Experimental Results

Substituted Pyrroles (I).—The procedure for preparing the pyrroles of Table II was that of Broadbent, *et al.*,[4] in which PhMe was used in place of C_6H_6 as given in their method F.

Substituted 3-Pyrrolecarboxaldehydes (II).—The intermediate aldehydes in Table II were prepared by the procedure of Rips and Buu-Hoï.[2] Others were purchased.[3]

1-Substituted-2,5-dimethyl-3-pyrrolemethylamines (IV).—As a general procedure 0.54 mole of polyamine[8] was rapidly added to a soln of 0.5 mole of pyrrolecarboxaldehyde in 700 ml of PhMe heated to about 90° with stirring. The mixt was refluxed until about the theoretical amt of H_2O (9 ml) collected in a Dean–Stark trap; this usually required about 2 hr. The solvent was removed in a rotary evaporator and the residue, dissolved in one-third its vol of EtOH, was added during 1.5 hr to a stirred mixt of 50 g of KBH_4 in 700 ml of MeOH at 5–10°. The mixt was stirred overnight at room temp, then evapd on the steam bath. The residue was stirred vigorously with a soln of 35 g of NaOH in 200 ml of H_2O and extd with PhMe, which in turn was extd with an excess of AcOH (70 ml of glacial AcOH in 200 ml of H_2O). The aq ext was treated with an excess of solid KOH with stirring, extd with PhMe, and fractionally distd.

All of the piperazine derivatives of Table I were water miscible and required care in the work-up. They also had an initial decompn period during distn before high vacuum could be obtained.

In the prepn of salts, an equiv of citric acid or H_2SO_4 dissolved in MeOH was added to a warm soln of the base in about 5 vol of MeOH. If the salt did not cryst readily when the soln was cooled overnight, crystn was induced by addition of Me_2CO. HCl salts were found less desirable in that they darkened on storage and often were very hygroscopic.

(8) All intermediate amines were obtained from chemical supply companies in the United States except 1-(3-aminopropyl)piperazine, which was kindly donated by Badische Anilin- & Soda-Fabrik AG, Ludwigschafen, West Germany. We are especially grateful to Dr. W. H. Rieger of Reilly Tar & Chemical Corp., Indianapolis, Ind., for a generous supply of 4-(2-aminoethyl)piperidine.

Acknowledgments.—We are indebted to colleagues at The Wm. S. Merrell Company for special assistance: Dr. Albert A. Carr, who coordinated this joint research program and offered valuable suggestions; Dr. T. Tsai, who did the spinal cat work; Miss Ruth Hattan, who made a comprehensive chemical literature search; Mr. Martin Gordon, who supplied the ir and uv spectra. The research at Emory University was made possible by the support of Dr. R. A. Day, Jr., Chairman of the Department of Chemistry, and a generous grant from Richardson-Merrell Inc., both of which are gratefully acknowledged.

5,8-Dihydroharman Derivatives. Their Preparation and Biological Activities

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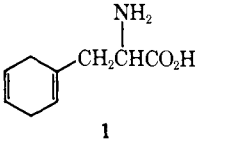
Received August 13, 1970

Li–NH_3 reductions of harmine, 6-methoxyharman, their 9-Me homologs, and 1,2,3,4-tetrahydroharmans afforded, among other products, the corresponding 5,8-dihydro derivatives. Imipramine was converted into its inactive 6,9-dihydro analog by the same technique. 5,8-Dihydro derivatives of harmine and 6-methoxyharman appeared to be at least as active as the parent compounds in inhibiting tetrabenazine-induced depression. Both harmine and 5,8-dihydroharmine reversed reserpine-induced hypothermia in mice. *In vitro* MAO inhibition assay and tetrabenazine assay data are given for a variety of harman congeners, and structure–activity relationships are discussed.

