

Synthesis of Nitrogen Heterocycles by Condensation of the Conjugate Base of Open-Chain Reissert Compound Analogs with Vinyltriphenylphosphonium Bromide (Schweizer's Salt)

John V. Cooney* and Bruce D. Beaver [1]

Chemistry Division, Naval Research Laboratory,
Washington, DC 20375 USA

William E. McEwen*

Department of Chemistry, University of Massachusetts,
Amherst, Massachusetts 01003 USA

Received October 4, 1984

Reaction of the conjugate base of several open-chain Reissert compound analogs with vinyltriphenylphosphonium bromide is shown to afford a convenient route to substituted pyrroles. The condensation is a two-step process involving an initial reversible addition to form an unstabilized Wittig reagent followed by an intramolecular Wittig reaction upon the carbonyl group of the tertiary amide functionality with concomitant elimination of HCN. Several applications to the synthesis of 1,2,5-trisubstituted pyrroles are presented, together with attempts to expand this methodology to the synthesis of other heterocyclic systems.

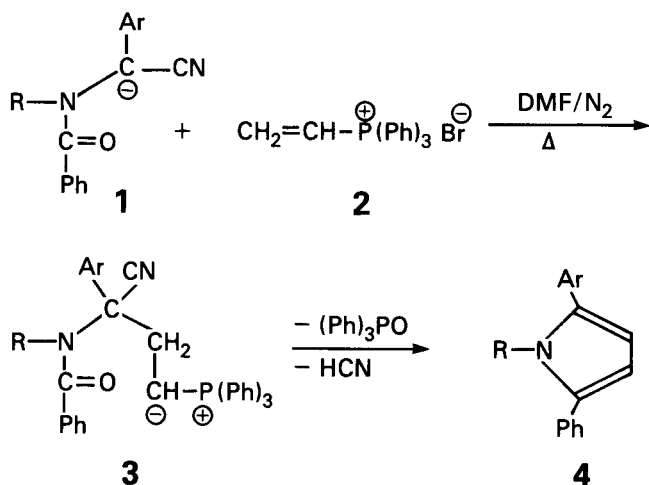
J. Heterocyclic Chem., **22**, 635 (1985).

The study of the chemistry of Reissert compounds and related heterocycles has led to the development of several useful synthetic procedures for the construction of a variety of natural products [2-6]. In previous work, we have shown that open-chain analogs of Reissert compounds (*i.e.*, derivatives of *N*-acyl- α -aminoacetonitrile) are readily prepared, and have demonstrated several synthetic uses of these compounds under both acidic and basic conditions [2,7-10]. In 1981, we reported that the condensation of the conjugate base of open-chain Reissert analogs derived from mandelonitrile with vinyltriphenylphosphonium bromide (VTB) afforded a one-pot synthesis of 1,2,5-trisubstituted pyrroles [9]. The reaction represents an extension of Schweizer's excellent methodology for the construction of heterocyclic systems *via* an intramolecular Wittig reaction [11-20]. A key feature of the reaction, sum-

marized in Scheme 1, is an unprecedented Wittig olefination wherein an unstabilized phosphorus ylide condenses with the carbonyl group of a tertiary amide. Since our initial report, Le Corre *et al.* [21] provided a second example of this general type of olefination when they generated substituted indoles in high yields from *o*-acylaminobenzyltriphenylphosphonium salts upon treatment with base.

Our interest in the study of this novel "amide-Wittig" reaction has led us to examine several additional open-chain Reissert analogs as substrates in an effort to understand better the effects of substitution in the reaction. To this end, we have sought to prepare the pyrroles **6a-j** indicated in Scheme 2 from the base-induced reaction of open-chain Reissert analogs **5a-j** with VTB (**2**) in refluxing DMF. Such a sequence could permit the facile, selective synthesis of 1,2,5-trisubstituted pyrroles bearing differing

SCHEME 1



SCHEME 2

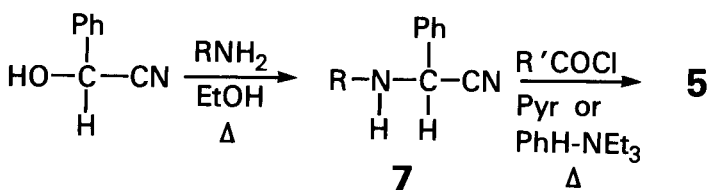


- 5a**: R, R' = Ph, R'' = 4-Cl-Ph
b: R, R'' = Ph, R' = 4-Cl-Ph
c: R, R' = Ph, R'' = 3,4-di-MeO-Ph
d: R, R'' = Ph, R' = 3,4-di-MeO-Ph
e: R, R' = Ph, R'' = n-Bu
f: R, R'' = Ph, R' = n-Bu
g: R = 4-Cl-Ph, R' = Me, R'' = Ph
h: R = Mesityl, R' = Me, R'' = Ph
i: R = 2-Picolyl, R', R'' = Ph
j: R = 2-Pyridyl, R', R'' = Ph

substituents at each ring position from readily available amines, aldehydes and acid chlorides. The classic alternative, the Paal-Knorr synthesis, would often require the use of less-available 1,4-dicarbonyl compounds.

When the anion of *N*-benzoylanilino(4-chlorophenyl)acetonitrile (**5a**) was treated with VTB in refluxing DMF for 24 hours and allowed to cool, the expected pyrrole product precipitated from the reaction mixture and was recovered in 88% yield. An alternative synthesis of **6a** employed the anion of open-chain Reissert analog **5b**, in which the 4-Cl-phenyl moiety is present as part of the amide functionality. Compound **5b** was generated in 88% overall yield from mandelonitrile. Scheme 3 indicates the sequence used for the synthesis of all newly prepared open-chain Reissert analogs **5b,d,f,i,j**. The acylation of **7** (R = Ph) to give **5b** proceeded well in benzene when one equivalent of triethylamine was present. Attempted acylation in pyridine resulted in predominant formation of 4-chlorobenzoic anhydride after work-up. Reaction of **5b** with VTB afforded the expected pyrrole **6b** (identical to **6a**) in high yield (89%).

SCHEME 3



The effect of the presence of an electron-donating substituent in the aryl group of the original cyanohydrin moiety upon the pyrrole synthesis was next examined. The anion of **5c** reacted with VTB to produce the expected product, 1,2-diphenyl-5-(3,4-dimethoxyphenyl)pyrrole (**6c**), in an isolated yield of 65%. The alternative synthesis of

the product required the use of compound **5d**, which was afforded in 67% overall yield following the procedure of Scheme 3 (using pyridine). Subsequent reaction of the anion of **5d** with VTB afforded the anticipated pyrrole **6d** in 67% yield. Again, it was observed that the placement of a substituted phenyl group either on the acetonitrile group or in the amide functionality had little net effect on the yield of the pyrrole obtained. The preparation of **5d** in pyridine was accompanied by the formation of side-product **8** in 17% yield (after column chromatography). It was shown that **8** does not arise from a fragmentation of the open-chain Reissert analog **5d** since: (a) refluxing **5d** in pyridine for 8 hours and (b) refluxing **5d** with veratroyl chloride for 8 hours in pyridine gave no **8**. A possible mechanism for the formation of α -phenyliminophenylacetonitrile (**8**) is shown in Scheme 4.

