Anal. Calcd. for $C_{21}H_{25}N_5O_6 \cdot {}^1/_2H_2O$: C, 55.8; H, 5.79. Found: C, 55.9; H, 5.90.

The mother liquors from the separation of the above material (0.080 g.) were diluted with 2.5 ml. of water and chilled, giving 0.100 g. (21.3% calculated as the hydrate with 2.5 moles of water), of crystalline solid which showed the same melting behavior as the hemihydrate (*cf.* above); λ_{max}^{Nujol} (μ) 2.98 (NH), 5.84–5.92 (carboxyl and amide C=O), 6.21 (pyrimidine and phenyl rings), 6.60 (amide NH), 11.95 (disubstituted phenyl), 13.10 (pyrimidine ring). The paper chromatographic behavior of the sample was identical with that of the hemihydrate.

Anal. Calcd. for $C_{21}H_{25}N_5O_6 \cdot 2{}^1/_2H_2O$: C, 51.6; H, 6.19; N, 14.3. Found: C, 51.7, 51.7; H, 5.89, 6.11; N, 14.2.

B. From the N-acetyl aldehyde XIV. A suspension of 0.47 g. (2.00 mmoles) of aldehyde XIV, 0.53 g. (2.00 mmoles) of *p*-aminobenzoyl-L-glutamic acid, 0.050 g. of platinum oxide, and 10 ml. of 2-methoxyethanol was vigorously stirred with hydrogen at 35° and atmospheric pressure for 3.5 hr., when 1 molar equivalent of hydrogen had been absorbed. The mixture was filtered, the filtrate was concentrated *in vacuo* to 3 ml., water (2 ml.) was added, and the solution was chilled. A black gum deposited and was removed by decantation of the supernatent liquid which was evaporated *in vacuo*, leaving 0.90 g. (93%) of residue. The residue was dissolved in 40 ml. of 0.1*M* aqueous sodium hydroxide, the solution heated on the steam bath for 30 min., filtered and the filtrate adjusted to *p*H 3–4 with 1*M* hydrochloric acid. The precipitate (0.60 g.) was stirred with 4.0 ml. of hot (100°) *N,N*-dimethylformamide and the insoluble, white crystalline material removed by filtration to give 0.033 g. (3.65% calculated as the hemihydrate) of solid which had the same melting behavior, infrared spectrum and paper chromatographic behavior as the hemihydrate isolated from procedure A (*cf.* above).

Anal. Calcd. for $C_{21}H_{25}N_5O_6 \cdot {}^1/_2H_2O$: C, 55.8; H, 5.79; N, 15.5. Found: C, 56.0, 55.9; H, 5.80, 5.83; N, 15.0, 15.2.

The *N,N*-dimethylformamide solution, after removal of the hemihydrate, was diluted with 4 ml. of water and chilled. The crystalline precipitate was washed with *N,N*-dimethylformamide, then water; yield 0.156 g. (16.5% calculated as the sesquihydrate) of solid whose melting and chromatographic behaviors were identical with those of the hemihydrate and whose infrared spectrum was almost identical with that of the compound containing 2.5 moles of water isolated from procedure A (*cf.* above).

Anal. Calcd. for $C_{21}H_{25}N_5O_6 \cdot 1{}^1/_2H_2O$: C, 53.6; H, 5.99; N, 14.9. Found: C, 53.8, 53.8; H, 6.21, 6.29; N, 14.7, 14.8.

Acid hydrolysis of I. A solution of 5 mg. of the hemihydrate of I (prepared by procedure A) in 5 ml. of 6*M* hydrochloric acid was heated at 100° for 1 hr. and was evaporated to dryness *in vacuo*. Water (1 ml.) and 2 drops of 10% aqueous sodium hydroxide were added to the residue and the *p*H was adjusted to 5 with 1*M* hydrochloric acid. The precipitate was separated by centrifugation and the supernatent liquid was removed. Both the solid (3.5 mg.) and the supernatent liquid were subjected to paper chromatography in solvent A. The solution showed the presence of glutamic acid (R_f 0.30) and the solid showed two spots at R_f 0.65 and 0.80 which lined up exactly with the spots from the product of a similar acid hydrolysis of the *N*-acetylpteroic acid XVIII.

Acknowledgment. The authors are indebted to Dr. Peter Lim for interpretation of the infrared spectra and to his staff for the paper chromatography. They also wish to thank Mr. O. P. Crews, Jr., and his staff for large-scale preparation of certain intermediates and Dr. J. Greenberg for the microbiological assays.

