Synthesis of Some Amino-substituted Furanopyrimidines and Styrylpyrimidines (1)

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5-*p*-Chlorophenyl-6,6-dimethyl-5,6-dihydro-3*H*-furano[2,3-*d*]pyrimidine-4-one is readily converted to 4,6-dichloro-5-β,β-dimethyl-α-(*p*-chlorostyryl)pyrimidine by warming in phosphorus oxychloride and acetic acid, behavior which is in strong contrast to that of the analogous 5-phenyl derivative. The reaction provides a convenient source of 4-amino-6-chloro-5-β,β-dimethyl-α-(*p*-chlorostyryl)pyrimidines and 4,6-diamino-5-β,β-dimethyl-α-(*p*-chlorostyryl)pyrimidines, compounds of potential biological interest.

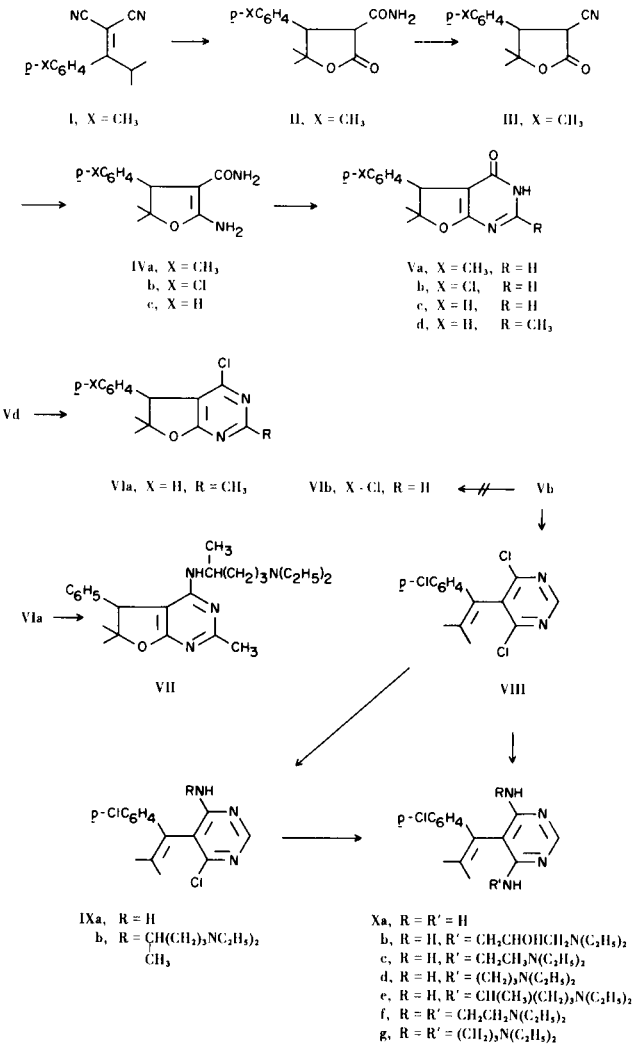
A number of 5-aryl-6,6-dimethyl-5,6-dihydrofurano-[2,3-*d*]pyrimidines bearing a 4-dialkylaminoalkyl side-chain and their precursors have previously been described (2,3). Since some of these compounds were of interest to the antimalarial program, an effort was made to synthesize some representative analogs bearing a *p*-tolyl or *p*-chlorophenyl group in the 5-position.

The desired starting materials for the projected syntheses were the 5-aryl-6,6-dimethyl-5,6-dihydro-3*H*-furano-[2,3-*d*]pyrimidine-4-ones (V) and it was necessary to prepare these compounds *via* the ylidenemalononitrile synthesis already described (4). The general synthesis is outlined in Scheme 1. The phenyl compound, Vc, has already been reported (4), but the *p*-tolyl and *p*-chlorophenyl derivatives, Va and Vb, are new. It was necessary to synthesize IVa from the known *p*-methylisobutyrophenone (5) *via* the ylidenemalonotrile I as shown in Scheme 1. The syntheses of IVb and IVc have been reported previously (3).