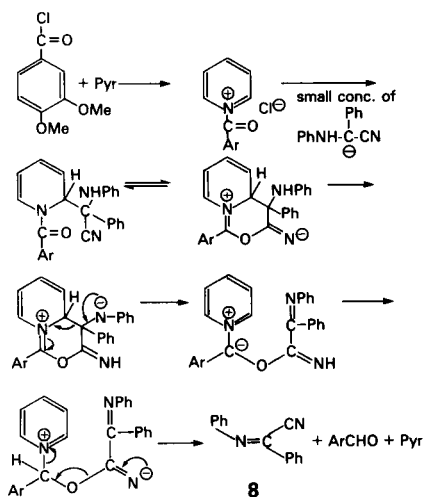
In order to examine the effect of alkyl substitution on the pyrrole synthesis, *N*-benzoyl-2-anilinohexanenitrile (**5e**) was studied. De-protonation was effected at -78° in THF with LDA as the base for this less acidic compound. Upon addition of VTB in DMF (resulting in a mixed solvent system), and after application of heat, the desired product 1,2-diphenyl-5-*n*-butylpyrrole (**6e**) was isolated in 55% yield, together with a 27% recovery of unreacted **5e**. As an alternative route to **6e** (**6f**), the anion of *N*-valeryl-anilino-phenylacetonitrile (**5f**) was treated with VTB under the usual conditions (*i.e.*, NaH/DMF/reflux). Compound **5f** was synthesized in 50% yield from α -anilino- α -phenylacetonitrile and valeryl chloride in anhydrous pyridine. After column chromatography and recrystallization, only a 4.4% yield of the pyrrole was obtained. Thus, it would appear that the placement of an alkyl group in the amide functionality (*i.e.*, open-chain Reissert analogs derived from aliphatic acid halides) in some way interferes with the required intramolecular Wittig reaction. The lack of reactivity may in part be attributable to inductive electron donation rendering the amide carbonyl less electrophilic. However, a more significant factor may be the formation of an enolate anion involving the alkyl group, a process which may be extensive in the polar DMF medium.

Reaction of *N*-acetyl-*p*-chloroanilino-phenylacetonitrile (**5g**) with VTB led to the expected formation of 1-(4-chlorophenyl)-2-phenyl-5-methylpyrrole (**6g**), a pyrrole bearing three different substituents. The relatively low yield (30%) of the product is not unexpected since the Reissert analog is derived from an aliphatic acid chloride, acetyl chloride. Evidence in support of the structure of **6g** was obtained by infrared and nmr spectra as well as by elemental analysis.

An attempt was made to prepare a sterically hindered pyrrole, 1-mesityl-2-phenyl-5-methylpyrrole (**6h**), by treating the anion of 2-(*N*-2,4,6-trimethylphenyl)acetamido-phenylacetonitrile with VTB. The preparation was unsuccessful, with the *N*-acetyl derivative of mesitylamine

SCHEME 4

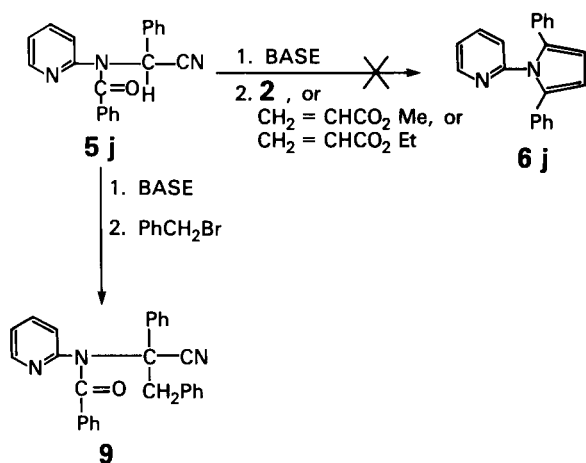
(Ar is 3,4-dimethoxyphenyl)



(2,4,6-trimethylaniline acetate) resulting as the sole isolated product (in 86% yield). If the assumption is made that the initially formed anion of **5h** added to VTB to generate the expected ylide (the characteristic color of the anion of **5h** was observed to rapidly change upon addition of VTB), then decomposition of the adduct can be envisioned to occur by several possible pathways which would result in the formation of the observed mesitylamine acetate. It is conceivable that the desired Wittig olefination was hindered by steric constraints imposed by the presence of the mesityl moiety in combination with the "aliphatic acid halide" effect noted earlier.

Open-chain Reissert analog **5i**, derived from 2-aminomethylpyridine, was found to react with VTB in the anticipated manner to afford a 54% yield of the pyrrole **6i**. Replacement of the 2-picolyl moiety in **5i** by a 2-pyridyl group (as in **5j**) was observed to alter the chemistry of the Reissert analog markedly. Compound **5j** was afforded conveniently in 65% overall yield from mandelonitrile by the usual two-step sequence. Surprisingly, the anion formed from **5j** in NaH/DMF is colorless, rather than the usual deep red (which is characteristic for the anions of both Reissert compounds and their analogs). Repeated attempts to effect reaction of this anion with VTB were unsuccessful, as evidenced by recovery of the starting Reissert analog after work-up. Attempts to effect reaction with methyl and ethyl acrylate were also unsuccessful. However, it did prove possible to alkylate the anion of **5j** with benzyl bromide in DMF to form **9** (Scheme 5).

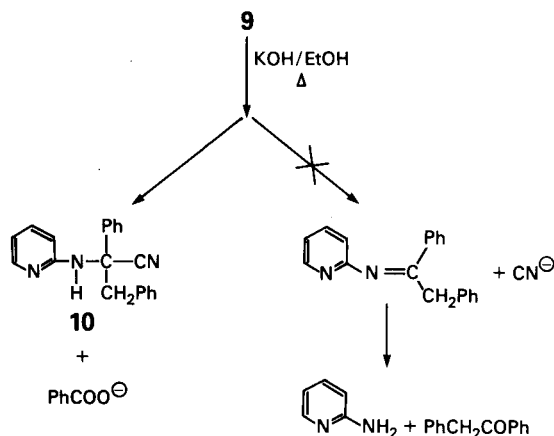
SCHEME 5



Presumably, the lack of effective reaction of the anion of **5j** with VTB and the acrylates is the result of an inductive (or other) effect of the pyridyl moiety. The fact that a pyridyl group is strongly electron-withdrawing when compared to a phenyl group is supported by many lines of evidence [22]. As a further probe of this effect, compound **9** was subjected to alkaline hydrolysis with ethanolic potas-

sium hydroxide (Scheme 6). Under these conditions, alkylated open-chain Reissert analogs generally hydrolyze to form desoxybenzoins [2,7,8]. Compound **9** was observed to form aminonitrile **10**, with no desoxybenzoins being isolated. Apparently, the conjugate base of **10**, which forms by way of conventional amide hydrolysis of **9**, is a relatively stable anion (owing to the stabilization effect of the pyridyl group) which is unable to eliminate the cyanide anion in the usual way. Thus, it would appear that the synthesis of 1-(2-pyridyl)-2,5-disubstituted pyrroles by way of the conjugate addition/intramolecular cyclization methodology employing open-chain Reissert analogs with either VTB or acrylates is not a favored process.