MENLO PARK, CALIF.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF KANSAS]

Condensation of Isocyanates with Reissert Compounds; Synthesis of an Analog of Lidocaine

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O-Benzoyl-*N*-phenylisoquinaldamide and *O*-benzoyl-*N*-(α-naphthyl)isoquinaldamide were prepared by the reaction of phenyl and 1-naphthyl isocyanate, respectively, with the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile. Hydrolysis of the *O*-benzoyl derivatives gave *N*-phenylisoquinaldamide and *N*-(α-naphthyl)isoquinaldamide, respectively, plus benzoic acid. There was no analogous reaction between the isocyanates and the lithium salt of 1-benzoyl-1,2-dihydroquinaldonitrile.

Catalytic hydrogenation of *N*-phenylisoquinaldamide gave the tetrahydro derivative, and treatment of the latter compound with ethyl iodide afforded *N*-phenyl-2-ethyl-1,2,3,4-tetrahydroisoquinaldamide, an analog of the local anesthetic Lidocaine.

Although Reissert compounds, 1-acyl-1,2-dihydroquinaldonitriles (I) and 2-acyl-1,2-dihydroisoquinaldonitriles (II), are mainly noted for their ability to form aldehydes on acid-catalyzed hydrolysis, increased attention in recent years has been directed toward the use of such compounds in the synthesis of diverse quinoline and isoquinoline derivatives.[1-11] The present communication describes an extension of the latter area of work, one leading to the production of the *O*-acyl derivatives

(1) W. E. McEwen and R. L. Cobb, *Chem. Revs.*, **55**, 511 (1955).

(2) R. L. Cobb and W. E. McEwen, *J. Am. Chem. Soc.*, **77**, 5042 (1955).

(3) A. P. Wolf, W. E. McEwen, and R. H. Glazier, *J. Am. Chem. Soc.*, **78**, 861 (1956).

(4) F. D. Popp and W. E. McEwen, *J. Am. Chem. Soc.*, **79**, 3773 (1957).

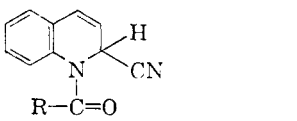
(5) L. R. Walters, N. T. Iyer, and W. E. McEwen, *J. Am. Chem. Soc.*, **80**, 1177 (1958).

(6) F. D. Popp and W. E. McEwen, *J. Am. Chem. Soc.*, **80**, 1181 (1958).

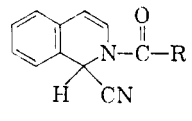
(7) N. C. Rose and W. E. McEwen, *J. Org. Chem.*, **23**, 337 (1958).

(8) N. C. Rose, L. R. Walters, and W. E. McEwen, *J. Org. Chem.*, **23**, 341 (1958).

of *N*-substituted isoquinaldamides. One such condensation product has been converted by a series of three reactions into an analog of Lidocaine (III), a prominent local anesthetic.



I



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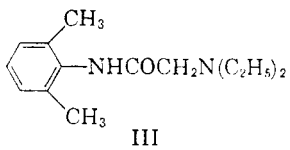
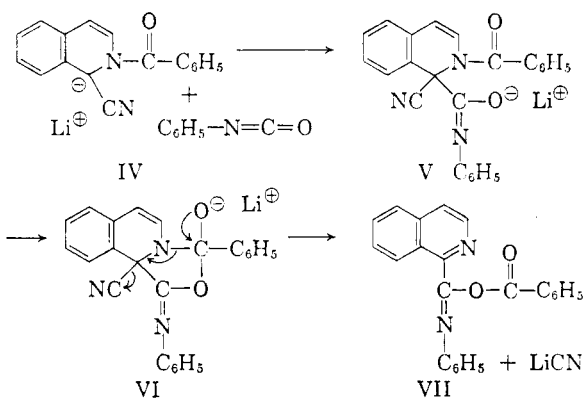


