1565-cm^{-1} band), 2180 (s, C≡N), 1565 cm^{-1} (vs, C=C-N=C); nmr (CCl_4) δ 0.861 [$C(CH_3)_3$, 9 H], 0.983 [$C(CH_3)_3$, 9 H], 1.417 [$C(CH_3)_2$, 6 H], 1.667 [$C(CH_3)_2$, 6 H], 1.760 (CH_2, 2 H), 1.959 (CH_2, 2 H), 3.884 (NH, 1 H, disappears upon deuteration), 7.084 ppm (N=CH, 1 H).

Attempted Acid-Catalyzed Hydrolysis of 4. Formation of 5. To a solution of 1.0 g of 4 in 15 ml of tetrahydrofuran was added 10 ml of water. The addition of 0.2 ml of methanesulfonic acid caused the yellow color to fade to colorless. After 24 hr at room temperature, one-quarter of this solution was treated with excess solid potassium carbonate. This resulted in formation of an aqueous layer and a yellow organic layer. The organic layer was separated, the solvent was removed *in vacuo*, and the residue was dissolved in hot hexane. The hexane solution was dried ($MgSO_4$), filtered, and cooled (−5°) to give 0.187 g of starting material (4), identified by mixture melting point determination and identity of infrared spectra.

The remaining three-quarters of the original solution was heated at reflux of tetrahydrofuran for 1 hr. The tetrahydrofuran was then removed *in vacuo*. This resulted in formation of an aqueous layer and an organic layer which solidified upon cooling. The crystals were collected by filtration and dissolved in hot hexane. The hexane solution was dried ($MgSO_4$), filtered, and cooled (−5°) to yield 0.55 g of colorless crystals, identified as **5** by mixture melting point determination and identity of infrared spectra.

1-Methyl-4-methylamino-5-cyanoimidazole (11). To a solution of 2.75 g (0.125 mol) of 4-cyano-5-*tert*-octylaminoimidazole (9) in 30 ml of acetone were added 3.15 g (2.37 ml, 0.025 mol) of dimethyl sulfate and 5 g of finely powdered potassium carbonate. The stirred mixture was heated at reflux for 2 hr. The acetone was removed *in vacuo*, and the residue was heated at 100° for an additional 2 hr. After cooling, 25 ml of concentrated ammonia was added to decompose excess dimethyl sulfate, and the mixture was heated at 60° for 30 min. Filtration yielded a solid residue, which was dissolved in 15 ml of chloroform. The chloroform solution was dried ($MgSO_4$), treated with Norit, and after filtration was chilled at −5° for 5 hr. The crystalline precipitate was redissolved in 50 ml of chloroform containing a trace of methanesulfonic acid. The solution was allowed to stand at room temperature for 12 hr. It was then concentrated to a 10-ml volume and chilled at −5° for 5 hr. Filtration yielded 0.62 g of **11** as colorless crystals, mp 162.0–163.7°. *Anal.* Calcd for $C_8H_8N_4$: C, 52.91; H, 5.93; N, 41.15. Found: C, 52.92; N, 5.91; N, 41.16. Mass spectrum (70 eV) *m/e* 136 (M^+); uv max (methanol) 275.5, 230 nm (ε × 10^{-3} 9.26, 4.53); ir ($CHCl_3$) 3435 (s, NH), 2188 (vs, C≡N), 1585 cm^{-1} (vs, C=C-N=C); Raman (crystals) 2188 (vs, C≡N), 1590 cm^{-1} (s, C=C-N=C); nmr ($CDCl_3$) δ 3.63 ($NHCH_3$, 3 H), 2.96 (NCH_3, 3 H), 4.12 ($NHCH_3$, 1 H, disappears upon deuteration), 7.12 ppm (N=CH, 1 H).

Registry No.—**4**, 51248-29-4; **5**, 51248-30-7; **9**, 30771-61-0; **11**, 15353-10-3; **12**, 30768-59-3; **12**·CH_3SO_3H, 51248-31-8; TMP, 107-40-4; HCN, 74-90-8; HF, 7664,39-3.

References and Notes

(1) J. A. Deyrup, M. M. Vestling, W. V. Hagan, and H. Y. Yun, *Tetrahedron*, **25**, 1467 (1969).
(2) J. P. Ferris and J. E. Kuder, *J. Amer. Chem. Soc.*, **92**, 2527 (1970).
(3) J. P. Ferris, J. E. Kuder, and A. Catalano, *Science*, **166**, 765 (1969).
(4) L. deVries, *J. Org. Chem.*, **36**, 3442 (1971).
(5) A. Mannschreck, W. Seitz, and H. A. Staab, *Ber. Bunsenges. Phys. Chem.*, **67**, 480 (1973).
(6) Compound **11** is prepared by treating 4-*tert*-octylamino-5-cyanoimidazole[4] (**9**) with 2 equiv of dimethyl sulfate and excess potassium carbonate in refluxing acetone, followed by thermolysis of the product (Scheme II). In this process, both the amino group and a ring nitrogen of **9** are methylated. Evidently, in the presence of potassium carbonate, Hofmann elimination of 2,4,4-trimethylpentene-1 (**6**) occurs, even though a quarternary ammonium salt is not involved. It appears that the *tert*-octyl substituent in the salt hinders approach of the base to the α NH but that β-elimination occurs readily. Generation of **6** is confirmed by glpc. The initial product appears to be a mixture of **11** and its isomer **10**, since the nmr spectrum shows three *N*-methyl resonances at 2.96, 3.03, and 3.63 ppm. Upon addition of a trace of methanesulfonic acid, the nmr spectrum simplifies to two resonances at 3.03 and 3.63 ppm. This suggests acid-catalyzed conversion of the less stable isomer **10** to the more stable **11**. The presence of the imidazole ring in **11** is evident from a resonance at 7.12 ppm. (See above.)
(7) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970, p 169.
(8) S. H. Graham and A. J. S. Williams, *Tetrahedron*, **21**, 169, 3263 (1965).

Synthesis of Aryl-Substituted 1,3- and 1,4-Diazocine Derivatives

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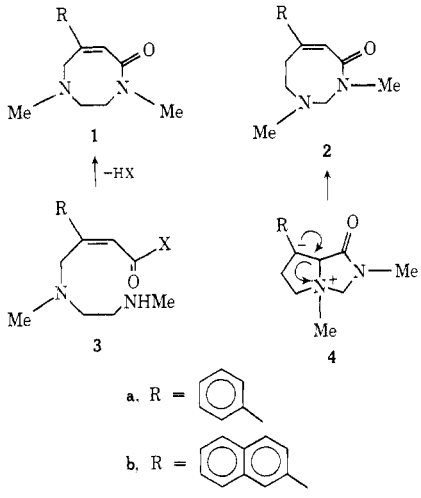
The synthesis of aryl-substituted 1,3- and 1,4-diazocine derivatives was undertaken because their structural features suggested potential CNS activity. Reaction of methyl β-bromomethylcinnamate with *N,N'*-dimethylethylenediamine gave *N,N'*-dimethyl-2-phenylpiperazine-2-acetic acid methyl ester (**10a**), which was converted to 1,4-dimethyl-7-phenyl-1,2,3,4-tetrahydro-1,4-diazocin-5(8*H*)-one (**1a**). Catalytic and hydride reductions of **1a** led ultimately to the 6-phenylperhydro-1,4-diazocine **14.** The cis and trans isomers of 3-phenylproline, **34** and **33,** were prepared by a multistep synthesis starting from cinnamaldehyde and acetamidomalonate. Conversion of **33** to the methylthiohydantoin **36,** followed by desulfurization and quaternization with methyl iodide, gave the bicyclic intermediate **42,** which upon treatment with sodium hydride or lithium–ammonia underwent transannular ring opening to give 1,3-dimethyl-6-phenyl-1,2,3,7-tetrahydro-1,3-diazocin-4(8*H*)-one (**2**) and its perhydro analog **44,** respectively. On the other hand, reaction of **42** with sodium methylate or with sodium borohydride led to peripheral ring cleavage, giving *N*-methyl-3-phenylproline methyl ester (**46**) and the corresponding alcohol **45,** respectively.

Our interest in medium-ring heterocycles stems from an effort to develop structurally novel antipsychotic drugs. Tricyclic antipsychotic agents related to chlorpromazine have the following physicochemical parameters in common: a nearly flat aromatic ring system, substituted with an electronegative function, and a basic amine group separated by three carbon atoms from the aromatic ring system. In those compounds in which the aminoalkyl side chain is connected by a carbon–carbon double bond, only the cis isomers (side chain oriented toward the electronegative substituent) are active,[1] and this has led to the hypothesis[2] that for optimum activity the amine function should be in close proximity to the electronegative substituent. Therefore it was intriguing to incorporate these features in novel frameworks and to determine whether such nontricyclic structures would exhibit antipsychotic activity.