Compound VIa, 2,6,6-trimethyl-4-chloro-5-phenyl-5,6-dihydrofurano[2,3-*d*]pyrimidine, was readily prepared by condensation of IVc with triethyl orthoacetate to give Vd, followed by treatment with phosphorus oxychloride and a trace of acetic acid. Compound VIa was converted to VII by heating in α-methyl-δ-diethylaminobutylamine. No oxygen cleavage was observed in this case, although such cleavages have been observed under similar conditions (4).

When Vb was heated to 100° with phosphorus oxychloride and a trace of acetic acid, the usual conditions for converting V to VI (4), no VIb was formed. Instead, the product was shown to be VIII, 4,6-dichloro-5-[β,β-dimethyl-α-(*p*-chlorostyryl)]pyrimidine. The compound was identified by analyses and the nearly congruent infrared spectrum with that of 4,6-dichloro-5-(β,β-dimethyl-α-styryl)pyrimidine (4). This result is a surprising difference between 5-*p*-chlorophenyl and 5-phenyl derivatives Vb and Vc, since we have found that heating Vc with phosphorus oxychloride and acetic acid at 140° did not produce any of the dichloropyrimidines (4).

SCHEME 1



Since it had already been shown that 2,6-dichloropyrimidines like VIII could be converted to the corresponding aminochloropyrimidines IX, and these in turn to the 2,6-diaminopyrimidines, X (4), a ready pathway was now open for the synthesis of a series of unsymmetrically substituted 5-*p*-chlorostyryl-4-amino-6-dialkylaminoalkylaminopyrimidines, Xb-e, which are structurally related to pyrimethamine, (5-*p*-chlorophenyl-6-ethyl-2,4-diaminopyrimidine). 4-Amino-6-chloro-5-[β,β-dimethyl-α-(*p*-chlorostyryl)]pyrimidine (IXa) was obtained in excellent yield by heating VIII in aqueous ammonium hydroxide in a sealed bomb at 125°. Compound IXa was in turn converted into a series of diamines (Xa-e) by heating with the appropriate amines. Finally the diamines Xf and Xg were synthesized directly from the dichloropyrimidine VIII by refluxing in the appropriate high-boiling diamines.

These compounds were screened for potential antimalarial activity by the Walter Reed Army Institute of Research, using the procedure described by Osdene, *et.al.* (6). We are indebted to the W.R.A.I.R. for the results of these tests. None of the compounds submitted (VII, VIII, IXa-b, Xa-g) were active at the 640 mg./kg. dose level.

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EXPERIMENTAL

Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana. Infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord. The NMR spectra were recorded on a Varian Model A-60 Spectrometer, using tetramethylsilane as an internal reference, in solvents specified, and are in agreement with structures assigned.

p-Methylisobutyrophenone.

To a solution of 92.1 g. of toluene and 267 g. of aluminum chloride in 500 ml. of toluene, 106.5 g. of isobutyryl chloride was added dropwise. When the addition was complete, the reaction was heated at 60° for 6 hours, poured into a mixture of ice and 100 ml. of concentrated hydrochloric acid, extracted with benzene, dried over anhydrous magnesium sulfate, filtered and the benzene and toluene removed. The residue was distilled, giving 140 g. (85%) of ketone; b.p. (0.5 mm.) 66-67° as reported (5).

α-Isopropyl-*p*-methylbenzylidenemalononitrile (I).

A mixture of 128 g. of *p*-methylisobutyrophenone (0.79 mole), 53 g. of malononitrile (0.8 mole), 7 g. of ammonium acetate and 20 ml. of glacial acetic acid in 500 ml. of benzene were refluxed until the amount of water in the Dean-Stark trap remained constant. The reaction was washed twice with water, twice with 10% sodium bicarbonate and twice more with water. The benzene layer was dried over anhydrous magnesium sulfate, filtered, the benzene removed and the residue distilled. After 48 g. of starting ketone (b.p. 66-67°/0.5 mm.), 95 g. of product (84%) b.p. 110-112° (0.5 mm.) was collected; I.R. (liquid film) 4.4 μ (CN).

Anal. Calcd. for $C_{14}H_{14}N_2$: C, 79.96; H, 6.71; N, 13.32. Found: C, 79.87; H, 6.89; N, 13.13.

α-Carboxamido-γ,γ-dimethyl-β-(*p*-tolyl)butyrolactone (II).