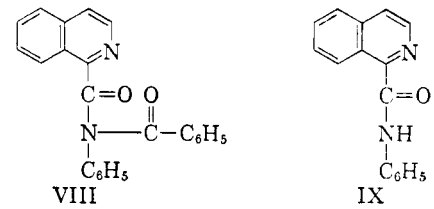
III

The reaction of the lithium salt (IV) of 2-benzoyl-1,2-dihydroisoquinaldonitrile (II. R = C_6H_5) with phenyl isocyanate to give *O*-benzoyl-*N*-phenylisoquinaldamide (VII) plus lithium cyanide will be taken as the basis for a discussion of the condensation reactions. There can be little doubt that the mechanism of the reaction involves an initial nucleophilic addition of the anion of the Reissert compound to the carbonyl carbon atom of phenyl isocyanate to form V, which then gives the cyclic intermediate VI. Elimination of lithium cyanide (see curved arrows) affords VII, and, in common with other similar reactions of Reissert compounds, the gain in resonance energy accompanying the elimination-rearrangement step provides an important driving force for the reaction.



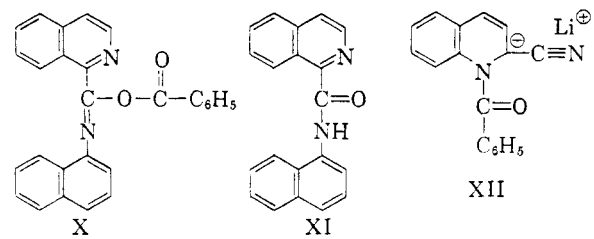
IV V VI VII

The structure *O*-benzoyl-*N*-phenylisoquinaldamide (VII) rather than *N*-benzoyl-*N*-phenylisoquinaldamide (VIII) was assigned to the final condensation-rearrangement product on the basis of the infrared spectrum of the product, which had absorption peaks at 1690 and 1600 cm.$^{-1}$ If VIII had been formed, the infrared absorption spectrum should have contained peaks in the regions 1790–1720 and 1710–1670 cm.$^{-1}$ [12] It should also be noted that hydrolysis of the condensation product gave *N*-phenylisoquinaldamide (IX) and benzoic acid as the sole products. That the hydrolysis product was IX was established beyond question by its unequivocal synthesis; an authentic sample of the compound was prepared by the reaction of isoquinaldoyl chloride with aniline.



VIII IX

O-Benzoyl-*N*-(α-naphthyl)isoquinaldamide (X) was obtained by the condensation of IV with α-naphthyl isocyanate. Hydrolysis of X afforded *N*-(α-naphthyl)isoquinaldamide (XI) and benzoic acid. However, no condensation product was obtained when IV was treated with *p*-tolyl isocyanate, and, furthermore, the lithium salt, XII, of 1-benzoyl-1,2-dihydroquinaldonitrile (I. R = C_6H_5) did not give condensation products in attempted reactions with phenyl isocyanate and α-naphthyl isocyanate.



X XI XII

As yet, the electronic and steric influences on the course of the condensation-rearrangement reactions have not been clarified completely. However, it appears that in the case of the anion of the lithium salt, XII, the diffusion of the negative charge by resonance decreases the nucleophilic character of the 2-position of the quinoline ring to such an extent that condensation with the isocyanates does not take place.[13] Even in the case of the anion of the lithium salt, IV, the nucleophilicity of the carbon atom at the 1-position of the isoquinoline ring appears to be very nearly the minimum value possible for a successful condensation reaction, inasmuch as even a relatively small

(9) R. F. Collins and T. Henshall, *J. Am. Chem. Soc.*, 80, 159 (1958).

(10) J. W. Davis, Jr., *J. Org. Chem.*, 24, 1691 (1959).

(11) J. W. Davis, Jr., *J. Org. Chem.*, 25, 376 (1960).

(12) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen and Co., Ltd., London, 1954, p. 190.

(13) In the anion of XII the negative charge is shared mainly by the nitrogen atom of the cyano group and by the carbon atoms in the 2 and 4 positions of the quinoline ring. These structures having a formal negative charge on carbon carry double the weight of the structures in which the negative charge appears on carbons 5, 7, and 8a of the quinoline ring because of the presence of an intact benzene ring in the former, but not the latter structures. In the anion of IV, on the other hand, the negative charge is shared mainly by the nitrogen atom of the cyano group and the carbon atom in the 1-position of the isoquinoline ring. Thus, the negative charge density is greater at the 1-carbon of the anion of IV than at the 2-carbon of the anion of XII.

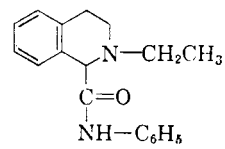
decrease in the electrophilicity of the carbonyl carbon atom of phenyl isocyanate, caused by the presence of a mildly electron-repelling methyl group in the para position of the benzene ring, causes the reaction to be inhibited.