The diazocinone derivatives (**1** and **2**) are novel compounds which fulfill the above criteria; the aryl substituent serves as part of the aromatic ring system and the amide carbonyl as the electronegative substituent, with the basic ring nitrogen located appropriately in close proximity to the carbonyl group. We planned to synthesize **1** by cyclization of a linear precursor such as **3,** and **2** by transannular ring opening of a bicyclic precursor such as **4** (Scheme I).

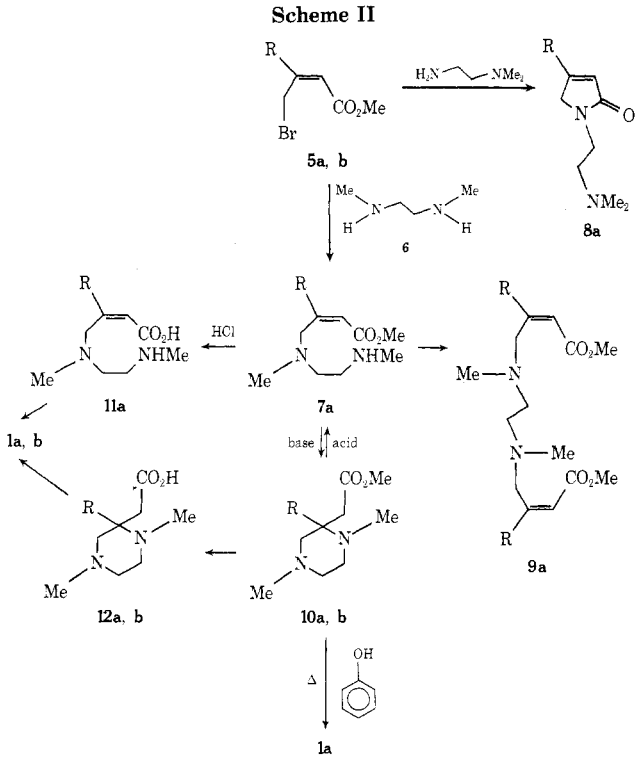
Scheme I



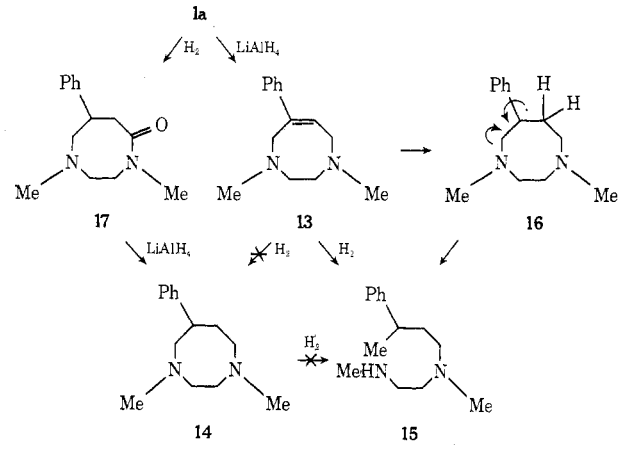
In the synthesis of **1a** (R = phenyl), methyl β-bromomethylcinnamate (**5a**)[3] was treated with *N,N'*-dimethylethylenediamine (**6**) to give the diamine **7a** (Scheme II). Whereas reaction of **5a** with *N,N*-dimethylethylenediamine led to spontaneous ring closure to give the pyrrolinone derivative **8a** (R = phenyl), no such ring closure to an eight-membered ring was observed in the reaction with **6.** In fact, since the dialkylated product **9a** was a major by-product of this reaction, a large excess of **6** was required, which suppressed the formation of **9a,** and under these basic conditions **7a** isomerized (*via* a Michael addition) to the piperazine derivative **10a.** Under acidic conditions, **10a** rearranged back to **7a** in moderate yield. Conversion of **7a** to **1a** was not possible either thermally or with a variety of basic catalysts. However, a good yield of **1a** was obtained by saponification of either **7a** or **10a** and treatment of the resulting acids **11a** and **12a** with triethylamine and dicyclohexylcarbodiimide. Heating **7a** in phenol also gave **1a,** but in low yield. The β-naphthyl derivative **1b** was prepared analogously.

In order to further explore the chemistry of this ring

Scheme II



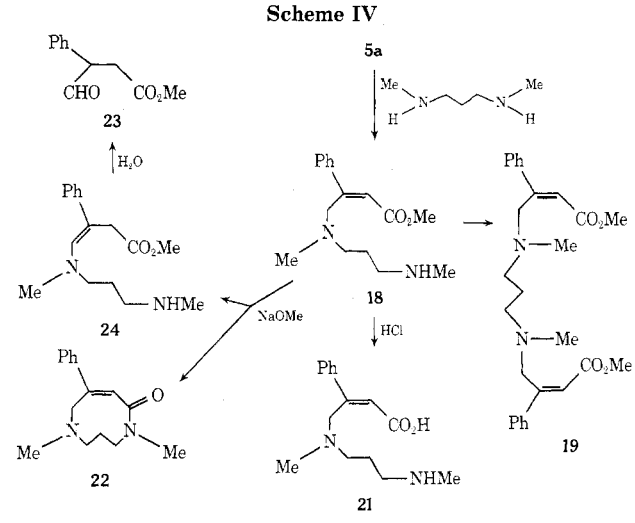
Scheme III



system, we examined the reactivity of **1a** with a few common reducing reagents (Scheme III). Treatment of **1a** with lithium aluminum hydride gave cleanly the hexahydrodiazocine **13.** Surprisingly, hydrogenation of **13** with palladium on carbon gave not the expected octahydro derivative **14,** but the ring-opened product **15,** which results from preferential cleavage of one of the allylic carbon–nitrogen bonds. Curiously, the crude reaction mixture did not contain any product resulting from cleavage of the other allylic carbon–nitrogen bond, and this observation can be rationalized by postulating a stepwise addition of hydrogen to give a resonance-stabilized intermediate such as **16,** which then collapses with C–N bond breakage to an olefin, which is hydrogenated to **15.** Consistent with this proposal, **14** was stable under the same catalytic hydrogenation conditions. On the other hand, hydrogenation of **1a** proceeded without cleavage of the allylic C–N bond, giving **17,** which was reduced further with lithium aluminum hydride to the octahydro derivative **14.**

In an attempt to extend this reaction scheme to the homologous diazoninone system, **5a** was treated with *N,N'*-dimethylpropylenediamine. In this case the diamine **18** and the dialkylated derivative **19** were isolated, but, in contrast to the lower homolog, no cyclization to the homopiperazine derivative **20** was observed. Furthermore, the reactions which had been successful in the synthesis of the eight-membered ring system, such as heating of **18** in phenol or treating the acid **21** with triethylamine and dicyclohexylcarbodiimide or EEDQ, failed to give any of the desired diazoninone **22.** A small amount of **22** (identified by mass spectrometry) was ultimately obtained by treating **18** with sodium methylate in methanol. However, the major prod-