In a biologically active molecule, conversion of a benzene ring into its nonconjugated dihydro derivative represents a structure modification of considerable interest. However, this modification has received practically no attention.[1] Its potential significance lies in the expectation that whereas the size and shape of the molecule are altered only to a small extent and the polarity is not greatly different, its potential for biochemical reactivity might be significantly affected. Thus, it is conceivable that the nonconjugated diene system might approximate the benzene ring closely enough to allow interaction with important receptor sites, yet the molecule might not undergo metabolic processes such as aromatic hydroxylation. One example of a biologically active dihydroaromatic which appeared during the course of our investigation in this area[2] is 1,4-cyclohexadiene-L-alanine (**1**), a potent antagonist of the parent phenylalanine. The cyclohexadiene ring of **1** was shown to be planar by X-ray diffraction.[3] Another interesting dihydroaromatic is 4,7-dihydro-L-tryptophan.[4a,b] In the present article we describe the reduction of certain harmans and 1,2,3,4-tetrahydroharmans to the corresponding 5,8-dihydro derivatives and compare the biological activities of these derivatives with the parent compounds as well as related 3,4-dihydroharmans.



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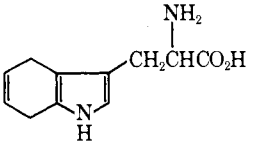

2

The pyrido[3,4-*b*]indole nucleus of harman and its derivatives presents a variety of possible sites for reduc-

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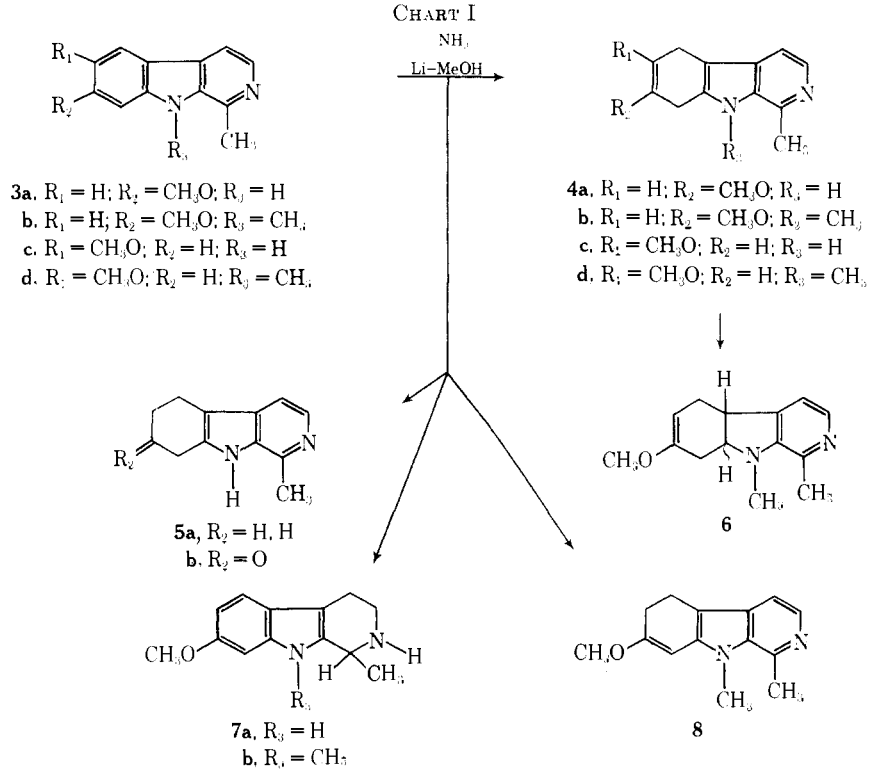
(1) The reduction of 3-methoxyestratriene derivatives to the corresponding 1,4-dihydro derivatives is an important step in the preparation of 19-nor steroids, for example, see L. Miramontes, G. Rosenkranz, and C. Djerassi, *J. Amer. Chem. Soc.*, **73**, 3540 (1951). However, little has been reported about the biological activities of these dihydro intermediates.