A mixture of 30 g. (0.14 mole) of I and 300 g. of polyphosphoric acid was heated at 75° (oil bath temperature) for 6 hours, then poured into 1600 ml. of water. The mixture was stirred for 24 hours and filtered. The solid was air dried and recrystallized from ethyl acetate and cyclohexane to yield 21 g. (60%) of white crystals; m.p. 138-139°; I.R. (potassium bromide) 2.92 (NH), 5.65 (C=O lactone), 5.96 μ (C=O amide).

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 68.15; H, 6.88; N, 5.75.

α-Cyano-β-(*p*-tolyl)-γ,γ-dimethylbutyrolactone (III).

A solution of 5 g. (0.02 mole) of II and 18 ml. of phosphorus oxychloride were heated at 90° (oil bath temperature) for 1.5 hours, cooled and the mixture poured over water. The solid which formed was filtered, taken up in chloroform, washed well with water and dried over anhydrous magnesium sulfate, filtered and the chloroform removed. The residue was recrystallized from benzene and hexane, giving 4 g. (87%), of white crystals; m.p. 139-140°; I.R. (potassium bromide) 4.4 (CN), 5.65 μ (C=O, lactone).

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.08; H, 6.53; N, 6.33.

2-Amino-3-carboxamido-5,5-dimethyl-4-(*p*-tolyl)-4,5-dihydrofuran (IVa).

When 8 g. (0.036 mole) of III was dissolved in 50 ml. of concentrated ammonium hydroxide, after 5 minutes a white precipitate appeared. The mixture was stirred at room temperature for 3 hours, filtered, washed with water, dried, and recrystallized from benzene, giving 7 g. (60%) of white crystals; m.p. 147-149°; I.R. (potassium bromide) 2.9 to 3.05 (NH), 6.0 (C=O amide), 9.8 μ (furan ring).

Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.26; H, 7.36; N, 11.38. Found: C, 68.48; H, 7.61; N, 11.32.

5-(*p*-Tolyl)-6,6-dimethyl-5,6-dihydro-3*H*-furano[2,3-*d*]pyrimidine-4-one (Va).

A mixture of 6 g. (0.024 mole) of IVa and 50 ml. of triethyl orthoformate was heated at 120°, and the ethanol formed during the reaction collected in a Dean-Stark trap. After 5 hours, the reaction mixture was cooled overnight, the solid filtered and recrystallized from benzene, giving 6 g. (98%) of white crystals; m.p. 201-203°; I.R. (potassium bromide) 2.9 (NH), 6.0 μ (C=O).

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.58; N, 6.47; N, 10.84.

4-(*p*-Chlorophenyl)-6,6-dimethyl-5,6-dihydro-3*H*-furano[2,3-*d*]-pyrimidine-4-one (Vb).

A solution of 50 g. (0.18 mole) of 2-amino-3-carboxamido-4-(*p*-chlorophenyl)-5,5-dimethyl-4,5-dihydrofuran (IVb) (3) and 275 ml. of triethyl orthoformate was heated at 120° for 6 hours. The ethanol formed during the reaction was collected in a Dean-Stark trap. After the reaction had been heating for 30 minutes the product began to precipitate. The reaction mixture was cooled in the refrigerator, filtered, the solid was washed with hexane and recrystallized from ethyl acetate, giving 45 g. (90%) of crystals; m.p. 228-231°; I.R. (potassium bromide) 6.05 (C=O) and 6.25 μ (C=C).

Anal. Calcd. for $C_{14}H_{13}ClN_2O_2$: C, 60.76; H, 4.74; N, 10.12. Found: C, 60.96; H, 4.69; N, 10.22.

5-Phenyl-2,6,6-trimethyl-5,6-dihydro-3*H*-furano[2,3-*d*]pyrimidine-4-one (Vd).

Three grams (0.0129 mole) of IVc (2) and 17 ml. of triethyl orthoacetate were heated at reflux for 12 hours, the ethanol formed in the reaction being removed continously by distillation. The reaction mixture was chilled to 0° overnight, the white solid collected by filtration, washed with a small amount of ether and dried at reduced pressure yielding 3 g. of crude product. Recrystallization from 95% ethanol yielded 2.6 g. (79%) of colorless crystals of m.p. 233-236°; I.R. (potassium bromide) 6.04 (C=O), 6.25 (C=C), and 9.75 μ (COC).