All of the condensation reactions were carried out in ether-dioxane solution at a temperature not exceeding 30°, with but one exception to be mentioned later. The lithium salt of the Reissert compound was first prepared by a metalation reaction with phenyllithium. Following this, the isocyanate was added to the organometallic reagent. The lithium salt of each Reissert compound possesses a deep red color in ether-dioxane solution, and this color disappears as the condensation reaction with the isocyanate progresses. It is noteworthy that in those cases in which both the nucleophilicity of the Reissert anion and the electrophilicity of the isocyanate are relatively great, as evidenced by theoretical considerations, rapid discharge of the red color of the anion of the Reissert compound, and isolation of a high yield of the *O*-benzoylamide, the final reaction mixture, before the hydrolysis step, was nearly colorless. In the case of the attempted condensation of IV with *p*-tolyl isocyanate, the bright red color remained unchanged throughout the entire reaction period and, after the hydrolysis step, II (R = C_6H_5) was recovered in 81% yield. The attempts to effect condensation of XII with phenyl and α-naphthyl isocyanate gave orange reaction mixtures which, upon hydrolysis, afforded only intractable materials.

The above mentioned exception to the usual reaction conditions was in one of the attempted condensation reactions between XII and phenyl isocyanate. In this case, an attempt was made to carry out the reaction in refluxing dioxane subsequent to the initial formation of the lithium salt and addition of the isocyanate at 0°, but the increased reaction temperature proved to have no beneficial effect.

The introduction of Lidocaine (III) into the field of medicinal chemistry as a local anesthetic agent by Löfgren[14] in 1948 marked a departure from the benzoate ester type of structure commonly associated with such agents. Lidocaine (III), which has an aminoacyl amide structure, was found to be about two and one-half times as active as procaine.

On the basis of the success of Lidocaine as a local anesthetic, an attempt was made to determine the effect of the incorporation of the basic side chain into a ring system. The compound considered for synthesis was *N*-phenyl-2-ethyltetrahydroisoquinaldamide (XIII), wherein the nitrogen and one ethyl radical of the tertiary amino group form a part of the isoquinoline ring system. The analogy between the two compounds is readily apparent in a comparison of the structural formulas.



XIII

N-Phenylisoquinaldamide (IX), after conversion to the hydrochloride, was successfully reduced to *N*-phenyltetrahydroisoquinaldamide in 84% yield in a Parr low pressure hydrogenator at 52 p.s.i. gauge.

An initial attempt to convert *N*-phenyltetrahydroisoquinaldamide into *N*-phenyltetrahydroisoquinaldamide ethiodide by refluxing with ethyl iodide failed. However, when a solution of N-phenyltetrahydroisoquinaldamide and ethyl iodide was heated in a Parr bomb for five hours at 135°, there was obtained, after treatment with base, *N* - phenyl - 2 - ethyltetrahydroisoquinaldamide (XIII). Use of benzene as solvent resulted in a 55% yield; use of the polar solvent ethanol gave an 88% yield based on unrecovered starting material.

N-Phenyl-2-ethyltetrahydroisoquinaldamide hydrochloride was formed in quantitative yield by passing a stream of anhydrous hydrogen chloride gas through a solution of *N*-phenyl-2-ethyltetrahydroisoquinaldamide (XIII) in anhydrous ethanol.

Pharmacological testing. The pattern of activity suggests that *N*-phenyl-2-ethyltetrahydroisoquinaldamide hydrochloride may be a weak central nervous system depressant. This compound produced clonic convulsions in the mice at 150 mg./kg. The compound, while not exhibiting significantly strong effect in the mouse behavior test (i.p. dosing), was somewhat unusual in that the toxicity was much less than that commonly associated with isoquinoline compounds.[15]

EXPERIMENTAL[16]

1-Benzoyl-1,2-dihydroquinaldonitrile (I. R = C_6H_5). This compound was prepared by the method of Rupe, Paltzer, and Engel.[17] Recrystallization from ethanol yielded light yellow crystals, melting point 151–153° (reported,[17] m.p. 154–155°).

2-Benzoyl-1,2-dihydroisoquinaldonitrile (II. R = C_6H_5). This compound was prepared by the method of Padbury and Lindwall.[18] Recrystallization from ethanol yielded colorless crystals, melting point 124–127° (reported,[18] m.p. 125–126°).