(2) See M. J. Weiss, G. R. Allen, Jr., G. J. Gibs, J. F. Poletto, and W. A. Remers, First International Congress of Heterocyclic Chemistry, Albuquerque, New Mexico, 1967, Abstracts of the Meeting; "Topics in Heterocyclic Chemistry," R. C. Castle, Ed., Wiley-Interscience, New York, N. Y., 1969, for preliminary experiments in this area.

(3) B. A. Shoulders, R. M. Gipson, R. J. Jandacek, S. H. Simonsen, and W. Shive, *J. Amer. Chem. Soc.*, **90**, 2992 (1968).

(4) (a) O. Yonemitsu, P. Cerutti, and B. Witkop, *ibid.*, **88**, 3941 (1966); (b) see also J. E. Dolfini, H. E. Applegate, G. Bach, H. Basch, J. Bernstein, J. Schwartz, and F. L. Weisenborn, *J. Med. Chem.*, **14**, 117 (1971), for the synthesis of certain semisynthetic penicillins and cephalosporins derived from D-2-(1,4-cyclohexadienyl)glycine.

CHART I



tion by Li–NH_3. Since ring selectivity in the reductions of certain indoles and quinolines could be varied according to the reaction conditions,[5,6] it was interesting to apply these conditions to harman derivatives. The structures shown in Chart I illustrate the products obtained under a variety of reduction conditions.

As anticipated from its extended π-orbital system (LUMO at −0.635B),[7] 9-methylharmine (**3b**) readily consumed 2 equiv of Li. Addition of NH_4Cl or MeOH to the presumed dianion afforded 5,8-dihydro derivative **4b** as the main product isolated (25% yield), plus small amounts of 5,6-dihydro isomer **8**, 5,5a,8,8a-tetrahydro derivative **6**, and starting material. Formation of tetrahydro derivative **6** possibly occurs by way of **4b**, which has a complete azaindole π-electron system.

Reduction of **3b** in the presence of excess MeOH led to 1,2,3,4-tetrahydro derivative **7b**, 5,6-dihydro derivative **8**, and tetrahydro **6**, plus a relatively high amount of starting material. We could find no 5,8-dihydro derivative **4b**. Thus a degree of ring selectivity exists in the Li–NH_3 reduction of 9-methylharmine.

Unlike **3b**, harmine (**3a**) has an acidic H on the (indolic) 9-N. Consequently addition of Li to a soln of **3a** in liq NH_3 resulted in salt formation. One equiv of Li was consumed in this process, with very little reduction occurring (tlc evidence). In contrast to the salts obtained from simpler indoles,[5,8] this salt of harmine could be reduced by excess Li. When a mixture containing Li and **3a** was quenched with Fe^{3+} after 5 hr, only 9% of starting material was isolated. The products of this reaction, **7a**, **4a**, and **5a**, reflected reduction in either of the pyridine or benzene rings. Much amorphous solid was also obtained. Reduction of the intermediate salt possibly takes place by way of a radical dianion, which should have one electron dispersed throughout the LUMO of its π system and the other negative charge localized mostly in the lone pair of its indole N. Such a radical dianion is a reasonable intermediate since harmine has a LUMO of lower energy than carbazole which gives a dianion radical with Na–K alloy.[9]

When harmine was reduced in the presence of excess MeOH the products were also 5,8-dihydro derivative **4a** and 1,2,3,4-tetrahydro derivative **7a**; both isolated in very low yield. Addition of MeOH to the intermediate anion in the presence of excess Li afforded these same two products with a slight increase in the amount of **4a**.

6-Methoxyharman (**3c**) and 6-methoxy-9-methylharman (**3d**) were also reduced by Li and MeOH in NH_3. The corresponding 5,8-dihydro derivatives (**4c** and **4d**, respectively) were the sole products isolated, in addition to starting material.[10] Thus these reductions appear to be less complex than those of the corresponding 7-MeO isomers **3a** and **3b**.