Scheme IV



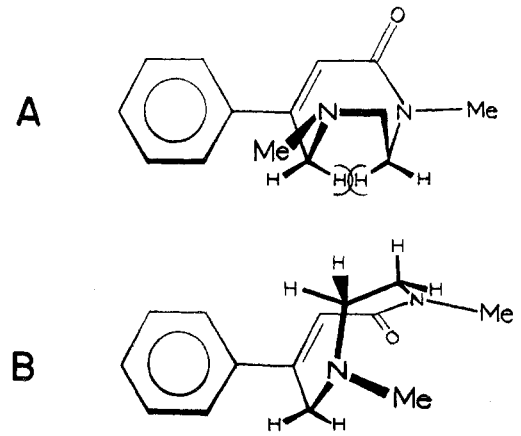


Figure 1. Planar (A) and twisted (B) conformation of **1a.**

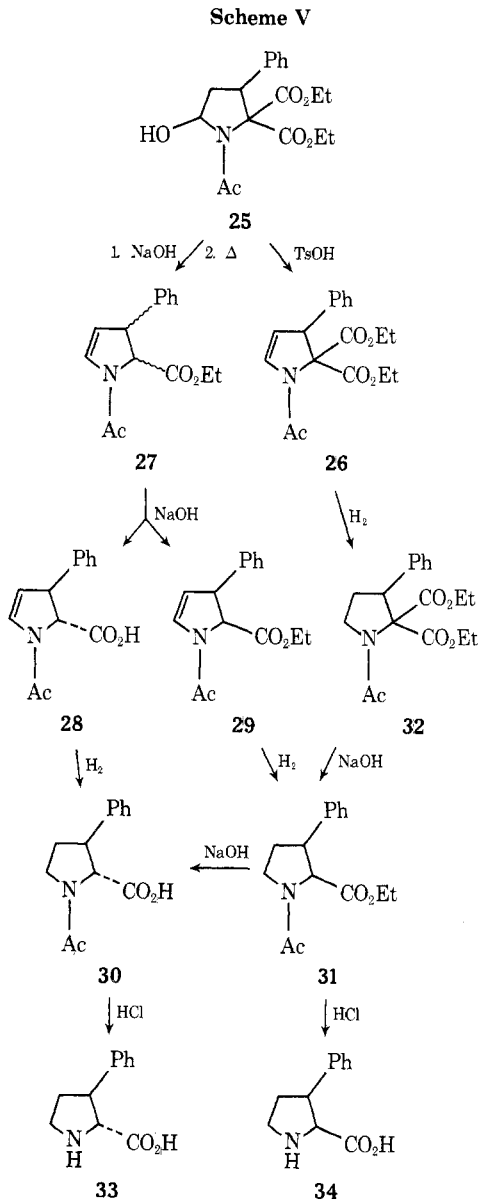
uct of this reaction was the ester aldehyde **23,** which presumably arises from isomerization of **18** to the enamine **24,** which hydrolyzes during work-up (Scheme IV).

The ultraviolet spectrum of **1a** in methanol, with an absorption maximum at 250 nm (ϵ 11,750), resembles that of styrene (ϵ_{244} 12,000) rather than the expected dimethyl cinnamoylamide spectrum (ϵ_{280} 22,200). This indicates that the carbonyl group is not in conjugation with the double bond, probably because the required planar arrangement would lead to serious nonbonded interaction of the hydrogens on C-3 and C-8 as indicated in Figure 1A. The twisted conformation shown in Figure 1B, on the other hand, appears free of strain and steric interference.

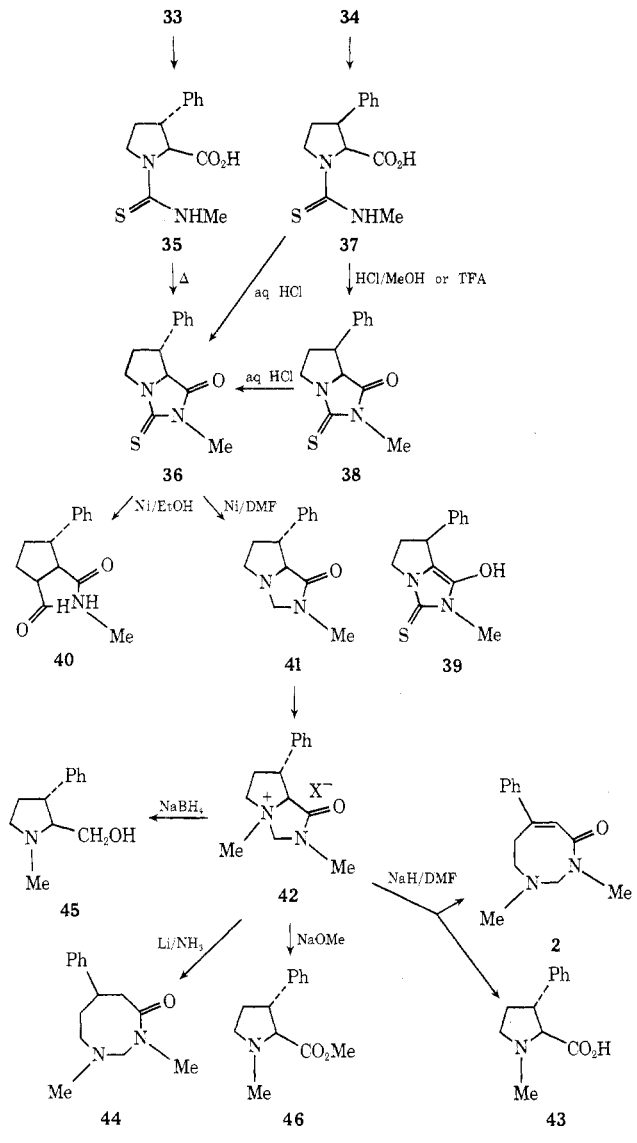
The synthesis of the bicyclic intermediate **4** (R = phenyl) proceeded from the hydroxypyrrolidine derivative **25,** prepared according to the method of Cox, *et al.*,[4] which was dehydrated to **26** (Scheme V). Saponification and decarboxylation of **25,** followed by dehydration, gave a mixture of cis and trans monoesters (**27**). Preferential alkaline saponification[5] of **27** under mild conditions gave a clean separation into trans acid **28** and cis ester **29.** Hydrogenation of **28** and **29** gave **30** and **31,** and these in turn were hydrolyzed with acid to give *trans-* and *cis*-3-phenylproline[6] (**33** and **34,** respectively). Surprising results were obtained when this reaction sequence was altered: hydrogenation of **26** to **32,** followed by alkaline saponification, gave predominantly the cis ester **31.** Basic saponification of **31** required vigorous alkaline conditions and led predominantly to the trans acid **30.** We conclude that the ester groups cis to the phenyl substituent in **31** and **32** are much more resistant to basic hydrolysis than the cis ester groups in **25** and that in fact the hydrolysis of the ester group in **31** is preceded by isomerization to the corresponding trans ester.

Treatment of *trans*-3-phenylproline (**33**) with methyl isothiocyanate gave the trans methylthiourea **35,** which was cyclized to the trans methylthiohydantoin **36** by heating in methanol or chloroform (Scheme VI). By contrast, the cis isomer **37,** obtained from **34,** required acid catalysis for cyclization. Interestingly, anhydrous conditions such as trifluoroacetic acid or HCl–methanol gave rise to the cis hydantoin **38,** whereas treatment with aqueous HCl gave the trans isomer **36.** Similarly, treatment of **38** with aqueous HCl gave **36,** presumably again *via* an intermediate such as **39.** All subsequent reactions were carried out with the trans isomer **36.** Desulfurization of **36** with Raney nickel in ethanol[7] gave only a poor yield of **41,** the major by-product being the ring-opened compound **40.** However, toluene, or preferably dimethylformamide, were found to be excellent solvents for this reaction, resulting in high yields of **41;** methylation with methyl iodide then gave **42.** This quarternary derivative (X = OH) was expected to undergo a transannular Hofmann elimination to the desired 1,3-diazocinone **2.** However, heating of **42** (X = OH) gave only demethylated material[8] (**41**), and treatment under a variety of basic conditions led to no reaction, demethylation, or complex reaction mixtures. Small amounts of **2** were ultimately isolated from a reaction of **42** with sodium hydride and dimethylformamide and identified by mass spectrometry. Under these conditions the major product was *N*-methyl-3-phenylproline (**43**). This result prompted efforts to achieve a reductive transannular ring opening of **42.** Lithium in ammonia in the presence of 1-methoxy-2-propanol[9] gave a clean transannular ring opening to the octahydrodiazocine derivative **44,** whereas aqueous sodium borohydride resulted in the exclusive formation of the alcohol **45.** It is also noteworthy that treatment of **42** with sodium methylate in methanol gave a high yield of the methyl ester **46,** while the nonquaternary **41** was stable to these conditions or to aqueous sodium borohydride. This difference in the reactivities of **41** and **42** leads us to postulate the following mechanisms, in which opening of the strained bicyclic quaternary ring system is the driving force, for the reactions involving **42.** Treatment with sodium hydride leads to small amounts of the anion at C-7 (bearing the phenyl ring) which then rearranges to **2** (Scheme VII, path A). However, the major reaction product results from rearrangement of the more

Scheme V



Scheme VI



stable anion at C-7a (adjacent to the carbonyl) to give, possibly *via* the ketene intermediate, **43** (Scheme VII, path B). The methoxide adduct obtained by reaction with sodium methylate collapses to give the ester **46** (Scheme VII, path C), whereas the corresponding hydride adduct from the sodium borohydride reaction collapses to an aldehyde, which is then reduced to the alcohol **45** by the excess reagent present (Scheme VII, path D). Finally, the lithium-induced transannular ring opening to **44** can be rationalized as a rearrangement of the radical anion, in analogy to the rearrangements observed in ketones with good leaving groups in the α position[10] (Scheme VII, path E).