SCHEME 6



An effort was made to extend the amide-Wittig procedure using VTB to the synthesis of other heterocyclic systems. Since pyrrole rings had been formed by an intramolecular Wittig reaction involving the carbonyl group of a tertiary amide, it was considered possible to generate a furan ring by an analogous scheme. The production of a dihydrofuran by use of an intramolecular Wittig reaction (of a stabilized ylide) upon an ester has been reported [23]. The appropriate substrate was mandelonitrile benzoate (**11**, Scheme 7), which can be regarded as an "oxygen analog" of an open-chain Reissert compound analog. Treatment of the conjugate base of mandelonitrile benzoate with VTB was found to result ultimately in the formation of benzoin benzoate **12** in an amount 82% of theoretical; none of the desired 2,5-diphenylfuran was detected. Although the addition of the anion of **11** to VTB may have occurred (a rapid color change was noted upon addition of VTB to the anion), the rate of intramolecular Wittig condensation was not competitive with the principal reaction pathway. It is believed that benzoin, which was produced from benzaldehyde and cyanide ion (products of the hydrolysis of **11**), may have reacted further with unchanged **11** to generate **12** directly, with concomitant regene-

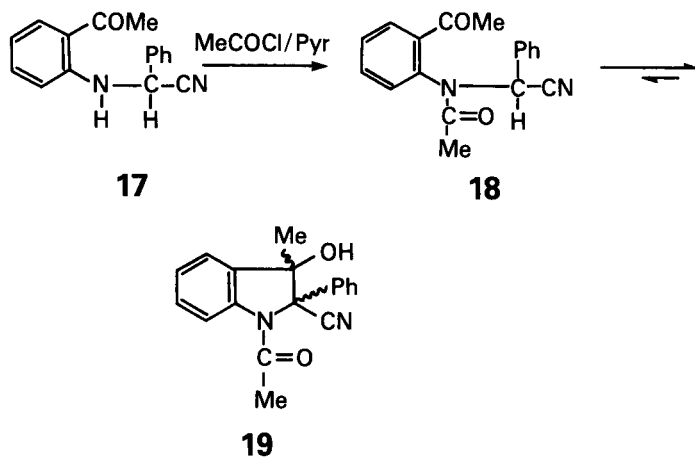
ration of the anion of mandelonitrile. The isolation of a significant amount (78% of theoretical) of triphenylphosphine suggests that free, unreacted VTB may have been hydrolyzed during aqueous work-up.

Several attempts were made to cause VTB to react with the anion of 1,2-dihydro-2-benzoyl-1-cyanoisoquinoline (**13**), a conventional Reissert compound. It was anticipated that the ultimate product of the amide-Wittig reaction would be 3-phenylpyrrolo[2,1-*a*]isoquinoline (**14**), a known compound [24,25]. All attempts to effect the desired cycloaddition were unsuccessful. The fact that sodium cyanide was recovered in nearly quantitative yield, combined with the recovery of triphenylphosphine by column chromatography, suggests that the Reissert anion did not add productively to the VTB; rather, an intramolecular rearrangement to form sodium cyanide and 1-benzoylisoquinoline may have occurred [26,27]. However, many products were formed in the reaction with little separation being effected by column chromatography, and the presence of 1-benzoylisoquinoline in the reaction mixture could not be demonstrated.

Finally, it was decided to attempt a synthesis of the benzazepine ring system utilizing an intramolecular Wittig reaction (**16**, Scheme 7). In this instance, it was anticipated that the addition of the anion of an open-chain Reissert

quent addition of benzyl chloride, gave a complex intractable oil. Similarly, attempted reaction with VTB led to the isolation of a complex, intractable oil.

SCHEME 8



EXPERIMENTAL

All melting points were taken in open capillary tubes using a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were recorded on Beckman IR-10 and Perkin Elmer 727 spectrophotometers. The ¹H-nmr spectra were recorded on a Varian A-60. Elemental analyses were performed by the Microanalysis Laboratory of the University of Massachusetts, Amherst. Thin layer chromatography (tlc) was conducted on pre-coated silica gel plates containing fluorescent indicator, Eastman Chromagram No. 13181. Silica gel for column chromatography was 100-200 mesh, Fisher reagent grade, which was deactivated by adding water to the extent of 10% by weight. All solvents were dried by standard procedures: benzene and hexane were distilled from calcium hydride, ethyl ether and THF were distilled from sodium benzophenone ketyl, and DMF was distilled at reduced pressure from anhydrous barium oxide and stored over fresh molecular sieves.

Compounds **2** [28], **5a,c,e** [7], **5g** [29], **5h** [30], **7** [7], **11** [31], and **13** [32] were synthesized according to methods reported in the literature. Synthetic procedures for all new compounds appear below.

1,2-Diphenyl-5-(4-chlorophenyl)pyrrole (**6a**).

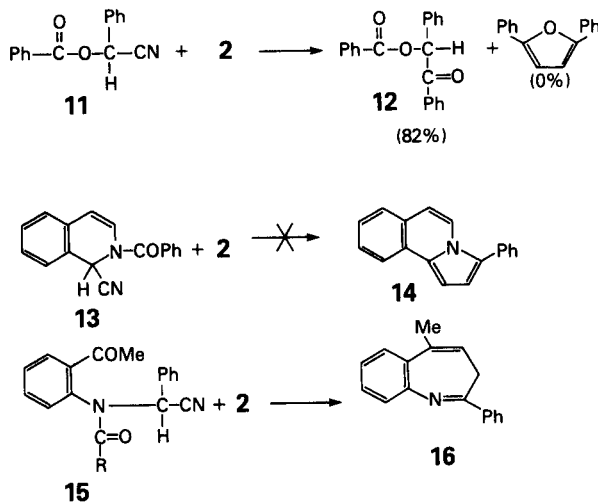
To a 0.53 g (0.011 mole) quantity of 50% sodium hydride, maintained under a nitrogen atmosphere, was added with stirring a solution of 3.47 g (0.010 mole) of *N*-benzoylanilino-(4-chlorophenyl)acetone nitrile (**5a**) in 25 ml of dry DMF. Evolution of hydrogen gas was observed to occur for 10 minutes, the reaction mixture becoming a cherry red color. A solution of 4.24 g (0.0115 mole) of vinyltriphenylphosphonium bromide (**2**) in 30 ml of dry DMF was added, and the color changed to a dark brown. The stirred reaction mixture was refluxed under a nitrogen atmosphere for 24 hours, allowed to cool to room temperature, then further cooled in a freezer to -25°. The precipitate which formed was collected, washed with a few ml of cool acetic acid, and recrystallized from glacial acetic acid to give 2.89 g (88%) of white solid. Additional recrystallization from ethanol afforded **6a** as a fluffy white solid, mp 229.5-231.5°; ir (chloroform): 1601 cm⁻¹ (C=C); nmr (deuteriochloroform): δ = 6.55 (m, 2H), 6.95-7.4 (m, 14H).