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.30; H, 6.29; N, 10.93. Found: C, 70.04; H, 6.16; N, 10.81.

2,6,6-Trimethyl-4-chloro-5-phenyl-5,6-dihydrofurano[2,3-*d*]pyrimidine (VIa).

Two hundred ml. of phosphorus oxychloride were carefully added to a round bottom flask containing 49 g. (0.191 mole) of Vd. After addition of 5 ml. glacial acetic acid, the mixture was refluxed for 1 hour. After removal of the excess phosphorus oxychloride at reduced pressure, the reaction mixture was cooled to ambient temperature and poured slowly (in portions) into a 2 l. beaker containing 500 g. of crushed ice. After stirring for 15 minutes, concentrated ammonium hydroxide was carefully added in portions with stirring until the solution became basic to litmus paper. After chilling in the refrigerator overnight, the precipitated white product was collected by filtration, washed with a small amount of water, air dried and recrystallized from 95% ethanol, affording 34 g. (65%) of white crystals with m.p. 88-89.5°; I.R. (potassium bromide) 6.29 (pyrimidine C-N) and 9.76 μ (COC); λ max (ethanol), 267 mμ (ϵ = 6,750) and 230 mμ (sh) (ϵ = 7,550). The NMR spectrum (deuteriochloroform), δ 7.18 (5H-M), 4.33 (1H-S), 2.62 (3H-S), 1.62 (3H-S) and 1.08 (3H-S).

Anal. Calcd. for $C_{15}H_{15}ClN_2O$: C, 65.58; H, 5.50; N, 10.20. Found: C, 65.29; H, 5.77; N, 9.94.

2,6,6-Trimethyl-4-(δ-diethylamino-α-methylbutylamino)-5-phenyl-5,6-dihydrofurano[2,3-*d*]pyrimidine (VII).

A mixture of 4.11 g. (0.015 mole) of VIa and 2.85 g. (0.018 mole) of δ-diethylamino-α-methylbutylamine in a round bottom flask was heated with stirring in an oil bath at 200° for 2 hours. The reaction mixture was dissolved in 70 ml. of hot 20% acetic acid, cooled, made alkaline by addition of sodium hydroxide pellets and extracted with ether three times. The combined organic layers were washed with a small volume of water, dried (magnesium sulfate) and the filtrate condensed to a yellow oil. Distillation gave 3.0 g. (50%) of product at 220°/0.1 mm.; I.R. (neat) 3.02 (N-H) and 6.26 μ (pyrimidine C=N).

Anal. Calcd. for $C_{24}H_{36}N_4O$: C, 72.69; H, 9.25; N, 14.13. Found: C, 72.71; H, 9.34; N, 13.99.

4,6-Dichloro-5-β,β-dimethyl-α-(*p*-chlorostyryl)pyrimidine (VIII).

Fifty g. (0.18 mole) of 5-(*p*-chlorophenyl)-6,6-dimethyl-5,6-dihydro-3*H*-furano[2,3-*d*]pyrimidine-4-one (Vb), 125 ml. of phosphorus oxychloride and 2 ml. of glacial acetic acid were heated at 100° (oil bath temperature) for 2 hours, and the excess phosphorus oxychloride distilled off. The residue was poured over ice and made basic with concentrated ammonium hydroxide and filtered. The solid was taken up in chloroform, washed with water, and dried over anhydrous magnesium sulfate, filtered and the chloroform removed. The solidified residue was recrystallized from 95% ethanol, yielding 48 g. (85%) of crystals, m.p. 101-102°; I.R. (potassium bromide) no carbonyl and no furan band, 3.25-3.50 (CH), 6.70 μ (C-Cl).

Anal. Calcd. for $C_{14}H_{11}Cl_3N_2$: C, 53.68; H, 3.53; N, 8.92. Found: C, 53.98; H, 3.79; N, 8.89.

4-Amino-6-Chloro-5-β,β-dimethyl-α-(*p*-chlorostyryl)pyrimidine (IXa).