The enol ether function of **4a** was readily hydrolyzed by dil HCl. This reaction afforded 7-oxo-5,6,7,8-tetrahydroharmine (**5b**).

1,2,3,4-Tetrahydroharmans (*e.g.*, **9a** and **9b**) possess the indole π-electron system. Previously it had been found that various indoles, including tryptamines, could be reduced to their nonconjugated dihydro derivatives[2,4b,5,6,8] by Li and MeOH in liq NH_3. Similar results were obtained when typical 1,2,3,4-tetrahydroharmans were treated under the same conditions.

(5) W. A. Remers, G. J. Gibs, C. Pidacks, and M. J. Weiss, *J. Amer. Chem. Soc.*, **89**, 5513(1967).

(6) W. A. Remers, G. J. Gibs, C. Pidacks, and M. J. Weiss, *J. Org. Chem.*, **36**, 279 (1971).

(7) LCAO–MO calculations based upon the parameters $\alpha_N = \alpha_C + 0.5\beta$, $\alpha_{N'} = \alpha_C + 1.5\beta$, $\alpha_O = \alpha_C + 2.0\beta$, $\beta_{CN} = \beta_{CC}$, $\beta_{CO} = 0.8\beta_{CC}$.

(8) S. O'Brien and D. C. C. Smith, *J. Chem. Soc.*, 4609 (1960).

(9) N. L. Bauld and H. Zoeller, Jr., *Tetrahedron Lett.*, 885 (1967).

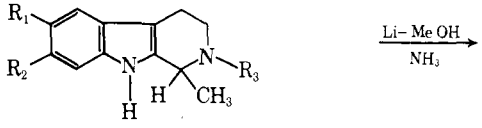
(10) In the case of **3c** the limit of chromatographic separation (lower liquid phase began to come off of the support) occurred after starting material was eluted. Therefore, it is conceivable that the 1,2,3,4-tetrahydro derivative of **3c** was actually formed in the reduction, but not found in the chromatographic separation. However, this possibility does not exist for the resolution of the product mixture from **3d**.

Table I
Monamine Oxidase Inhibition and Antitetrabenazine Activity of β-Carbolines

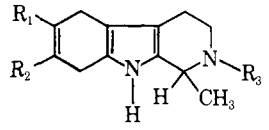
Compound	MAO inhibition level *in vitro*,[a] *M*	Lowest active dose for antagonism of tetrabenazine-induced depression in mice (mg/kg) at 1.5 hr[b,c]
Harmine·HCl (**3a**)	68% at 10^{-7}	12.5[d]
5,8-Dihydroharmine·AcOH (**4a**)	50% at 10^{-7}	3–6
7-Oxo-5,6,7,8-tetrahydroharman (**5b**)	50% at 10^{-5}	12.5
6-Methoxyharman·AcH (**3c**)	32% at 10^{-6}	Inactive at 25
5,8-Dihydro-6-methoxyharman·AcOH (**4c**)	Not measured	5
3,4-Dihydro-7-methoxyharman·HCl (harmaline)	73% at 10^{-7}	3[d]
3,4-Dihydro-6-methoxyharman·AcOH	39% at 10^{-6}	25
6-Methoxy-1,2,3,4-tetrahydroharman·AcOH (**9a**)	Inactive at 10^{-5}	Inactive
6-Methoxy-1,2,3,4,5,8-hexahydroharman·AcOH (**10a**)	Inactive at 10^{-5}	Inactive
7-Methoxy-2-propyl-1,2,3,4-tetrahydroharman·HCl (**9b**)	61% at 10^{-6}	Inactive
7-Methoxy-2-propyl-1,2,3,4,5,8-hexahydroharman·AcOH (**10b**)	50% at 10^{-5}	Inactive

[a] A detailed description of this assay is given by R. J. Taylor, E. Markley, and L. Ellenbogen, *Biochem. Pharmacol.*, **16**, 79 (1967). [b] See E. N. Greenblatt and A. C. Osterberg, *Toxicol. Appl. Pharmacol.*, **7**, 566 (1965) for details of this assay. [c] Imipramine was active at 2.4 mg/kg in this assay. 6,9-Dihydroimipramine was inactive at 25 mg/kg. [d] Administered 2.5 hr before testing.