In animal models, **1a**, **1b**, and **44** did not exhibit activities characteristic for tricyclic antipsychotic compounds.

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by the Analytical Department of Pfizer Central Research. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer. Uv spectra were obtained on a Cary 11 spectrometer. Nmr spectra were obtained on Varian T-60 and A-60 instruments.

Ethyl β-Methyl-2-naphthaleneacrylate (47). This compound was prepared by the procedure of Rahman and Gastaminza[11] in 37% overall yield, bp 154–156° (0.15 mm), mp 54–55°.

Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.30; H, 6.31.

Methyl β-Bromomethyl-2-naphthaleneacrylate (5b). This compound was prepared in analogy to the procedure of Geyde and Nechvatal[12] by bromination of **47** with *N*-bromosuccinimide in 60% yield. After recrystallization from cyclohexane–hexane, the sample had mp 77–78°.

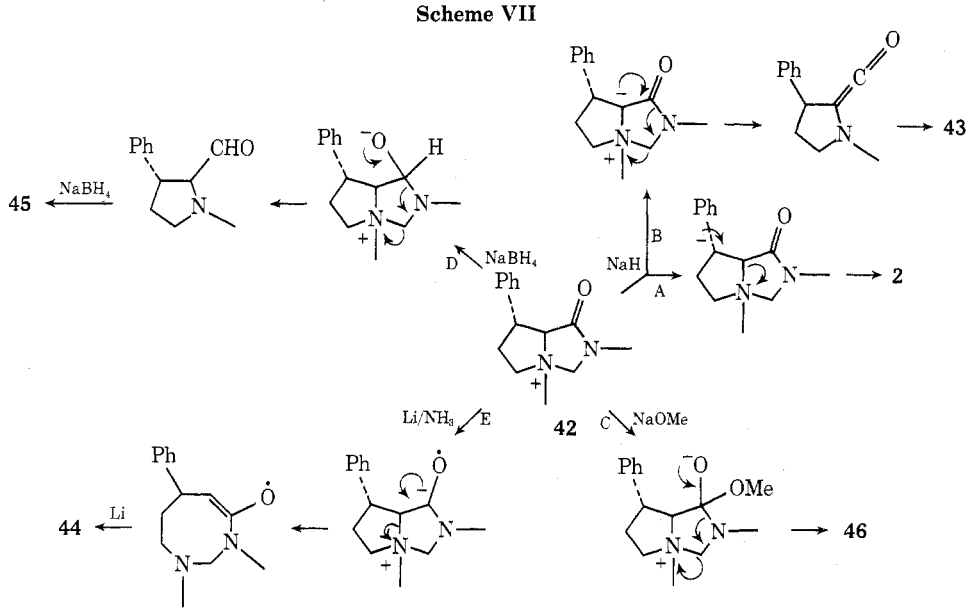
Anal. Calcd for $C_{15}H_{13}BrO_2$: C, 59.07; H, 4.30. Found: C, 59.40; H, 4.41.

1-(β-Dimethylaminoethyl)-4-phenyl-2(5*H*)-pyrrolone (8a). A mixture of 1.2 g (0.0047 mol) of methyl β-bromomethylcinnamate (**5a**)[3] and 352 mg of *N,N'*-dimethylethylenediamine (**6**) in 50 ml of Et_2O was kept for 17 hr at room temperature. After an aqueous work-up for basic material (evaporation followed by dissolution of the residue in 1 *N* HCl, washing with Et_2O, adjustment of the aqueous phase to pH 9 with 4 *N* NaOH, and extraction with Et_2O) there was obtained after recrystallization from Et_2O–hexane 0.355 g (31%) of **8a**: mp 93–95°; nmr ($CDCl_3$) δ 2.3 (s, 6 H), 2.55 (t, 2 H, J = 6.5 Hz), 3.65 (t, 2 H, J = 6.5 Hz), 4.5 (d, 2 H, J = 2 Hz), 6.45 (t, 1 H, J = 2 Hz), 7.45 (m, 5 H).

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 72.95; H, 8.06; N, 12.23

1,4-Dimethyl-2-phenylpiperidine-2-acetic Acid Methyl Ester (10a). A solution of 35 g (0.137 mol) of **5a** in 500 ml of $CHCl_3$ was added dropwise over a period of 4 hr to a mixture of 120 g (1.37 mol) of *N,N'*-dimethylethylenediamine (**6**) in 1 l. of $CHCl_3$ at room temperature. After standing for 17 hr, the mixture was evaporated. An aqueous work-up for basic material (see above), followed by treatment with HCl gas in Et_2O, gave 32 g (69%) of

Scheme VII



10a as the hydrochloride hydrate: mp 210–212° dec; nmr (D_2O) δ 2.95 (s, 3 H), 3.15 (s, 3 H), 3.65 (s, 5 H), 3.9 (s, 4 H), 4.45 (s, 2 H), 7.7 (s, 5 H).

Anal. Calcd for $C_{15}H_{22}N_2O_2 \cdot 2HCl \cdot H_2O$: C, 51.01; H, 7.42; N, 7.94. Found: C, 51.05; H, 7.54; N, 7.92.

Similarly was prepared 1,4-dimethyl-2-(2-naphthyl)piperidine-2-acetic acid methyl ester (**10b**) in 39% yield from **5b** and **6**: dihydrochloride mp 228–230°; nmr (D_2O) δ 3.25 (s, 3 H), 4.6 (s, 3 H), 3.95 (s, 3 H), 4.1 (m, 2 H), 4.25 (m, 4 H), 5.85 (s, 2 H), 7.8–8.7 (m, 7 H).

Anal. Calcd for $C_{19}H_{24}N_2O_2 \cdot 2HCl$: C, 59.22; H, 6.81; N, 7.28. Found: C, 59.09; H, 6.65; N, 7.04.

When this reaction was carried out with **5a** using only 1 equiv of **6**, the major product was ***N,N'*-dimethyl-*N,N'*-di(3-methoxycarbonyl-2-phenylallyl)ethylenediamine (9a)**: mp 57–59°; nmr ($CDCl_3$) δ 2.15 (s, 6 H), 2.45 (s, 4 H), 3.75 (s, 6 H), 3.9 (s, 4 H), 6.15 (s, 2 H), 7.1–7.6 (m, 10 H).

Anal. Calcd for $C_{26}H_{32}N_2O_4$: C, 71.53; H, 7.39; N, 6.42. Found: C, 71.19; H, 7.41; N, 6.43.

***N,N'*-Dimethyl-*N*-(3-methoxycarbonyl-2-phenylallyl)ethylenediamine (7a).** This compound is formed in moderate yield by heating a solution of **10a** in 1 *N* methanolic HCl for 17 hr. Alternatively, the compound is formed by esterification of **11a** (see below) with methanolic HCl at room temperature. The dihydrochloride of **7a** had mp 174–175° after recrystallization from MeOH–Et_2O; nmr (D_2O) δ 2.7 (s, 3 H), 2.75 (s, 3 H), 3.5 (s, 4 H), 3.75 (s, 3 H), 4.6 (s, 2+ H), 6.55 (s, 1 H), 7.5 (s, 5 H).

Anal. Calcd for $C_{15}H_{22}N_2O_2 \cdot 2HCl$: C, 53.74; H, 7.22; N, 8.36. Found: C, 53.77; H, 7.26; N, 8.29.

***N,N'*-Dimethyl-*N*-(3-carboxy-2-phenylallyl)ethylenediamine (11a) and 1,4-Dimethyl-2-phenylpiperidine-2-acetic Acid (12a).** A solution of 23 g (0.065 mol) of **10a** in 500 ml of 6 *N* HCl was heated under reflux for 2 hr. After evaporation the residue was crystallized from 50 ml of MeOH–100 ml of Et_2O to give 8.2 g (39%) of **12a** as the dihydrochloride: mp 218–219° dec; nmr (D_2O) δ 2.9 (s, 3 H), 3.2 (s, 3 H), 3.55 (m, 2 H), 3.8 (s, 4 H), 4.4 (s, 2 H), 7.6 (s, 5 H).

Anal. Calcd for $C_{14}H_{20}N_2O_2 \cdot 2HCl$: C, 52.35; H, 6.91; N, 8.73. Found: C, 52.46; H, 7.00; N, 8.82.