Anal. Calcd. for C₂₂H₁₆ClN: C, 80.11; H, 4.89; N, 4.25. Found: C, 79.98; H, 4.90; N, 4.22.

N-(4-Chlorobenzoyl)anilinophenylacetone nitrile (**5b**).

To a stirred mixture of 10.41 g (0.050 mole) of **7**, 5.10 g (0.050 mole) of

SCHEME 7



analog derived from *o*-aminoacetophenone to VTB would result in an intramolecular condensation upon the carbonyl group of the ketone in preference to amide attack. The reaction of *o*-aminoacetophenone with mandelonitrile afforded the appropriate aminonitrile **17** in greater than 90% yield, however repeated attempts to benzoylate **17** proved unsuccessful. Finally, the action of acetylpyridinium chloride afforded **19**, a tautomer of the desired **18**, as a mixture of diastereomers. Attempts to generate the anion of **18** *in situ* by action of sodium hydride, with subse-

dry triethylamine, and 50 ml of dry benzene was added dropwise 8.75 g (0.050 mole) of *p*-chlorobenzoyl chloride. The mixture was stirred for 15 minutes at room temperature, then heated to reflux. After 1 hour at reflux, the orange reaction mixture, which contained a large amount of semi-solid material, was poured into 400 ml of cold water, and the reaction vessel was rinsed with 200 ml of ether, which was added to the benzene-water layers contained in a separatory funnel. The organic layer was washed with 175 ml portions of 10% hydrochloric acid and water, 5% sodium hydroxide and water, then was dried (anhydrous magnesium sulfate). Removal of the ether and benzene afforded 18.93 g of a tarry orange solid. Recrystallization (ethanol) gave 15.20 g (88%) of a light orange solid, mp 106-112°. Additional recrystallizations (ethanol, carbon tetrachloride) gave a pure white crystalline solid, mp 120.5-122°, identified as **5b**; ir (chloroform): 1655 cm⁻¹ (C=O); nmr (deuteriochloroform): δ = 6.7-7.2 (m, 15H).

Anal. Calcd. for C₂₁H₁₅ClN₂O: C, 72.72; H, 4.36; N, 8.08; Cl, 10.22. Found: C, 72.69; H, 4.20; N, 7.83; Cl, 10.26.

1,2-Diphenyl-5-(4-chlorophenyl)pyrrole (**6b**).

Following the above procedure for **6a**, 3.47 g (0.010 mole) of **5b** was used. A brick red solution of the anion resulted, which immediately lightened in color to a yellow brown following addition of **2**. After 23 hours of reflux, 2.93 g (89%) of the crude pyrrole **6b** was isolated as an amorphous white solid, mp 228-230.5°. Recrystallizations from ethanol afforded pure **6b**, mp 229.5-231.5°, which was shown to be identical to **6a** by ir and nmr spectra as well as mixed mp.

1,2-Diphenyl-5-(3,4-dimethoxyphenyl)pyrrole (**6c**).

To a 0.53 g (0.011 mole) quantity of 50% sodium hydride, maintained under a nitrogen atmosphere, was added with stirring a solution of 3.72 g (0.010 mole) of *N*-benzoylanilino-(3,4-dimethoxyphenyl)acetonitrile (**5c**) in 40 ml of dry DMF. Evolution of hydrogen gas was observed to occur for 10 minutes whereupon the reaction mixture became blood red in color. A solution of 4.24 g (0.0115 mole) of **2** in 30 ml of dry DMF was added and the color lightened to a brownish-green. The stirred reaction mixture was refluxed under a nitrogen atmosphere for 20 hours, allowed to cool to room temperature, then further cooled in a freezer to -25°. The precipitate which formed was collected and recrystallized from ethanol to give 2.31 g (65%) of a white flaky solid, mp 158.5-159.5°. Purified **6c** was obtained by additional recrystallizations from ethanol and also had mp 158.5-159.5°; ir (chloroform): 2280 cm⁻¹ (OCH₃), 1020 cm⁻¹ (C-O-C); nmr (deuteriochloroform): δ = 3.50 (s, 3H), 3.82 (s, 3H), 6.46 (s, 2H), 6.75-7.35 (m, 13H).

Anal. Calcd. for C₂₄H₂₁NO₂: C, 81.10; H, 5.96; N, 3.94. Found: C, 80.88; H, 5.93; N, 3.84.

N-(3,4-Dimethoxybenzoyl)anilinophenylacetonitrile (**5d**).

A mixture of 18.22 g (0.100 mole) of veratric acid and 25 ml (41.38 g or 0.35 mole) of thionyl chloride was stirred and refluxed for 3 hours. Subsequent removal of excess thionyl chloride by vacuum distillation left a viscous purple oil which solidified with standing as it cooled. The crude 3,4-dimethoxybenzoyl chloride was used without further purification. A solution of 20.83 g (0.100 mole) of **7** in 100 ml of dry pyridine was cooled to 0°, then the freshly prepared 3,4-dimethoxybenzoyl chloride was added in small portions over a 10 minute period. After addition was complete, the reaction mixture was allowed to warm to room temperature and was stirred for 19 hours. The brown reaction mixture (which contained pyridine hydrochloride as precipitate) was poured with vigorous stirring into 500 g of ice water, and a yellow tarry solid formed. The mixture was extracted with ether (2 × 250 ml), which in turn was washed with 175 ml portions of 10% hydrochloric acid and water, 10% sodium hydroxide and water. After drying (anhydrous magnesium sulfate) the ether was removed to afford 35.0 g of yellow-brown solid. Recrystallization (ethanol) gave 28.72 g of light orange and brown crystals, mp 94-100°. A 23.37 g portion of this crude product was separated by wet column chromatography to afford two compounds. First eluted (with pure dichloromethane) was a bright yellow solid (leaves); 2.92 g (13% by weight of the crude pro-

duct, 0.0142 mole), which corresponds to an overall yield of 17% with mp 68.5-70° (lit 72° [33]); identified by spectra and elemental analysis as α -phenylimino- α -phenylacetonitrile (**8**); R_f was 0.85 in dichloromethane.

Anal. Calcd. for C₁₄H₁₀N₂: C, 81.53; H, 4.89; N, 13.59. Found: C, 81.44; H, 4.97; N, 13.59.