Thus 6-methoxy-1,2,3,4-tetrahydroharman (**9a**) and 7-methoxy-2-propyl-1,2,3,4-tetrahydroharman (**9b**) were readily converted into their 1,2,3,4,5,8-hexahydro derivatives **10a** and **10b**, respectively. In contrast to our experience with the fully aromatic harman derivatives, these tetrahydro derivatives each afforded a single product in good yield.



9a, $R_1 = CH_3O$; $R_2 = H$; $R_3 = H$
b, $R_1 = H$; $R_2 = CH_3O$; $R_3 = C_3H_7$



10a, $R_1 = CH_3O$; $R_2 = H$; $R_3 = H$
b, $R_1 = H$; $R_2 = CH_3O$; $R_3 = C_3H_7$

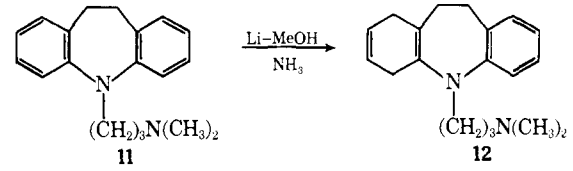
Biological Activity.—Harmine (**3a**) and related compounds are known to be potent reversible inhibitors of monamine oxidase (MAO), both *in vitro* and in intact experimental animals.[11–14] They are also effective in inhibiting tetrabenazine-induced depression in mice. Similar potencies in these 2 assays are shown by the 3,4-dihydro derivative harmaline. 1,2,3,4-Tetrahydroharmans, which are inactive in the tetrabenazine assay, also inhibit MAO, but at much higher concentrations than their less highly saturated analogs.[15]

The relative potencies of the 5,8-dihydro derivatives, their precursors, and certain related compounds are compared in Table I. Because of their solubility most of these compounds were tested as their HCl or acetate salts. The 5,8-dihydro derivatives of fully aromatic harmans appear to be at least as active as the parents, especially in the inhibition of tetrabenazine assay (Table I). The 3,4-dihydro analogs are similarly active. A MeO group at the 7 position of a harman derivative seems to confer greater potency than one at the 6 position in both assays. No simple relationship can be drawn between the relative activities of compounds in the *in vitro* MAO inhibition and tetrabenazine antidepressant assays, except that compounds inhibitory at 10^{-7} *M* in the former assay also have good potency in the latter.

The 9-Me homologs **3b**, **3d**, **4b**, and **4d** of the harmine and 6-methoxyharman derivatives discussed above were all inactive in the tetrabenazine assay. 5,8-Dihydro-6-methoxy-9-methylharman (**4d**) was toxic, showing some lethality even at a dose of 1 mg/kg. However, none of the other compounds described above showed such toxicity (*e.g.*, the LD_{50} for **4a** was 100 mg/kg).

Reversal of the hypothermia induced by reserpine in mice has been suggested as a sensitive assay for potential antidepressant activity, especially for compounds related to imipramine.[15,16] Although harmans are not closely related in structure to imipramine, it was nevertheless interesting to examine the behavior of harmine (**3a**) and its 5,8-dihydro derivative **4a** in this useful assay. Both of these compounds showed a statistically significant reversal of such hypothermia at 10 mg/kg ip, with **3a** appearing to be more efficacious than **4a** (Table II). The related compounds 6-methoxyharman (**3c**) and its 5,8-dihydro derivative **4c** were also tested in this assay, but the results were not statistically significant.