From the original mother liquor of **12a** a solid was isolated which after crystallization from MeOH–Et_2O gave 11.1 g (53%) of **11a** as the dihydrochloride: mp 198–199° dec; nmr (D_2O) δ 2.8 (s, 3 H), 2.85 (s, 4 H), 3.6 (s, 4 H), 4.8 (s, 2+ H), 6.6 (s, 1 H), 7.6 (s, 5 H).

Anal. Calcd for $C_{14}H_{20}N_2O_2 \cdot 2HCl$: C, 52.35; H, 6.91; N, 8.73. Found: C, 52.42; H, 6.97; N, 8.71.

The β-naphthyl derivative **12b** was obtained similarly in 82% yield: dihydrochloride mp 188–189°; nmr δ 2.85 (s, 3 H), 3.2 (s, 3 H), 3.5–3.8 (m, 6 H), 4.4 (s, 2 H), 7.6–8.4 (m, 7 H).

Anal. Calcd for $C_{18}H_{22}N_2O_2 \cdot 2HCl$: C, 58.24; H, 6.52; N, 7.55. Found: C, 58.16; H, 6.47; N, 7.63.

1,4-Dimethyl-7-phenyl-1,2,3,4-tetrahydro-1,4-diazocin-5(8*H*)-one (1a). A suspension of 5 g (0.0156 mol) of **12a**, 3.21 g of dicyclohexylcarbodiimide, and 6.8 ml (3 equiv) of triethylamine in 250 ml of tetrahydrofuran was stirred at room temperature for 17 hr. The reaction mixture was filtered and the filtrate was evaporated to give, after an aqueous work-up for basic material, conversion to the hydrochloride, and two recrystallizations from MeOH–Et_2O, 2.8 g (68%) of **1a** hydrochloride: mp 213–215°; nmr (D_2O) δ 3.0 (s, 3 H), 3.15 (s, 3 H), 3.4 (m, 4 H), 4.4 (s, 2 H), 6.6 (s, 1 H), 7.6 (s, 5 H); mass spectrum *m/e* 230 (M^+), 187, 174, 158, 144 (base peak), 116, 115; uv (MeOH) 250 nm (ε 11,750).

Anal. Calcd for $C_{14}H_{18}N_2O \cdot HCl$: C, 63.03; H, 7.17; N, 10.50. Found: C, 63.17; H, 7.19; N, 10.48.

This compound was also obtained from **11a** under identical reaction conditions in 20% yield. Heating of 110 mg of **10a** in 1.1 g of phenol to 140° for 1 hr followed by the usual work-up gave a 10% yield of **1a**.

Similarly, the β-naphthyl analog **1b** was prepared in 55% yield by treating 2.4 g of **12b** with triethylamine and dicyclohexylcarbodiimide, hydrochloride mp 218–219°.

Anal. Calcd for $C_{18}H_{20}N_2O \cdot HCl$: C, 68.24; H, 6.69; N, 8.85. Found: C, 68.13; H, 6.69; N, 8.73.

1,4-Dimethyl-6-phenyl-1,2,3,4,5,8-hexahydro-1,4-diazocine (13). A mixture of 1.6 g (0.007 mol) of **1a** and 500 mg of lithium aluminum hydride in 50 ml of tetrahydrofuran was refluxed for 2 hr. After cooling, 50 ml of tetrahydrofuran was refluxed for 2 hr. After cooling, 50 ml of EtOAc and then 100 ml of H_2O were added, the pH was adjusted to 10 with 4 *N* NaOH, and the layers were separated. The aqueous layer was extracted with two 150-ml portions of EtOAc, the combined organic solvents were dried and evaporated, and the residue was dissolved in 100 ml of Et_2O and treated with HCl gas to give a hygroscopic solid, which after recrystallization from hot MeOH–Et_2O (1:1) gave 1.84 g (91%) of **13** as the hydrochloride: mp 255–256° dec; nmr (D_2O) δ 2.9 (s, 3 H), 3.05 (s, 3 H), 3.8 (s, 4 H), 4.2 (d, 2 H, J = 10 Hz), 4.6 (s, 2 H), 6.6 (t, 1 H, J = 10 Hz), 7.55 (s, 5 H).

Anal. Calcd for $C_{14}H_{20}N_2 \cdot 2HCl$: C, 58.14; H, 7.67; N, 9.68. Found: C, 57.90; H, 7.65; N, 9.44.

***N,N'*-Dimethyl-*N*-(3-phenylbutyl)ethylenediamine (15).** During the hydrogenation of 700 mg (0.0024 mol) of **13** dihydrochloride in 40 ml of MeOH over 200 mg of Pd/C at atmospheric pressure the smooth uptake of 2 equiv of H_2 was observed. According to nmr analysis, this crude reaction mixture contained at least 60% of **15**. From this mixture was isolated 160 mg (22%) of **15** as the dihydrochloride: mp 165–168°; nmr (D_2O) δ 1.3 (d, 3 H, J = 8 Hz), 1,8–2.3 (m, 2 H), 2.7 (s, 3 H), 2.85 (s, 3 H), 2.6–3.2 (m, 3 H), 3.45 (s, 4 H), 7.35 (s, 5 H).

Anal. Calcd for $C_{14}H_{24}N_2 \cdot 2HCl$: C, 57.35; H, 8.93; N, 9.55. Found: C, 57.17; H, 8.74; N, 9.22.

1,4-Dimethyl-7-phenyl-1,2,3,4,6,7-hexahydro-1,4-diazocin-5(8*H*)-one (17). The hydrogenation of 5.35 g (0.02 mol) of **1a** hydrochloride over 1 g of Pd/C in 200 ml of MeOH under atmospheric pressure gave 3.2 g (61%) of **17** as the hydrochloride hydrate: mp 190–191° dec; nmr (D_2O) δ 3.1 (s, 6 H), 3.0–4.3 (m, 9 H), 7.4 (s, 5 H).

Anal. Calcd for $C_{14}H_{20}N_2O \cdot HCl \cdot \frac{3}{4}H_2O$: C, 59.66; H, 8.04; N, 9.93. Found: C, 59.31; H, 7.64; N, 9.68.

1,4-Dimethyl-6-phenyloctahydro-1,4-diazocine (14). A mixture of 1.2 g (0.005 mol) of **17** and 500 mg of lithium aluminum hydride in 100 ml of tetrahydrofuran was heated under reflux for 2 hr. After the usual work-up (see preparation of **13**) there was obtained 1.19 g (79%) of **14** as the dihydrochloride: mp 255–256° dec; nmr (D_2O) δ 2.4 (m, 2 H), 3.0 (s, 6 H), 3.2–4.2 (m, 9 H), 7.3 (s, 5 H).

Anal. Calcd for $C_{14}H_{22}N_2 \cdot 2HCl$: C, 57.74; H, 8.30, N, 9.62. Found: C, 57.66; H, 8.08, N, 9.49.

***N,N'*-Dimethyl-*N*-(3-methoxycarbonyl-2-phenylallyl)-1,3-propanediamine (18).** A solution of 5.1 g (0.02 mol) of **5a** in 250 ml of $CHCl_3$ was treated with 10.2 g (0.1 mol) of *N,N'*-dimethyl-1,3-propanediamine in 250 ml of $CHCl_3$ as described for the preparation of **10a**. After chromatography of the basic material over a silica gel column using a 90:5:5 mixture of benzene, MeOH, and diethylamine, respectively, as the mobile phase, there was obtained 1.46 g (27%) of **18** as the hydrochloride: mp 174–175°; nmr (D_2O) δ 2.0–2.5 (m, 2 H), 2.8 (s, 3 H), 2.85 (s, 3 H), 2.9–3.6 (m, 6 H), 3.9 (s, 3 H), 6.6 (s, 1 H), 7.6 (s, 5 H).

Anal. Calcd for $C_{16}H_{24}N_2O_2 \cdot 2HCl \cdot \frac{1}{4}H_2O$: C, 54.29; H, 7.48; N, 7.91. Found: C, 54.24; H, 7.34; N, 7.94.

From an earlier column fraction was obtained a 3% yield of ***N,N'*-dimethyl-*N,N'*-di(3-methoxycarbonyl-2-phenylallyl)-1,3-propanediamine (19)**: dihydrochloride hydrate mp 100–110° dec; nmr (D_2O) δ 2.1–2.4 (m, 2 H), 2.9 (s, 6 H), 3.0–3.8 (m, 8 H), 4.0 (s, 6 H), 6.6 (s, 2 H), 7.65 (s, 5 H).