Also obtained from the column (eluted with dichloromethane then dichloromethane-acetone) was a yellow-brown solid, homogeneous to tlc (R_f = 0.35 in dichloromethane), 20.37 g (87% by weight of the crude product, 0.0547 mole), which corresponds to an overall yield of 67%, mp 119-122.5°. Several recrystallizations (ethanol) afforded analytically pure **5d** as light brown crystals, mp 125.5-127°; ir (chloroform): 2270 cm⁻¹ (CN), 1640 cm⁻¹ (C=O); nmr (deuteriochloroform): δ = 3.61 (s, 3H), 3.74 (s, 3H), 6.6-7.6 (m, 14H).

Anal. Calcd. for C₂₃H₂₀N₂O₃: C, 74.17; H, 5.41; N, 7.52. Found: C, 73.89; H, 5.22; N, 7.28.

1,2-Diphenyl-5-(3,4-dimethoxyphenyl)pyrrole (**6d**).

Following the above procedure for **6c**, 3.72 g (0.010 mole) of **5d** was used. A brick red solution of the anion resulted, which immediately lightened in color following addition of **2**. After 43 hours of reflux, 2.40 g (68%) of crude **6d** was isolated as a flaky light tan solid (following one recrystallization from ethanol), mp 156-158°. Additional recrystallization (ethanol) gave a flaky white solid with mp 158.5-159.5°, which was shown to be identical to **6c** by ir and nmr spectra as well as mixed mp.

1,2-Diphenyl-5-*n*-butylpyrrole (**6e**).

A solution of 1.11 g (0.011 mole) of dry diisopropylamine in 5 ml of dry THF was cooled to -78° under nitrogen atmosphere. To this solution was added 6.88 ml (0.011 mole) of a 1.6 *M* solution of *n*-butyllithium in hexane, and the mixture was stirred for 15 minutes at -78°. A solution of 2.92 g (0.010 mole) of *N*-benzoyl-2-anilinohexanenitrile (**5e**) in 10 ml of dry THF was added dropwise, evolution of hydrogen was observed, and a blood red color developed. After the addition was complete, the anion solution was stirred for 15 minutes (still at -78°). A solution of 4.24 g (0.0115 mole) of **2** in 30 ml of dry DMF was then added to the reaction mixture, which lightened to a mustard color. After 30 minutes of additional stirring (under nitrogen) at -78°, the reaction mixture was allowed to warm to room temperature (over a 1.5 hour period), then was heated and refluxed for 21 hours becoming a dark green color. The mixture was allowed to cool to 25° before being poured into 300 ml of cold water. The aqueous suspension was extracted with ether (3 × 250 ml), the combined ether layers were dried (anhydrous magnesium sulfate) and the ether was removed to yield 5.47 g of a yellow-brown oil. Wet column chromatography (elution with dichloromethane) afforded 1.51 g (55%) of light yellow crystals, mp 62.5-63.5° (after recrystallization from ethanol) homogeneous to tlc (R_f was 0.82 in dichloromethane) identified as **6e**. Also recovered from the column as a later fraction was 0.78 g (27%) of unreacted **5e**, mp 64-65.5°, as light tan crystals, homogeneous to tlc (R_f of 0.44), identified by ir, nmr and mixed mp with an authentic sample of

5e. Analytical data for **6e** was: ir (chloroform): 2910 cm⁻¹ (alkyl C-H) and 1600 cm⁻¹ (C=C); nmr (deuteriochloroform): δ = 0.7-2.7 (m, 9H), 6.13 (d, 1H, J = 4.5 Hz), 6.41 (d, 1H, J = 4 Hz), 7.1-7.5 (m, 10H).

Anal. Calcd. for C₂₀H₂₁N: C, 87.22; H, 7.69; N, 5.09. Found: C, 87.00; H, 7.78; N, 4.83.

N-Valeryl-anilinophenylacetonitrile (**5f**).

To a solution of 10.41 g (0.050 mole) of **7** in 50 ml of dry pyridine, maintained at 0-5° in an ice water bath, was added dropwise with stirring 6.03 g (0.050 mole) of valeryl chloride over a period of 10 minutes. After 15 minutes of additional stirring at 0°, stirring was continued for 4 days at room temperature. The orange reaction mixture, which contained a good quantity of precipitated pyridine hydrochloride, was poured with vigorous stirring into 250 ml of ice water, and a yellow-orange tarry oil resulted. The aqueous mixture was extracted with ether (2 × 125 ml), which in turn was washed with 175 ml portions of 10% hydrochloric acid and water, 10% sodium hydroxide and water, then was dried (anhydrous magnesium sulfate) to yield (after removal of the ether) ca. 12 g of a

yellow orange oil which could not be induced to crystallize. Subjecting the oil to wet column chromatography (with 80:20 hexane/methylene chloride as eluant) afforded 7.54 g (50%) of a clear red-orange oil as the initially eluted material, shown to be **5f** by ir, nmr and elemental analysis. The R_f was 0.51 in 2:1 hexane/methylene chloride; ir (chloroform): 1660 cm^{-1} (C=C); nmr (deuteriochloroform): $\delta = 0.7\text{--}2.1$ (m, 9H), $\delta = 7.5$ (m, 1H).

Anal. Calcd. for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}$: C, 78.05; H, 6.90; N, 9.58. Found: C, 78.04; H, 6.94; N, 9.83.

1,2-Diphenyl-5-*n*-butylpyrrole (**6f**).

To a 0.53 g (0.011 mole) quantity of 50% sodium hydride, maintained under a nitrogen atmosphere, was added with stirring a solution of 2.92 g (0.010 mole) of **5f** in 20 ml of dry DMF. Evolution of hydrogen gas was observed to occur for 10 minutes, the solution becoming a dark brown color. A solution of 4.24 g (0.0115 mole) of **2** in 30 ml of dry DMF was added, and the color lightened to a honey brown. The stirred reaction mixture was refluxed under nitrogen for 23 hours, allowed to cool to room temperature, and poured with stirring into 300 ml of cold water. Extraction with ether (3 \times 250 ml), followed by drying of the combined extracts (anhydrous magnesium sulfate) and removal of the ether gave 5.75 g of orange oil. Purification of the oil by wet column chromatography (1:1 hexane/methylene chloride, eluant) afforded 0.21 g of an oily yellow solid as the first eluted compound. Recrystallization (ethanol) gave 0.12 g (4.4%) of very light yellow crystals, mp 62.5–63.5°, identified as the desired product **6f**, shown to be identical to **6e** by spectra and mixed mp.

1-(4-Chlorophenyl)-2-phenyl-5-methylpyrrole (**6g**).