(14) N. Löfgren, *Studies on Local Anesthetics. Xylocaine, A New Synthetic Drug*, Ivar Haeggströms, Stockholm, 1948.

(15) We are indebted to Dr. Dwight D. Morrison of the Eli Lilly Co. who made the arrangements for the testing of this compound.

(16) All melting points are corrected. Analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(17) H. Rupe, R. Paltzer, and K. Engel, *Helv. Chim. Acta*, **20**, 209 (1937).

(18) J. J. Padbury and J. G. Lindwall, *J. Am. Chem. Soc.*, **67**, 1268 (1945).

Phenyllithium. Freshly prepared phenyllithium, made by the method of Gilman,[19] was used for each experiment. The lithium bromide formed during the reaction was not removed.

O-Benzoyl-N-phenylisoquinaldamide (VII). To a solution of 10.4 g. (0.04 mole) of 2-benzoyl-1,2-dihydroisoquinaldonitrile (II. R = C_6H_5) in 150 ml. of anhydrous ether and 75 ml. of anhydrous dioxane maintained at −10° in an atmosphere of pure nitrogen was added with mechanical stirring an ether solution of 0.04 mole of freshly prepared phenyllithium. To the resultant red solution was added dropwise with stirring a solution of 4.7 g. (0.04 mole) of phenyl isocyanate in 25 ml. of anhydrous ether. The mixture was stirred for an hour at −10°, then warmed to room temperature and stirred for an additional 8 hr., at the end of which time it was cream colored.[20] Sufficient ether was added to increase the total volume of the mixture to 500 ml., and 12 ml. of water was added. This caused a solid to precipitate. The solid material was collected by filtration, and, when dried, it amounted to 8.82 g. (63.4%) of crude VII, m.p. 170–190°. Several recrystallizations from acetone-water gave colorless, crystalline material of m.p. 203.2–205.5°.

Anal. Calcd. for $C_{23}H_{16}N_2O_2$: C, 78.40; H, 4.56; N, 7.95. Found: C, 78.12; H, 4.84; N, 7.84.

The yield of VII could be raised to 96% by the use of a twofold excess of the lithium salt, IV, of 2-benzoyl-1,2-dihydroisoquinaldonitrile.

Hydrolysis of O-benzoyl-N-phenylisoquinaldamide (VII). A solution of 3.0 g. of VII in 45 ml. of ethanol was added to a solution of 3.0 g. of potassium hydroxide, and the resulting mixture was refluxed for 7 hr. Some of the ethanol was removed by distillation *in vacuo*, and a solid precipitated from the cooled residue. This was collected by filtration, washed with water, and dried to give 1.77 g. (51%) of crude *N*-phenylisoquinaldamide (IX), m.p. 105–118°. An additional 0.89 g. (26%) of the same compound could be obtained by further concentration of the mother liquor. Several recrystallizations from ethanol gave colorless, crystalline material of m.p. 119–121°.

Anal. Calcd. for $C_{16}H_{12}N_2O$: C, 77.43; H, 4.87; N, 11.23. Found: C, 77.66; H, 4.94; N, 11.30.

Benzoic acid was obtained by acidification of the alkaline filtrate, from which the last traces of organic solvents and solids had been removed.

N-Phenylisoquinaldamide (IX). To a solution of 0.5 g. of isoquinaldic acid in 30 ml. of anhydrous benzene was added a solution of 1.5 ml. of thionyl chloride in 10 ml. of benzene. The mixture was refluxed until evolution of hydrogen chloride ceased. The bright red solution was cooled to room temperature, and to it was added a solution of 1 ml. of aniline in 10 ml. of benzene. A colorless solid which precipitated was collected by filtration, washed with water, dried, and recrystallized from ethanol. There was obtained colorless crystals of *N*-phenylisoquinaldamide (IX), m.p. 119–121°, also in admixture with the sample obtained by hydrolysis of VII. The infrared spectra of the two samples, taken in chloroform solution, were identical.

O-Benzoyl-N-(α-naphthyl)isoquinaldamide (X). The condensation reaction between IV and α-naphthyl isocyanate was carried out in exactly the same manner as described for the preparation of VII. There was obtained a 90% yield of crude X. After several recrystallizations from acetone-water, its m.p. was 214.5–216.5° dec.