A suspension of 12 g. (0.036 mole) of VIII in 250 ml. of concentrated ammonium hydroxide was heated at 125° for 16 hours in a glass-lined sealed bomb. The mixture was cooled, the solid material collected, washed with water and air-dried. After recrystallizing from benzene, 8.5 g. (80%) of white crystals, m.p. 208-209°, were obtained; I.R. (potassium bromide) 2.9 (NH), 3.3-3.5 (CH), 6.65 μ (C-Cl).

Anal. Calcd. for $C_{14}H_{13}Cl_2N_3$: C, 57.15; H, 4.45; N, 14.28. Found: C, 56.97; H, 4.73; N, 14.28.

6-Chloro-4-(δ-diethylamino-α-methylbutylamino)-5-β,β-dimethyl-α-(*p*-chlorostyryl)pyrimidine (IXb) Hydrochloride.

A solution of VIII and 5.2 g. of 5-diethylamino-2-aminopentane were heated with stirring in an oil bath at 170° for 3 hours, cooled to room temperature and extracted with ether. The ether layer was washed with water, dried over anhydrous magnesium sulfate, filtered and the ether evaporated. The excess 5-diethylamino-2-aminopentane was removed by distillation, and the oily residue dissolved in 95% ethanolic hydrogen chloride and ether added to the solution. The precipitate was collected and recrystallized from ethanol and ether, to give 2 g. (20%) of salt; I.R. (potassium bromide) 2.9-3.1 (NH), 3.8-4.0 (NH^+), 6.7 μ (C-Cl).

Anal. Calcd. for $C_{23}H_{32}Cl_2N_4 \cdot 2HCl$: C, 54.35; H, 6.74; N, 11.02. Found: C, 54.34; H, 6.68; N, 11.05.

4,6-Diamino-5-β,β-dimethyl-α-(*p*-chlorostyryl)pyrimidine (Xa).

Four and one-half g. (0.015 mole) of 4-amino-5-β,β-dimethyl-α-(*p*-chlorostyryl)-6-chloropyrimidine (IXa) and 125 ml. of methanolic ammonia were heated at 200° for 16 hours in a glass-lined sealed bomb. The mixture was cooled, filtered and the solid recrystallized from ethyl acetate, giving 1.5 g. (37%) of Xa; m.p. 260-262°; I.R. (potassium bromide) 2.9 to 3.05 μ (N-H).

Anal. Calcd. for $C_{14}H_{15}ClN_4$: C, 61.19; H, 5.50; N, 20.39. Found: C, 60.92; H, 5.78; N, 20.10.

6-Amino-4-γ-diethylamino-β-hydroxypropylamino-5-β,β-dimethyl-α-(*p*-chlorostyryl)pyrimidine (Xb).

Four g. (0.013 mole) of IXa and 20 ml. of 1-amino-3-diethylamino-2-propanol were heated at 200° for 5 hours and the excess amine distilled off (b.p. at 0.5 mm. - 65°). The residue was a dark oil and could not be crystallized. To purify the product, the sulfate salt was generated with dilute sulfuric acid, washed with ether and the free amine liberated with dilute sodium hydroxide. The free amine was extracted with ether, washed with water, dried and the ether removed. The latter procedure was repeated three times, until the free amine solidified. It was recrystallized from a mixture of benzene and hexane, to give 1.9 g. (36%) of white crystals; m.p. 127-130°; I.R. (potassium bromide) 2.9-3.2 μ (NH).

Anal. Calcd. for $C_{21}H_{30}ClN_5O$: C, 62.44; H, 7.48; N, 17.34. Found: C, 62.71; H, 7.48; N, 17.22.

6-Amino-4-β-diethylaminoethylamino-5-β,β-dimethyl-α-(*p*-chlorostyryl)pyrimidine (Xc).

Four g. (0.013 mole) of IXa and 20 ml. of *N,N*-diethylethylenediamine were heated at reflux for 4 hours and the excess amine distilled off (b.p. 144-146°). The solidified residue was taken up in benzene, washed with water, dried over anhydrous magnesium

sulfate, filtered and the benzene removed. The residue was recrystallized from a benzene-hexane mixture, to give 1.9 g. (40%) of white crystals; m.p. 194-196°; I.R. (potassium bromide) 3.0 μ (N-H).

Anal. Calcd. for $C_{20}H_{28}ClN_5$: C, 64.21; H, 7.56; N, 18.7; Cl, 9.5. Found: C, 64.62; H, 7.61; N, 18.2; Cl, 9.7.