To a 0.27 g (0.0055 mole) quantity of 50% sodium hydride, maintained under a nitrogen atmosphere, was added with stirring a solution of 1.42 g (0.0050 mole) of *N*-acetyl-*p*-chloroanilinoacetonitrile (**5g**) in 25 ml of dry DMF. Evolution of hydrogen gas was observed for 10 minutes, the reaction mixture becoming a greenish-brown. A solution of 2.12 g (0.0057 mole) of **2** in 20 ml of dry DMF was added, and the color darkened to brown. The stirred reaction mixture was refluxed under nitrogen for 23 hours, then allowed to cool to room temperature and poured into 150 ml of cold water. Extraction with ether (4 \times 125 ml) followed by drying (anhydrous magnesium sulfate) and removal of the ether gave 6.22 g of yellow-brown oil. Subjecting the oil to wet column chromatography (elution with 1:1 hexane/methylene chloride) afforded 0.40 g (30%) of crude **6g** as a light yellow solid, mp 114–118°; **6g** was the first substance eluted from the column, and had an R_f of 0.85 in pure dichloromethane. Analytically pure **6g** was obtained by repeated recrystallization (ethanol), and formed long needles, light pink in color, with mp 125.5–126.5°; ir (chloroform): 2955 cm^{-1} (alkyl C-H) and 1602 cm^{-1} (C=C); nmr (deuteriochloroform): $\delta = 2.10$ (s, 3H), 6.08 (d, 1H, $J = 4$ Hz), 6.31 (d, 1H, $J = 4$ Hz), 6.95–7.45 (m, 9H).

Anal. Calcd. for $\text{C}_{17}\text{H}_{14}\text{ClN}$: C, 76.25; H, 5.27; N, 5.23; Cl, 13.24. Found: C, 76.04; H, 5.27; N, 5.10; Cl, 12.95.

Reaction of 2-(*N*-2,4,6-Trimethylphenyl)acetamidophenylacetonitrile (**5h**) with **2**.

To a 0.53 g (0.011 mole) quantity of 50% sodium hydride, maintained under a nitrogen atmosphere, was added with stirring a solution of 2.92 g (0.010 mole) of 2-(*N*-2,4,6-trimethylphenyl)acetamidophenylacetonitrile in 40 ml of dry DMF. Evolution of hydrogen gas was observed for 12 minutes, during which time the color changed from green to yellow. A solution of 4.24 g (0.0115 mole) of **2** in 30 ml of dry DMF was added, and the color darkened to a clear red-brown. The stirred reaction mixture was refluxed under a nitrogen atmosphere for 18 hours, allowed to cool to room temperature, then was poured into 300 ml of cold water. The aqueous suspension was extracted with ether (3 \times 200 ml), the combined ether extracts dried (anhydrous magnesium sulfate) and the ether removed to afford 4.75 g of an orange oil which solidified upon standing. Recrystallization (ethanol) gave 1.52 g (86%) of white leafy crystals, mp 208–211° (lit mp 210° [34]), identified as 2,4,6-trimethylaniline acetate by spectra and mp; ir (chloroform): 3475 cm^{-1} (NH), 1680 cm^{-1} (C=O); nmr (deuteriochloroform): $\delta = 1.25$ (s, 3H), 1.64 (s, 1H), 2.08 (s, 3H), 2.22 (s, 3H), 2.26 (s, 3H), 6.92 (m, 2H).

N-Benzoyl-2-picolyaminophenylacetonitrile (**5i**).

A mixture of 6.00 g (0.045 mole) of mandelonitrile, 4.90 g (0.045 mole) of 2-aminomethylpyridine, and 100 ml of absolute ethanol was stirred and refluxed for 16 hours. Evaporation of the ethanol *in vacuo* yielded the crude aminonitrile, 2-picolyaminophenylacetonitrile, as a dark red oil which was used without further purification. To a solution of the aminonitrile in 100 ml of dry pyridine, stirred and maintained at 0–5°, was added dropwise 5.80 g (0.045 mole) of benzoyl chloride. After the addition was complete, the reaction mixture was stirred overnight at room temperature, then was poured into 100 ml of ice water and extracted (2 \times 100 ml) with methylene chloride. The combined organic layers were washed several times with cold water until the aqueous layer no longer had the odor of pyridine. The dried (anhydrous magnesium sulfate) organic phase afforded, after removal of the solvent, a dark brown oil which was induced to crystallize from ethanol yielding 5.30 g (40%) of a tan solid with mp 153–154°; ir (chloroform): 1660 cm^{-1} (C=O); nmr (deuteriochloroform): $\delta = 6.8\text{--}7.9$ (m, 15H), 4.6 (d, 2H, $J = 10$ Hz).

Anal. Calcd. for $\text{C}_{21}\text{H}_{17}\text{N}_3\text{O}$: C, 77.04; H, 5.23; N, 12.83. Found: C, 77.03; H, 5.59; N, 12.59.

1-(2-Picolyl)-2,5-diphenylpyrrole (**6i**).

To a 0.20 g (0.0055 mole) quantity of 60% sodium hydride, maintained under an argon atmosphere, was added with stirring a solution of 1.80 g (0.0055 mole) of **5i** in 55 ml of dry DMF. The mixture was allowed to react for 15 minutes with evolution of hydrogen observed and the color becoming a deep red. A solution of 2.00 g (0.0055 mole) of **2** in 20 ml of dry DMF was added, and the stirred reaction mixture was heated under argon in a 100° oil bath for 20 hours. After being allowed to cool to room temperature, the reaction mixture was poured into 100 ml of ice water. The resulting white precipitate was collected yielding 0.95 g (56%) of crude **6i**. Recrystallization (ethanol) gave white needles, mp 141–143°; ir (chloroform): 2950 cm^{-1} (aliphatic C-H), 1600 cm^{-1} (C=C); nmr (deuteriochloroform): $\delta = 5.40$ (s, 2H), 6.45 (s, 2H), 6.50–8.45 (m, 14H).

Anal. Calcd. for $\text{C}_{22}\text{H}_{18}\text{N}_2$: C, 85.17; H, 5.80; N, 9.03. Found: C, 84.91; H, 5.86; N, 8.93.

N-Benzoyl-2-pyridylaminophenylacetonitrile (**5j**).

A solution of 4.40 g (0.047 mole) of 2-aminopyridine and 6.20 g (0.047 mole) of mandelonitrile in 65 ml absolute ethanol was heated at reflux for 16 hours. Subsequent removal of the ethanol *in vacuo* gave an orange-brown oil which was induced to crystallize from 95% ethanol, affording 8.1 g (82%) of crude 2-pyridylaminophenylacetonitrile as yellow crystals. Additional recrystallization (ethanol) gave analytically pure aminonitrile, mp 140–200°; ir (chloroform): 3450 cm^{-1} (br, NH); nmr (deuteriochloroform/DMSO- d_6): $\delta = 4.4$ (br, exchangeable s, 1H), 6.5–8.0 (m, 10H).

Anal. Calcd. for $\text{C}_{13}\text{H}_{11}\text{N}_3$: C, 74.64; H, 5.26; N, 20.69. Found: C, 74.57; H, 5.27; N, 20.80.