Since two of the nonconjugated dihydroharman derivatives (**4a** and **4c**) showed significant activity in the tetrabenazine assay, we sought to prepare a nonconjugated dihydro derivative of the clinically important antidepressant, imipramine (**11**) (which is the standard



11 **12**

compound for this assay). One purpose of this preparation was to test the generality of the effect of this type of structural change on antitetrabenazine activity.

(11) S. Udenfriend, B. Witkop, B. G. Redfield, and H. Weissback, *Biochem. Pharmacol.*, **1**, 160 (1958).
(12) W. M. McIsaac and V. Estevez, *ibid.*, **15**, 1625 (1966).
(13) A. Pletscher, H. Besendorf, H. P. Bächtold, and K. F. Gey, *Helv. Physiol. Acta*, **17**, 204 (1959).
(14) B. T. Ho, W. M. McIsaac, K. E. Walker, and V. Estevez, *J. Pharm. Sci.*, **57**, 269 (1968).
(15) B. M. Askew, *Life Sci.*, 725 (1963).
(16) See also S. Garattini, A. Giachetti, A. Jori, L. Pieri, and L. Valzelli, *J. Pharm. Pharmacol.*, **14**, 509 (1962).

TABLE II

REVERSAL OF RESERPINE-INDUCED HYPOTHERMIA IN MICE BY HARMINE AND 5,8-DIHYDROHARMINE[a]

Treatment	Mean rectal temp, °F,[b] hr after treatment 0	1	2	3
Harmine·HCl (**3a**) + starch	82.8	93.0	93.7	95.5
Starch only	83.9	86.2	87.1	90.8
5,8-Dihydroharmine·AcOH (**4a**) + starch	80.7	90.2	90.4	90.8
Starch only	80.5	85.4	86.3	88.0

[a] Groups of 10 mice each were given 5 mg/kg ip injections of reserpine. After 18 hr one group was treated with the compd (10 mg/kg) in starch vehicle (ip) while another group received only the starch vehicle. Temps were detd then and each hr thereafter by an electronic rectal thermometer (See S. Garattini, A. Ghetti, A. Jori, L. Pieri, and L. Valzelli, *J. Pharm. Pharmacol.*, **14**, 509 (1962) for details of this procedure). [b] Mean temp for the group of 10 mice (95% confidence limits were calcd and statistical differences were shown by the "*t*" test).

Reduction of **11** with Li and MeOH in NH_3 afforded a mixt from which 6,9-dihydroimipramine (**12**) was isolated by partition chromatography. However, **12** showed no activity in the tetrabenazine assay, in contrast to the high potency of imipramine.

Experimental Section

General.—Melting points were determined on a Mel-Temp melting point apparatus and are corrected. Uv spectra were determined in MeOH on a Cary recording spectrophotometer, and ir spectra in KBr with a Model 21 Perkin-Elmer spectrophotometer. Solutions were dried ($MgSO_4$) and concd under reduced pressure on a rotary evaporator. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

9-Methylharmine (3b).—A soln of 28 mmoles of methylsulfinyl carbanion[17] in 13 ml of DMSO was treated with a soln of 6.36 g (28 mmoles) of **3a** in 13 ml of DMSO. After 1 hr, 4.03 g (28 mmoles) of MeI was added. The resulting soln was stirred overnight under N_2, then carefully dild with H_2O, whereupon the product crystd. Recrystn from Me_2CO–hexane gave 5.35 g (79%) of **3b**, mp 122–125°. Another recrystn gave mp 123–125° (lit.[18] mp 124–125°).

6-Methoxy-9-methylharman (3d).—This compd was prepd as described for **3b**. From 1.91 g of **3c** was obtained 1.57 g (77%) of **3d** as pale yellow prisms, mp 128–130° (lit.[19] mp 130–131°); picrate mp 278° (lit.[19] 277–278°); acetate mp 74–77°.