6-Amino-4-γ-diethylaminopropylamino-5-β,β-dimethyl-α-(*p*-chlorostyryl)pyrimidine (Xd).

Two g. (0.068 mole) of IXa and 15 ml. of *N,N*-diethylaminopropylamine were heated at reflux (170°) for 6 hours, and the excess *N,N*-diethylaminopropylamine then distilled off. The residue solidified. The solid material was partially soluble in benzene and partially soluble in water. The benzene layer was dried over anhydrous magnesium sulfate, filtered and the benzene removed. The solid material was recrystallized from a mixture of benzene-hexane, to give 1.1 g. (43%) of Xd; m.p. 138-140°; I.R. (potassium bromide) 2.95-3.1 μ (N-H).

Anal. Calcd. for $C_{21}H_{30}ClN_5$: C, 65.01; H, 7.79; N, 18.06. Found: C, 65.13; H, 7.69; N, 18.32.

6-Amino-4-γ-diethylamino-α-methylbutylamino-5-β,β-dimethyl-α-(*p*-chlorostyryl)pyrimidine (Xe).

Four g. (0.01 mole) of IXa and 15 ml. of 5-diethylamino-2-aminopentane were refluxed (190°) for 4 hours and the excess 5-diethylamino-2-aminopentane distilled off. The oily residue was taken up in benzene, washed with water, dried over anhydrous magnesium sulfate, filtered and the benzene removed. The residue, which did not solidify, was dissolved in dilute sulfuric acid, extracted with ether, treated with sodium hydroxide to liberate the free amine, and extracted with ether. The ether layer was dried over anhydrous magnesium sulfate, and filtered, and the ether removed. This procedure was repeated twice before the free amine was pure enough to crystallize. It was then recrystallized from a mixture of benzene-hexane, to give 1 g. (25%) of Xe; m.p. 109-111°; I.R. (potassium bromide) 2.9 to 3.1 μ (N-H).

Anal. Calcd. for $C_{23}H_{34}ClN_5$: C, 66.40; H, 8.24; N, 16.83. Found: C, 66.18; H, 7.97; N, 16.83.

4,6-Di-β-diethylaminoethylamino-5-β,β-dimethyl-α-(*p*-chlorostyryl)-pyrimidine (Xf).

Nine g. (0.03 mole) of 4,6-dichloro-5-β,β-dimethyl-α-(4′-chlorostyryl)pyrimidine (VIII) and 75 ml. of *N,N*-diethylethylenediamine were refluxed for 3 hours (145°). The excess *N,N*-diethylethylenediamine was then distilled off. The residue could not be solidified, therefore it was dissolved in sulfuric acid, washed with ether, and the aqueous layer neutralized with sodium hydroxide. The free amine was extracted with ether, dried over anhydrous magnesium sulfate, filtered and the ether removed. This procedure was repeated three times. The free amine was then recrystallized from a mixture of benzene-hexane, to yield 3 g. (21%) of Xf; m.p. 75-77°; I.R. (potassium bromide) 3.0 μ (N-H).

Anal. Calcd. for $C_{26}H_{41}ClN_6$: C, 66.02; H, 8.73; N, 17.76. Found: C, 66.39; H, 8.86; N, 17.66.

4,6-Di-γ-diethylaminopropylamino-5-β,β-dimethyl-α-(*p*-chlorostyryl)pyrimidine (Xg).

Nine g. (0.03 mole) of VIII and 75 ml. of *N,N*-diethylpropylenediamine were refluxed for 3 hours (169°). The excess *N,N*-diethylpropylenediamine was then distilled off. The oil was dissolved in sulfuric acid, washed with ether, and the aqueous layer neutralized. The free amine was extracted with ether, dried over anhydrous magnesium sulfate, filtered and the ether removed. This procedure was repeated three times, and the free amine then recrystallized from a mixture of benzene-hexane, giving 3.1 g. (20%) of Xg; m.p. 71-72°; I.R. (potassium bromide) 3.0 μ (N-H).

Anal. Calcd. for $C_{28}H_{45}ClN_6$: C, 67.10; H, 9.05; N, 16.77. Found: C, 67.20; H, 9.07; N, 16.36.

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