.8 g.), obtained after chromatography of the reduction product was dissolved in toluene (75 ml.) and the solution refluxed overnight with azeotropic removal of water. The solvent was evaporated and the product isolated as the hydrochloride salt which, after purification by treatment with charcoal in acetone amounted to 4.2 g., 83%, m.p. 92–94°; $\lambda_{max.}$ 240 mμ (ε 25,500); $\lambda_{max.}$ 5.91 (amide), 6.08 μ (C=N).

Anal.—Calcd. for $C_{18}H_{17}ClN_2O \cdot HCl$: C, 61.89; H, 5.20. Found: C, 62.36; H, 5.22.

8-Chloro-3,4-dihydro-6-phenyl-1,3,3-trimethyl-1,5-benzodiazocin-2(1H)-one (XIb)—A solution of IX*b* (5.5 g., 0.016 mole) in methanol (100 ml.) was hydrogenated at room temperature and a pressure of 3.5 kg./cm.^{2} with active nickel catalyst[5] for 8 hr. The catalysts was filtered off and the solvent evaporated affording a viscous oil (5.1 g., 97%). The NMR spectrum of this material was essentially identical to that of the analytical sample.

[5] Raney No. 28, W. R. Grace Co., So. Pittsburg, Tenn.
[6] Amberlite IR-45, Mallinckrodt, St. Louis, Mo.

The maleate salt was prepared by dissolving 0.9 g. of the oil in 8 ml. of ethyl acetate and adding to the hot solution maleic acid (0.4 g.) in ethyl acetate (10 ml.); 1.0 g. of salt was obtained, m.p. 132°. Recrystallization twice from ethyl acetate yielded the analytical sample as a hydrate, m.p. 132°; $\lambda_{max.}$ 246 mμ (ε 16,700); $\lambda_{max.}$ 5.95 (amide), 6.16 μ (C=N).

Anal.—Calcd. for $C_{23}H_{23}ClN_2O_5 \cdot H_2O$: C, 59.94; H, 5.47; N, 6.08. Found: C, 59.99; H, 5.56; N, 6.07.

The picrate salt (1.9 g.) was obtained by treatment of a solution of the free base (1.5 g.) in dilute HCl with aqueous picric acid solution. The analytical sample was obtained by recrystallizing twice from ethanol, m.p. 220°, $\lambda_{max.}$ 235, 355 mμ (ε 29,900, 15,100); $\lambda_{max.}$ 6.00 μ (amide); NMR (d_6-DMSO), δ = 1.08, 1.44 (H_3C-C-CH_3 3H, 3H, 2 singlets), 3.10 (N-CH_3, 3H, singlet) 3.16, 3.82 (N-CH_2, 1H, 1H,2 doublets, J = 12.2 cps.) p.p.m.

Anal.—Calcd. for $C_{25}H_{22}ClN_5O_8$: C, 54.01; H, 3.99; Cl, 6.38; N, 12.60. Found: C, 54.01; H, 4.04; Cl, 6.62; N, 12.65.

The picrate salt (0.4 g.) was placed on a column of alumina (12 g.) and eluted with benzene (100 ml., Fraction 1) and then $CHCl_3$ (400 ml., Fraction 2). After evaporation of solvents the free base was obtained from Fractions 1 and 2; 0.1 g., m.p. 125–126; $\lambda_{max.}$ 240 mμ (ε 17,300); $\lambda_{max.}$ 6.04 μ (amide); NMR ($CDCl_3$), δ = 1.10, 1.56 (H_3C-C-CH_3, 3H, 3H, 2 singlets), 3.11 (N-CH_3, 3H, singlet), 3.02, 3.75 (N-CH_2, 1H, 1H, 2 doublets, J = 12.2 cps.) p.p.m.

Anal.—Calcd. for $C_{19}H_{19}ClN_2O$: C, 69.81; H, 5.87; N, 8.57. Found: C, 69.44; H, 5.96; N, 8.46.

6-Chloro-3-cyano-4-phenyl-2(1H)-quinolone (XII)—Cyanoacetic acid (4.4 g., 0.052 mole) in benzene (300 ml.) and oxalyl chloride (7.2 g., 0.057 mole) were stirred at room temperature for 1 hr. and the solution was then refluxed for 3 hr. Benzene (100 ml.) was distilled from the reaction mixture which was subsequently cooled and a solution of III*a* (10 g.) in benzene (150 ml.) was added. The reaction mixture was stirred for 3 hr., filtered, and the filtrate evaporated. The solid residue was dissolved in $CHCl_3$, the solution washed with saturated $NaHCO_3$ followed by water, dried (Na_2SO_4), and the solvent evaporated to give crude XII (8.3 g., 69%). Recrystallization from acetone-methanol afforded the analytical sample, m.p. 358°; $\lambda_{max.}$ 214, 243 mμ (ε 39,200, 43,300); $\lambda_{max.}$ 4.50 (CN); 6.02 μ (amide).

Anal.—Calcd. for $C_{16}H_9ClN_2O$: C, 68.45; H, 3.23; Cl, 12.63; N, 9.98. Found: C, 68.16; H, 3.37; Cl, 12.45; N, 10.09.

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