Anal. Calcd for $C_{27}H_{34}N_2O_4 \cdot 2HCl \cdot H_2O$: C, 59.89; H, 7.07; N, 5.18. Found: C, 60.28; H, 7.24; N, 5.44.

Heating a mixture of 80 mg of **18** and 5 mg of NaOMe in 10 ml of MeOH under reflux for 2 hr gave 10 mg of a basic material whose mass spectrum [*m/e* 244 (M^+), 230, 220, 205, 174] is suggestive of **1,5-dimethyl-8-phenyl-1,2,3,4,5,9-hexahydro-1,5-diazonin-6-one (22)**. However, the major product of this reaction (and of other reactions involving treatment of **18** with basic catalysts) was **3-methoxycarbonyl-2-phenylpropionaldehyde (23)**: bp 103° (0.2 mm); nmr ($CDCl_3$) δ 2.55 (2 d, 1 H, J = 6, 17 Hz), 3.2 (2 d, 1 H, J = 8, 17 Hz), 3.65 (s, 3 H), 4.15 (d, 1 H, J = 6, 8 Hz), 7.1–7.5 (m, 5 H), 9.7 (s, 1 H).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.49; H, 6.02.

***N,N'*-Dimethyl-*N*-(3-carboxy-2-phenylallyl)-1,3-propanediamine (21).** A solution of 390 mg (0.0011 mol) of **18** in 25 ml of 6 *N* HCl was heated to reflux for 3 hr. After evaporation *in vacuo* and two crystallizations of the residue from MeOH–Et_2O, there was obtained 272 mg (73%) of **21** as the hydrochloride: mp 177–180° dec; nmr (D_2O) δ 2.1–2.5 (m, 2 H), 2.8 (s, 3 H), 2.85 (s, 3 H), 2.9–3.6 (m, 6 H), 6.55 (s, 1 H), 7.6 (s, 5 H).

Anal. Calcd for $C_{15}H_{22}N_2O_2 \cdot 2HCl \cdot \frac{1}{2}H_2O$: C, 52.32; H, 7.33; N, 8.14. Found: C, 51.92; H, 7.23; N, 8.22.

***N*-Acetyl-2,2-diethoxycarbonyl-3-phenyl-2,3-dihydroxypyrrole (26).** A solution of 102 g (0.293 mol) of **25**[4] and 3 g of *p*-toluenesulfonic acid in 1.5 l. of toluene was heated to reflux until no more water was collected in a Dean-Stark trap (approximately 2 hr). The reaction mixture was evaporated and the residue was re-

crystallized from Et_2O to give 85 g (88%) of **26**: mp 91–93°; nmr ($CDCl_3$) δ 0.8 (t, 3 H), 1.4 (t, 3 H), 2.25 (s, 3 H), 3.5 (q, 2 H), 4.35 (q, 2 H), 4.7 (t, 1 H, J = 3 Hz), 5.2 (2 d, 1 H, J = 3, 5 Hz), 6.7 (2 d, 1 H, J = 3, 5 Hz), 7.2 (s, 5 H).

Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 64.97; H, 6.23; N, 4.02.

N-Acetyl-2-ethoxycarbonyl-3-phenyl-2,3-dihydropyrrole (27). A mixture of 87.2 g (0.25 mol) of **25** and 720 ml of 1.5 *N* NaOH was stirred at room temperature overnight. The mixture was neutralized with 240 ml of 4.5*N* HCl and extracted with $CHCl_3$, the $CHCl_3$ extract was evaporated *in vacuo*, and the residue was dissolved in 1 l. of toluene and heated under reflux for 1.5 hr. After evaporation, the residue was distilled *in vacuo* to give a main fraction of 30.2 g (47%) of **27**, bp 160–165° (0.35 mm).

Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61. Found: C, 69.41; H, 6.48.

***cis*-N-Acetyl-2-ethoxycarbonyl-3-phenyl-2,3-dihydropyrrole (29)** and ***trans*-N-Acetyl-3-phenyl-2,3-dihydropyrrole-2-carboxylic Acid (28).** A mixture of 26 g (0.1 mol) of **27** and 113 ml of 4 *N* NaOH in 700 ml of MeOH was kept at room temperature for 90 min. Glacial acetic acid (31 ml) was added and the solution was concentrated *in vacuo* to a small volume (100 ml). After addition of 500 ml of water and 22 g of $NaHCO_3$, the mixture was extracted with three 100-ml portions of EtOAc. The EtOAc layers were dried and concentrated *in vacuo* and the residue was crystallized from EtOAc–hexane to give 11.8 g (45%) of yellow, crystalline **29**: mp 102–103°; nmr ($CDCl_3$) δ 0.8 (t, 3 H, J = 7 Hz), 2.2 (s, 1 H), 3.55 (m, 2 H), 4.6 (2 t, 1 H, $J_{2,3}$ = 12, $J_{3,4}$ = $J_{3,5}$ = 2 Hz), 5.1 (d, 1 H, $J_{2,3}$ = 12 Hz), 5.2 (2 d, 1 H, $J_{2,3}$ = 2, $J_{4,5}$ = 5 Hz), 6.75 (2 d, 1 H, $J_{3,5}$ = 2, $J_{4,5}$ = 5 Hz), 7.25 (s, 5 H).

Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.46; H, 6.63; N, 5.54.

The aqueous layer was acidified and extracted with four 50-ml portions of EtOAc. This extract was dried and evaporated *in vacuo* and the residue was recrystallized from EtOAc–hexane to give 10 g (43%) of **28**: mp 187–189°; nmr (DMSO-d_6) δ 2.2 (s, 3 H), 4.1 (m, 1 H), 4.35 (d, 1 H, $J_{2,3}$ = 5 Hz), 5.25 (2 d, 1 H, $J_{3,4}$ = 3, $J_{4,5}$ = 4 Hz), 7.05 (2 d, 1 H, $J_{4,5}$ = 4, $J_{3,5}$ = 2 Hz), 7.3 (s, 5 H).

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.47; H, 5.76; N, 6.10.

***trans*-N-Acetyl-3-phenylpyrrolidine-2-carboxylic Acid (30).** A solution of 5.75 g (0.025 mol) of **28** in 50 ml of EtOH was hydrogenated at atmospheric pressure over 1 g of 10% Pd/C. After the hydrogen uptake had ceased (25 min) the mixture was filtered, the filtrate was evaporated, and the residue was recrystallized from EtOAc–hexane to give 5.4 g (94%) of **30**: mp 180–181°; nmr (CD_3OD) δ 2.1 (s, 3 H), 2.2 (m, 2 H), 3.6 (m, 3 H), 4.4 (d, 1 H, J = 7 Hz), 7.3 (s, 5 H)

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.98; H, 6.57; N, 6.03.

Alternatively, **30** was prepared by heating a stirred solution of 80 g (0.24 mol) of **32** and 28.8 g (0.72 mol) of NaOH in 400 ml of dioxane and 100 ml of H_2O for 22 hr at 80°. The Na_2CO_3 was filtered off, the filtrate was evaporated, the residue was dissolved in H_2O, and this solution was acidified to give, after recrystallization from EtOAc–hexane, 39.1 g (70%) of **30**, mp 182–184°.

***cis*-N-Acetyl-2-ethoxycarbonyl-3-phenylpyrrolidine (31).** A solution of 7.77 g (0.03 mol) of **29** in 50 ml of EtOH was hydrogenated in the presence of 1 g of 10% Pd/C at atmospheric pressure. After the uptake of H_2 ceased (20 min), the mixture was worked up to give, after recrystallization from EtOAc–hexane, 5.6 g (73%) of **31**: mp 83–84°; nmr ($CDCl_3$) δ 0.8 (t, 3 H), 2.1 (s, 3 H), 2–3 (m, 3 H), 3.4–4.0 (m, 4 H), 4.75 (d, 2 H, J = 9 Hz), 7.3 (s, 5 H).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.78; H, 7.38; N, 5.33.

N-Acetyl-2,2-diethoxycarbonyl-3-phenylpyrrolidine (32). A solution of 82 g (0.25 mol) of **26** in 200 ml of EtOH was hydrogenated over 3 g of 10% Pd/C under 45 psi in a Parr apparatus overnight. The usual work-up gave 82.5 g (100%) of **32** as an oil. A small sample was distilled: bp 136–140° (0.2 mm); $n^{25}D$ 1.518; nmr ($CDCl_3$) δ 0.8 (t, 3 H), 1.3 (t, 3 H), 2.1 (s, 3 H), 1.7–2.8 (m, 2 H), 3.4–4.0 (m, 5 H), 4.2 (q, 2 H), 7.3 (s, 5 H).

Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.72; H, 6.92; N, 4.22.

***trans*-3-Phenylpyrrolidine-2-carboxylic Acid (*trans*-3-Phenylproline, 33).** A mixture of 8.1 g (0.035 mol) of **30** and 100 ml of 6 N HCl was heated under reflux for 17 hr. After evaporation *in vacuo*, the residue was recrystallized from EtOH–Et_2O to give 7.1 g (91%) of **33** as the hydrochloride: mp 218–222° dec; nmr (CD_3OD) δ 2.3–2.7 (m, 2 H), 3.5–3.9 (m, 3 H), 4.45 (d, 1 H, J = 10 Hz), 7.5 (s, 5 H).

Anal. Calcd for $C_{11}H_{13}NO_2$·HCl: C, 57.70; H, 6.21; N, 6.16. Found: C, 57.94; H, 6.04; N, 6.16.

***cis*-3-Phenylpyrrolidine-2-carboxylic Acid (*cis*-3-Phenylproline, 34).** Hydrolysis of 4.5 g (0.0173 mol) of **31** with 50 ml of 6 *N* HCl for 17 hr under reflux, followed by evaporation and recrystallization from EtOH–Et_2O, gave 3.6 g (92%) of **34** as the hydrochloride: mp 191–215° dec; nmr (CD_3OD) δ 2.2–2.6 (m, 2 H), 3.4–4.2 (m, 3 H), 4.65 (d, 1 H, J = 9 Hz), 7.3 (s, 5 H).

Anal. Calcd for $C_{11}H_{13}NO_2$·HCl: C, 57.70; H, 6.20; N, 6.15. Found: C, 57.92; H, 6.25; N, 6.23.

***trans*-2-Methyl-7-phenylhexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one-3-thione (Methylthiohydantoin of *trans*-3-Phenylproline, 36).** In analogy to the method of Edman,[13] 11 g (0.15 mol) of methyl isothiocyanate was added dropwise over 10 min to a solution of 17 g (0.075 mol) of **33** in a mixture of 225 ml of pyridine and 225 ml of H_2O, keeping the pH at 9.0 by the addition of 1 *N* NaOH. After washing with benzene, the aqueous layer was acidified to pH 2 with 6 *N* HCl and extracted three times with 150 ml of EtOAc. The organic layer was dried over $MgSO_4$ and evaporated to give the thiourea derivative **35** as a white solid. An attempt to recrystallize this compound from hot MeOH gave 14.25 g (78%) of **36**: mp 125–126°; nmr ($CDCl_3$) δ 1.8–3.2 (m, 3 H), 3.2 (s, 3 H), 3.2–4.1 (m, 2 H), 4.2 (d, 1 H, J = 10 Hz), 7.3 (s, 5 H).

Anal. Calcd for $C_{13}H_{14}N_2OS$: C, 63.39; H, 5.73; N, 11.37; S, 13.02. Found: C, 63.59; H, 5.75; N, 11.28; S, 13.23.

Alternatively, **36** was prepared in 91% yield by heating 10 g of **37** in a mixture of 140 ml of AcOH, 450 ml of 1 *N* HCl, and 20 ml of 6 *N* HCl under reflux for 2 hr. Under these reaction conditions **38** is also converted to its isomer **36.**

***cis*-2-Methyl-7-phenylhexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one-3-thione (Methyl Thiohydantoin of *cis*-3-Phenylproline, 38).** In analogy to the procedure described above, 1.14 g (0.005 mol) of **34** was converted to the methyl thiourea derivative **37**, mp 178–180° after recrystallization from hot MeOH, yield 1.22 g (92%).

Anal. Calcd for $C_{13}H_{16}N_2O_2S$: C, 59.08; H, 6.10; N, 10.60. Found: C, 58.99; H, 6.10; N, 10.58.

A solution of 1.2 g of **37** in 15 ml of trifluoroacetic acid was allowed to stand at room temperature for 1 hr. After evaporation, the residue was recrystallized twice from hot MeOH–H_2O to give 0.9 g (80%) of **38**: mp 155–157°; nmr ($CDCl_3$) δ 2.4–2.7 (m, 2 H), 2.85 (s, 3 H), 3.4–3.9 (m, 2 H), 4.15–4.65 (m, 1 H), 4.5 (d, 1 H, J = 9 Hz), 6.9–7.3 (m, 5 H).

Anal. Calcd for $C_{13}H_{14}N_2OS$: C, 63.39; H, 5.73; N, 11.37. Found: C, 63.34; H, 5.76; N, 11.43.

Alternatively, **38** was prepared by heating a solution of **37** in methanolic HCl under reflux for 30 min.

***trans*-2-Methyl-7-phenylhexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (41).** A solution of 11.4 g (0.046 mol) of **36** in 500 ml of DMF was added to a suspension of 100 ml of W4 Raney nickel in DMF, and the mixture was heated to 110° for 1 hr. After filtration through Celite, the filtrate was evaporated *in vacuo*, and the residue was dissolved in MeOH, converted to the hydrochloride, and recrystallized from MeOH–Et_2O to give a first crop of 8.8 g (75%) of **41** as the hydrochloride: mp 214–217°; nmr (CD_3OD) δ 2.3–2.8 (m, 2 H), 3.0 (s, 3 H), 3.4–4.4 (m, 3 H), 4.7 (d, 1 H, J = 7 Hz), 4.85 (d, 1 H, J = 8 Hz), 5.1 (d, 1 H, J = 8 Hz), 7.4 (s, 5 H).

Anal. Calcd for $C_{13}H_{16}N_2O$·HCl: C, 61.78; H, 6.78; N, 11.08. Found: C, 61.80; H, 6 81; N, 11.07.

When toluene was used as the solvent, the yield of **41** was 51%. When the reaction was carried out in ethanol,[7] the major product was ***trans*-1-formyl-3-phenylproline methylamide (40)**: mp 120–121° after recrystallization from MeOH–Et_2O; nmr ($CDCl_3$) δ 1.8–2.5 (m, 2 H), 2.75 (d, 3 H, J = 5 Hz), 3.4–4.2 (m, 3 H), 4.4 (d, 1 H, J = 7 Hz), 6.8 (broad s, 1 H), 7.2 (s, 5 H), 8.3 (s, 1 H).

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 66.83; H, 6.93; N, 11.90.

***trans*-2,4-Dimethyl-7-phenylhexahydro-1*H*-pyrrolo[1,2-*c*]imidazolium-1-one Iodide (42).** To a solution of 4.1 g (0.019 mol) of **41** as the free base in 100 ml of acetone was added 3.0 ml (0.048 mol) of MeI and the mixture was heated to reflux for 1 hr. After cooling, 6.2 g (91%) of the iodide of **42** was filtered off: mp 203–204° (on a previous occasion, a crystalline modification melting at 159–161° has been obtained from acetone–MeOH); nmr (CD_3OD) δ 2.4–2.8 (m, 2 H), 2.9 (s, 3 H), 3.5 (s, 3 H), 3.7–4.1 (m, 3 H), 5.6 (d, 1 H, J = 7 Hz), 4.9 (d, 1 H, J = 8 Hz), 5.2 (d, 1 H, J = 8 Hz), 7.2 (s, 5 H).

Anal. Calcd for $C_{14}H_{19}IN_2O$: C, 46.94; H, 5.35; N, 7.82. Found: C, 47.07; H, 5.30; N, 7.70.

Reaction of 42 with NaH in DMF. To a solution of 1 g (2.8 mmol) of **42** (X = I) in 30 ml of DMF was added 0.12 g of 57%

NaH and the mixture was heated to 85° for 2 hr. After cooling, the precipitate was filtered off to give, after recrystallization from MeOH–Et_2O, 150 mg of the sodium salt of *trans*-*N*-methyl-3-phenylproline (**43**): mp >300°; nmr (10% DCl in D_2O) δ 2.2–2.6 (m, 2 H), 3.1 (s, 3 H), 3.3–4.1 (m, 3 H), 4.3 (d, 1 H, J = 10 Hz), 7.3 (s, 5 H).

Anal. Calcd for $C_{12}H_{14}NO_2Na \cdot \frac{1}{2}H_2O$: C, 61.07; H, 6.41; N, 5.94. Found: C, 61.34; H, 6.18; N, 5.98.