Anal. Calcd. for $C_{27}H_{18}N_2O_2$: C, 80.56; H, 4.50; N, 6.96. Found: C, 80.44; H, 4.52; N, 7.17.

N-(α-Naphthyl)isoquinaldamide (XI). The hydrolysis of X was carried out in the same manner as the hydrolysis of VII. There was obtained a 49% yield of crude XI, m.p. 160–170°. After several recrystallizations from ethanol (Norite), XI was obtained as a yellow, crystalline solid, m.p. 168–170°.

Anal. Calcd. for $C_{20}H_{14}N_2O$: C, 80.52; H, 4.73; N, 9.39. Found: C, 80.48; H, 4.87; N, 9.67.

N-Phenyltetrahydroisoquinaldamide. *N*-Phenylisoquinaldamide (IX), 1.2 g. (0.0048 mole), was dissolved in 150 ml. of absolute ethanol. Addition of an equivalent amount of concentrated hydrochloric acid solution, 0.46 g. of 37% hydrochloric acid (0.0048 mole), resulted in the formation of a flocculent yellow precipitate. After addition of 50 mg. of platinum oxide, the mixture was reduced in a Parr low pressure hydrogenator at a pressure of approximately 52 p.s.i. gauge. After the solid had completely dissolved the reduction was stopped, and the catalyst was removed by filtration. The filtrate was evaporated to dryness under an air-jet and the residue suspended in an aqueous solution of sodium bicarbonate. The mixture was extracted several times with ether. After having been dried over Drierite, the combined ether extracts, on evaporation, yielded 1.00 g. (84%) of crude *N*-phenyltetrahydroisoquinaldamide, m.p. 125–129°. After three recrystallizations from ethanol-water the compound melted at 138.5–139.4°.

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.30; H, 6.55; N, 11.13.

Treatment of N-phenylisoquinaldamide with ethyl iodide. In an attempt to form a quaternary ammonium salt, *N*-phenylisoquinaldamide was refluxed for a short time with excess ethyl iodide in benzene solution. After evaporation of the volatile components, a mixed melting point test of the residue with an authentic sample of *N*-phenylisoquinaldamide showed no depression. Use of a large excess of ethyl iodide as solvent in the above reaction also yielded only starting material.

N-Phenyl-2-ethyltetrahydroisoquinaldamide (XIII). A Parr bomb was charged with 1.0 g. (0.0039 mole) of *N*-phenyltetrahydroisoquinaldamide, 0.70 g. (0.0049 mole) of ethyl iodide and 10 ml. of anhydrous ethanol. The bomb was then heated for 5 hr. in an oil bath maintained at 135°. After the bomb and its contents had been cooled, the bulk of the ethanol was evaporated and the residue stirred with a solution of sodium carbonate. The resulting mixture was extracted several times with ether, and, after drying and evaporation of the combined ether washes, there was obtained 0.76 g. of a tan solid. Recrystallization from an ethanol-water mixture yielded 0.56 g. (52% yield; 88% yield based on unrecovered starting material) of white, hair-like crystals, m.p. 99–101°. Several additional recrystallizations yielded a sample of m.p. 101–102°.

Anal. Calcd. for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.02; H, 7.06; N, 10.11.

N-Phenyl-2-ethyltetrahydroisoquinaldamide hydrochloride. Anhydrous hydrogen chloride gas, in excess, was passed into a solution of *N*-phenyl-2-ethyltetrahydroisoquinaldamide (XIII) in anhydrous ethanol. Evaporation of the solvent and recrystallization of the residue from anhydrous ethanol-acetone provided a quantitative yield of a fine white solid, m.p. 231–234°. Several additional recrystallizations gave a sample of m.p. 244–246° dec.

Anal. Calcd. for $C_{18}H_{21}N_2OCl$: C, 68.23; H, 6.68; N, 8.84; Cl, 11.19. Found: C, 68.32; H, 6.77; N, 8.84; Cl, 10.90.

Acknowledgment. This investigation was supported by a research grant, E-1961, from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health, Public Health Service.

LAWRENCE, KAN.

(19) H. Gilman, *J. Am. Chem. Soc.*, **55**, 1262 (1933).

(20) This procedure parallels that used by V. Boekelheide and J. C. Godfrey [*J. Am. Chem. Soc.*, **75**, 3679 (1953)] for the condensation of II with acrylonitrile and related compounds.