To a solution of 3.00 g (0.014 mole) of purified 2-pyridylaminophenyl acetonitrile in 60 ml of dry pyridine, cooled in an ice bath, was added 2.00 g (0.014 mole) of benzoyl chloride dropwise. The resulting yellow-orange solution was stirred for 16 hours at room temperature, poured into 200 ml of ice water, and the precipitate collected. The crude yellow solid was washed thoroughly with water and recrystallized (ethanol) to give 3.70 g (80%) of **5j** as fine yellow crystals, mp 216–218°; ir (chloroform): 1680 cm^{-1} (C=O); nmr (deuteriochloroform/DMSO- d_6): $\delta = 6.75\text{--}8.20$ (m); ^{13}C -nmr (DMSO- d_6): $\delta = 166.98$ (N-C=O).

Anal. Calcd. for $\text{C}_{20}\text{H}_{15}\text{N}_3\text{O}$: C, 76.69; H, 4.79; N, 13.42. Found: C, 77.03; H, 4.69; N, 13.66.

(*N*-Benzoyl-2-pyridylamino)benzylphenylacetonitrile (**9**).

To a 0.44 g (0.011 mole) quantity of 60% sodium hydride, maintained under an argon atmosphere, was added dropwise and with stirring a solution of 2.90 g (0.0090 mole) of **5j** in 75 ml of dry DMF. The vigorous evolution of hydrogen was observed. The solution was stirred for 15 minutes following completion of the addition with no color change being noted. A solution of 1.60 g (0.0090 mole) of benzyl bromide in 15 ml of dry DMF was added dropwise and allowed to stir at room temperature for 24 hours under argon. The reaction mixture was poured into ice water to afford a

yellow tar; recrystallization (ethanol) gave **9** as yellow crystals, mp 135-137°; ir (chloroform): 1660 cm^{-1} (C=O); nmr (deuteriochloroform): δ = 4.42 (d, 1H, J = 16 Hz), 5.8 (d, 1H, J = 16 Hz), 6.4-8.1 (m, 19H); ^{13}C -nmr (deuteriochloroform): δ = 171.19 (N-C=O).

Anal. Calcd. for $\text{C}_{27}\text{H}_{21}\text{N}_3\text{O}$: C, 80.37; H, 5.25; N, 10.42. Found: C, 80.19; H, 5.18; N, 10.37.

Reaction of **9** with Ethanolic Potassium Hydroxide.

A mixture of 6.10 g (0.015 mole) of **9**, 8.50 g of potassium hydroxide, 5 ml of water, and 100 ml of ethanol was stirred and heated at reflux for 24 hours. Removal of the ethanol *in vacuo* resulted in a brown solid, to which was added 100 ml of water. The aqueous mixture was extracted with methylene chloride (3 \times 50 ml), the combined organic layers dried (anhydrous magnesium sulfate) and the solvent removed to yield a brown oil which solidified upon standing. Recrystallization (ethanol) gave 2.1 g (44%) of aminonitrile **10** as red-brown needles, mp 122-124°; ir (chloroform): 3410 cm^{-1} (br, NH); nmr (deuteriochloroform): δ = 4.05 (br, d, 2H, J = 6 Hz), 6.5-7.8 (m, 14H).

Anal. Calcd. for $\text{C}_{20}\text{H}_{17}\text{N}_3$: C, 80.27; H, 5.68; N, 14.04. Found: C, 80.01; H, 5.70; N, 13.91.

Acidification of the aqueous layer with concentrated hydrochloric acid led to the precipitation of benzoic acid, 1.4 g (75%), identified by mixed mp with an authentic sample and spectra.

Reaction of **11** with **2** to Form Benzoin Benzoate (**12**).

To a 0.53 g (0.011 mole) quantity of 50% sodium hydride, maintained under nitrogen atmosphere, was added with stirring a solution of 2.37 g (0.010 mole) of **11** [31] in 25 ml of dry DMF. Evolution of hydrogen was observed for 10 minutes, after which time the reaction mixture was green in color and contained a large amount of precipitate. A solution of 4.24 g (0.0115 mole) of **2** in 30 ml of dry DMF was added to the reaction mixture, which became a brown and then orange color. The stirred reaction mixture was maintained under nitrogen and allowed to react at room temperature for 46 hours. The mixture was poured into 350 ml of cold water with the reaction vessel being rinsed with 50 ml of ether. The aqueous suspension was extracted with ether (4 \times 250 ml), the combined ether extracts dried (anhydrous magnesium sulfate) and the ether removed to yield 4.90 g of brown oil. Subjection of the oil to flash chromatography (2"/minute flow rate, 1:1 hexane/methylene chloride eluant) afforded two isolable products. First eluted was 1.48 g of triphenylphosphine, identified by tlc, nmr, and mp. Isolated as a later fraction from the column was 1.30 g of light green solid, mp 108-116°. Recrystallization (ethanol) gave white plates, mp 122-124° (lit 125° [35]). The 1.30 g of isolated **12** represents 0.0041 mole, hence, the overall yield of benzoin benzoate is 82% of theoretical; ir (chloroform): 1720 cm^{-1} (ester C=O) and 1690 cm^{-1} (ketone C=O); nmr (deuteriochloroform): δ = 7.13 (s, 1H), 7.20-7.75 (m, 11H), 7.90-8.20 (m, 4H); ms: M^+ = 316.

Anal. Calcd. for $\text{C}_{21}\text{H}_{16}\text{O}_3$: C, 79.72; H, 5.10; O, 15.17. Found: C, 79.36; H, 5.22; O, 15.42.

Reaction of **13** with **2**.

In a representative attempt to synthesize **14**, a 0.53 g (0.011 mole) quantity of 50% sodium hydride was allowed to react, under a nitrogen atmosphere, with a suspension of 2.60 g (0.010 mole) of **13** [32] in 80 ml of dry DMF. The stirred reaction mixture became a dark brown color and evolved hydrogen for 10 minutes. A solution of 4.24 g (0.0115 mole) of **2** in 30 ml of dry DMF was added, and the color lightened to a peach color and contained much precipitate. The stirred reaction mixture was refluxed under a nitrogen atmosphere for 24 hours, allowed to cool to room temperature, and filtered. The precipitate consisted of sodium cyanide (0.48 g, 98% recovery). The filtrate was poured into 300 ml of cold water, extracted with ether (4 \times 250 ml), the combined extracts dried (anhydrous magnesium sulfate) and the ether removed to give 8.20 g of brown oil. Subjection of the oil to wet column chromatography (packed with 1:1 hexane/methylene chloride, eluted with same; eluant gradually changed to methylene chloride, ether, acetone, then ethanol) afforded 2.03 g (77%) of triphenylphosphine (mp 79-81°), identified by spectral and mp

comparison to an authentic sample, with R_f of 0.78 in 1:1 hexane/methylene chloride. An authentic sample of **14** [24,25] had R_f of 0.80 in the same solvent. The crude triphenylphosphine was shown by nmr to not contain any **14** as a contaminant. Also isolated from the column as a later fraction was an intractable brown oil, shown by tlc to be very complex (R_f from 0.0 to 0.22). All attempts to isolate identifiable components of this oil were unsuccessful. Other attempts to form **14** employed such changes in conditions as: lower reaction temperatures, various times of reaction, and the use of alternative solvent systems (e.g., THF and mixed THF/DMF). Fundamentally the same results were obtained each time.