The filtrate from the reaction mixture was evaporated, the residue was dissolved in 1 *N* HCl and washed with Et_2O, and the aqueous layer was adjusted to pH 9 and extracted with Et_2O. The Et_2O layer was dried and evaporated, and the residue was dissolved in a small amount of Et_2O and treated with HCl gas. The precipitate (20 mg) was recrystallized twice from MeOH–Et_2O to give 5 mg of a crystalline solid, mp 155° dec. The mass spectrum of this compound [*m/e* 230 (M^+), 197, 173, 159, 144 (base peak), 115, 43] was similar to that of **7a** and indicative of **1,3-dimethyl-6-phenyl-1,2,7,8-tetrahydro-1,3-diazocin-4(3*H*)-one (2a).**

1,3-Dimethyl-6-phenyl-1,2,3,5,6,7-hexahydro-1,3-diazocin-4(8*H*)-one (44). To a solution of 3 g (0.0084 mol) of **42** (X = I) in 250 ml of liquid NH_3 was added 0.5 ml of 1-methoxy-2-propanol and 0.168 g (0.0244 mol) of lithium wire.[7] The mixture was kept at −40° for 2 hr while a deep blue color persisted. The solution was allowed to evaporate, and the residue was treated with 50 ml of H_2O and extracted with Et_2O (2 × 100 ml). The organic layers were combined and dried, and the residue was converted to the hydrochloride. Recrystallization from MeOH–Et_2O gave a first crop of 1.2 g (54%) of **44** as the hydrochloride: mp 158–159°; nmr ($CDCl_3$) δ 1.7–2.1 (m, 2 H), 2.1–3.0 (m, 5 H), 2.5 (s, 3 H), 3.1 (s, 3 H), 3.95 (d, 1 H, J = 14 Hz), 4.7 (d, 1 H, J = 14 Hz), 7.2 (s, 5 H).

Anal. Calcd for $C_{14}H_{20}N_2O \cdot HCl$: C, 62.56; H, 7.87; N, 10.42. Found: C, 62.84; H, 8.00; N, 10.28.

***trans*-1-Methyl-2-hydroxymethyl-3-phenylpyrrolidine (45).** A solution of 0.378 g (10 mmol) of $NaBH_4$ and 0.358 g (1 mmol) of **42** (X = I) in 10 ml of H_2O was stirred at room temperature for 1.5 hr. After addition of 5 ml of 2 *N* NaOH, the mixture was extracted with EtOAc (2 × 50 ml), and the organic layers were dried and evaporated to give an oil (180 mg) which was converted to the hydrochloride. Recrystallization from MeOH–Et_2O gave 0.125 g (55%) of **45**: white crystals, mp 139–140°; nmr ($CDCl_3$) δ 1.7–3.8 (m, 12 H), 7.3 (s, 5 H).

Anal. Calcd for $C_{12}H_{17}NO \cdot HCl$: C, 63.28; H, 7.96; N, 6.15. Found: C, 62.96; H, 7.87; N, 5.95.

Under these reaction conditions, **41** was inert.

***trans*-1-Methyl-3-phenyl-2-methoxycarbonylpyrrolidine (46).** A mixture of 0.5 g (1.4 mmol) of **42** (X = I) and 0.076 g (1.4 mmol) of sodium methylate in 25 ml of MeOH was heated under reflux for 2 hr. After evaporation, the residue was treated with 10 ml of H_2O and extracted with Et_2O. The Et_2O extract was dried and evaporated and the residue was converted to the hydrochloride to give after recrystallization from EtOH–Et_2O 0.23 g (65%) of **46** as the hydrochloride: mp 149–151°; nmr (CD_3OD) δ 2.3–2.7 (m, 2 H), 3.1 (s, 3 H), 3.4–4.1 (m, 3 H), 3.65 (s, 3 H), 4.5 (d, 1 H, J = 11 Hz), 7.3 (s, 5 H).

Anal. Calcd for $C_{13}H_{17}NO_2 \cdot HCl$: C, 61.00; H, 7.09; N, 5.47. Found: C, 60.80; H, 7.18; N, 5.46.

Under these reaction conditions, **41** was inert.

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Registry No.—1a, 51212-03-4; **1a** hydrochloride, 51212-04-5; **1b** hydrochloride, 51212-05-6; **2a,** 51212-06-7; **5a,** 3516-64-1; **5b,** 51212-07-8; **6,** 110-70-3; **7a** dihydrochloride, 51212-08-9; **8a,** 51212-09-0; **9a,** 51212-10-3; **10a,** 51212-11-4; **10a** dihydrochloride, 51212-12-5; **10b,** 51212-13-6; **10b** dihydrochloride, 51212-14-7; **11a,** 51212-15-8; **11a** dihydrochloride, 51212-16-9; **12a,** 51271-01-3; **12a** dihydrochloride, 51212-17-0; **12b,** 51212-18-1; **12b** dihydrochloride, 51212-19-2; **13** dihydrochloride, 51212-20-5; **14** dihydrochloride, 51212-21-6; **15** dihydrochloride, 51212-22-7; **17,** 51212-23-8; **17** dihydrochloride, 51212-24-9; **18,** 51212-25-0; **18** dihydrochloride, 51212-26-1; **19** dihydrochloride, 51212-27-2; **21** dihydrochloride, 51212-28-3; **23,** 51212-29-4; **25,** 3005-63-8; **26,** 51212-30-7; *trans*-**27,** 51212-31-8; **28,** 51212-32-9; **29,** 51212-33-0; **30,** 51212-34-1; **31,** 51212-35-2; **32,** 51212-36-3; **33,** 51212-37-4; **33** hydrochloride, 51212-38-5; **34,** 51212-39-6; **34** hydrochloride, 51271-02-4; **36,** 51608-58-3; **37,** 51212-41-0; **38,** 51212-42-1; **40,** 51212-43-2; **41,** 51212-44-3; **41** hydrochloride, 51212-45-4; **42,** 51212-46-5; **43,** 51212-47-6; **44** hydrochloride, 51212-48-7; **45** hydrochloride, 51212-49-8; **46** hydrochloride, 51212-50-1; **47,** 51212-51-2; *N*-bromosuccinimide, 128-08-5; dicyclohexylcarbodiimide, 538-75-0; triethylamine, 121-44-8; *N,N'*-dimethyl-1,3-propanediamine, 111-33-1; *p*-toluenesulfonic acid, 104-15-4; methyl isothiocyanate, 556-61-6; 1-methoxy-2-propanol, 107-98-2.

References and Notes

(1) (a) A. Weissman, *Psychopharmacologia*, **12,** 142 (1968); (b) K. Pelz and M. Protiva, *Collect. Czech. Chem. Commun.*, **32,** 2161 (1967); (c) C. L. Zirkle and C. Kaiser in "Medicinal Chemistry," 3rd ed, A. Burger, Ed., Wiley-Interscience, New York, N. Y., 1970, p 1410.
(2) (a) J. R. Tretter, J. F. Muren, B. M. Bloom, and A. Weissman, Presentation at the American Chemical Society Medicinal Symposium, Bloomington, Ind., 1966; (b) R. Sarges, J. R. Tretter, S. S. Tenen, and A. Weissman, *J. Med. Chem.*, **16,** 1003 (1973).
(3) M. U. S. Sultanbawa, T. Veeravagu, and T. Padmanathan, *J. Chem. Soc.*, 1262 (1960).
(4) D. A. Cox, A. W. Johnson, and A. B. Mauger, *J. Chem. Soc.*, 5024 (1964).
(5) The analogous preferential saponification of a 3-methylproline derivative has been described by A. B. Mauger, F. Irreverre, and B. Witkop, *J. Amer. Chem. Soc.*, **88,** 2019 (1966).
(6) Racemic 3-phenylproline has been described in ref 4.
(7) H. C. Carrington, C. H. Vasey, and W. S. Waring, *J. Chem. Soc.*, 3105 (1953).
(8) This is consistent with the results obtained by L. A. Paquette and M. K. Scott, *J. Org. Chem.*, **33,** 2379 (1968), who observed demethylation during an attempt to achieve transannular ring opening of the methohydroxide of 1,5-diazabicyclo[5.4.0]undecan-4-one.
(9) J. P. Yardley, R. W. Rees, and H. Smith, *J. Med. Chem.*, **10,** 1088 (1967).
(10) H. O. House in "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 56 ff.
(11) A. Rahman and A. E. Gastaminza, *Recl. Trav. Chim. Pays-Bas*, **81,** 645 (1962).
(12) R. N. Geyde and A. Nechvatal, *J. Chem. Soc.*, 5925 (1964).
(13) P. Edman, *Acta Chem. Scand.*, **4,** 277 (1950).