(*o*-Acetylanilino)phenylacetoneitrile (**17**).

A mixture of 10.40 g (0.077 mole) of *o*-aminoacetophenone, 10.25 g (0.077 mole) of mandelonitrile, and 100 ml of absolute ethanol was heated at reflux for 24 hours with stirring. The ethanol was evaporated *in vacuo* to yield 18.60 g (95%) of dark brown oil which crystallized on standing. Repeated recrystallizations (ethanol) afforded golden yellow crystals of **17**, mp 68.5-69.5°; ir (carbon tetrachloride): 1650 cm^{-1} (C=O); nmr (deuteriochloroform): δ = 2.6 (s, 3H), 5.6 (d, 1H, J = 6 Hz), 6.9-8.1 (m, 10H).

Anal. Calcd. for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}$: C, 76.80; H, 5.60; N, 11.20. Found: C, 76.88; H, 5.65; N, 11.29.

1-Acetyl-2-cyano-3-hydroxy-3-methyl-2-phenyl-2,3-dihydroindole (**19**).

To a chilled solution of **17** (6.76 g, 0.027 mole) in 45 ml of dry THF was added dropwise 2.16 g (0.027 mole) of acetylchloride with stirring. The ice bath was then removed and the mixture allowed to warm to room temperature, and 1.40 ml (0.027 mole) of dry pyridine was added dropwise. A tan solid precipitated immediately. The mixture was refluxed for 24 hours, then poured with stirring into 250 ml of ice water. The aqueous suspension was extracted with ether (2 \times 100 ml), and the combined ether layers were washed with 100 ml portions of water, 5% hydrochloric acid, water, cold 10% sodium hydroxide and water. The organic phase was dried (anhydrous magnesium sulfate) and the ether removed to afford 7.1 g (89%) of golden brown oil, which crystallized on standing. Several recrystallizations (ethanol) afforded pale yellow crystals, mp 96-100° (variable); identified as **19**, present as a ca. 1:1 mixture of diastereomers, on the basis of ir, nmr, and elemental analysis; ir (chloroform): 1680 cm^{-1} (N-C=O); nmr (deuteriochloroform): δ = 1.7 (s, 1.5H), 1.8 (s, 1.5H), 1.9 (s, 1.5H), 2.7 (s, 1.5H), 7.0-8.0 (m, 10H).

Anal. Calcd. for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_2$: C, 73.97; H, 5.49; N, 9.59. Found: C, 73.89; H, 5.35; N, 9.57.

REFERENCES AND NOTES

- [1] NRC-NRL Cooperative Research Associate Postdoctoral Fellow, 1984-1986.
- [2] J. V. Cooney, *J. Heterocyclic Chem.*, **20**, 823 (1983).
- [3] W. E. McEwen and R. L. Cobb, *Chem. Rev.*, **55**, 511 (1955).
- [4] F. D. Popp, *Adv. Heterocyclic Chem.*, **9**, 1 (1968).
- [5] F. D. Popp, *ibid.*, **24**, 187 (1979).
- [6] F. D. Popp, *Heterocycles*, **1**, 165 (1973).
- [7] W. E. McEwen, A. V. Grossi, R. J. MacDonald and A. P. Stamegna, *J. Org. Chem.*, **45**, 1301 (1980).
- [8] A. P. Stamegna and W. E. McEwen, *ibid.*, **46**, 1653 (1981).
- [9] J. V. Cooney and W. E. McEwen, *ibid.*, **46**, 2570 (1981).
- [10] J. D. Albright, *Tetrahedron*, **39**, 3207 (1983).
- [11] E. E. Schweizer and R. D. Bach, *J. Org. Chem.*, **29**, 1746 (1964).
- [12] K. B. Becker, *Tetrahedron*, **36**, 1717 (1980).
- [13] E. Zbiral, *Synthesis*, 775 (1974).
- [14] E. Zbiral in "Organophosphorus Reagents in Organic Synthesis", J. I. G. Cadogan, ed, Academic Press, New York, 1979, pp 223-268.
- [15] E. E. Schweizer and R. Schepers, *Tetrahedron Letters*, 979 (1963).
- [16] E. E. Schweizer, *J. Am. Chem. Soc.*, **86**, 2744 (1964).
- [17] E. E. Schweizer and K. K. Light, *ibid.*, **86**, 2963 (1964).
- [18] E. E. Schweizer and C. M. Kopay, *J. Org. Chem.*, **37**, 1561 (1972).
- [19] M. E. Kuehne and R. E. Damon, *ibid.*, **42**, 1825 (1977).

- [20] A. I. Meyers, J. P. Lawson and D. R. Carver, *ibid.*, **46**, 3119 (1981).
- [21] M. Le Corre, A. Hercouet and H. Le Baron, *J. Chem. Soc., Chem. Commun.*, 14 (1981).
- [22] For example, ^{13}C -nmr indicates that the methyl carbon in 2-picoline resonates at 24.7 ppm (A. Marker, A. Canty and R. Brownlee, *Aust. J. Chem.*, **31**, 1255 (1979)), while in toluene the shift is 21.4 ppm (Sadtler ^{13}C -nmr Spectra).
- [23] W. G. Dauben and D. G. Hart, *Tetrahedron Letters*, 4353 (1975).
- [24] W. E. McEwen, I. C. Mineo, Y. H. Shen and G. Y. Han, *ibid.*, 5157 (1968).
- [25] W. E. McEwen, I. C. Mineo and Y. H. Shen, *J. Am. Chem. Soc.*, **93**, 4479 (1971).
- [26] J. Knabe and A. Frie, *Arch. Pharm.*, **306**, 648 (1973).
- [27] F. D. Popp and J. M. Wefer, *J. Heterocyclic Chem.*, **4**, 185 (1967).
- [28] E. E. Schweizer and R. D. Bach in "Organic Syntheses", Collective Volume V, H. E. Baumgarten, ed, Wiley, New York, 1973, pp 1145-1148.
- [29] L. Kronick, B. S. Thesis, University of Massachusetts, Amherst, 1981.
- [30] R. C. Quirbach, B. S. Thesis, University of Massachusetts, Amherst, 1980.
- [31] F. Francis and O. C. M. Davis, *J. Chem. Soc.*, **95**, 1403 (1909).
- [32] B. C. Uff, J. R. Kershaw and J. L. Neumeyer in "Organic Syntheses", Vol **56**, G. H. Buchi, ed, 1977, pp 19-25.
- [33] Beilstein Handbook of Organic Chemistry, **H.9**, 521 **Ei.9**, 276.
- [34] *Ibid.*, **H.12**, 563.
- [35] *Ibid.*, **H.9**, 153.