Typical Li–NH_3 Reduction Procedures. A. Excess MeOH Present.—A soln of 10 mmoles of **3a** or **3b** in 6 ml of MeOH was added to 50 ml of distd liq NH_3. The resulting suspension was treated portionwise with 280 mg (40 mmoles) of Li wire, which reacted immediately. After evapn of the NH_3 and removal of MeOH under reduced pressure, the residue was treated with CH_2Cl_2 and H_2O. The org layer was dried and concd, and the residue was resolved by liquid–liquid partition chromatography on diatomaceous earth. For **3a**, 1.94 g of crude product was dissolved in 45 ml of the lower phase of a heptane–EtOAc–MeOH–H_2O solvent system (70:30:15:6), mixed with 60 g of diatomaceous earth, and packed atop a column prepared from 450 ml of the lower phase and 600 g of diatomaceous earth. The resulting column was eluted with the upper phase, and the effluent was passed through a recording uv spectrophotometer set at 300 mμ. Eluate corresponding to the recorded peaks was then concd, and the residue was weighed and further purified by cryst or picrate formation. Compds are listed in the order in which they came off the chromatography column. From **3a** the following products were obtained: **4a** (2%), **3a** (15%), **7a** (8%). These products are described in Tables III and IV. For **3b** the same chromatography procedure was used, except that the solvent system was heptane–methyl cellosolve. The products were **7b** (11%), **8** (12%), **6** (4%), and **3b** (30%).

TABLE III

PRODUCTS FROM LITHIUM–AMMONIA REDUCTION OF HARMAN DERIVATIVES

Compound	Mp, °C	Formula[c]
4a	225–227[b]	$C_{13}H_{14}N_2O$
4b	153–156[b]	$C_{14}H_{16}N_2O$
4c	205–208[b]	$C_{13}H_{14}N_2O$
4d	170–174[b]	$C_{14}H_{16}N_2O$
5a	184–188[b]	$C_{12}H_{14}N_2$
6·picrate	158–161[c]	$C_{20}H_{21}N_5O_8$
7a[a]	180–182[c]	
7b	145–150[b]	$C_{14}H_{18}N_2O$
8·picrate	188–190[c]	$C_{20}H_{19}N_5O_8$
10a	168–172[b]	$C_{14}H_{18}N_2O$
10b·acetate	112–114[d]	$C_{16}H_{24}N_2O \cdot C_2H_4O_2$[f]

[a] Compd **7a** was previously known. Our sample had an identical ir spectrum and the mp was not depressed upon admixture with an authentic sample prepared from **3a** according to the lit. procedure [M.-M. Janot, J. Keufer, and J. LeMen, *Bull. Soc. Chim. Fr.*, 230 (1952)]. [b] Recrystd from CH_2Cl_2–hexane. [c] Recryst from EtOH. [d] Recryst from EtOAc. [e] All compds except **7a** were analyzed for C, H, N. [f] N, H anal., calcd for C: 67.47; found: 68.00.

B. MeOH or NH_4Cl Added Later.—A soln of 10 mmoles of the harman derivative in 60 ml of distd NH_3 was treated portionwise with 20 mmoles of Li wire. **3a, 3c,** and **4c** were insol in NH_3, but dissolved upon addn of Li (salt formation). They were placed in the reaction flask and covered with a small amount of THF, and then the NH_3 was introduced. The mixt was stirred and treated with MeOH (or NH_4Cl in one example with **3a**) until the color was discharged. After evapn of the NH_3, the residue was worked up as described below.

The mixts obtained from **3a** and **3b** were resolved by partition chromatography as described in part A. From **3a** and MeOH the products were **4a** (7%), **3a** (6%), and **7a** (7%). From **3b** and 2 equiv of Li, with NH_4Cl added immediately, the products were **8** (2%), **6** (5%), **4b** (25%), and **3b** (8%). From **3b**, 2 equiv of Li, and MeOH, added after 1 hr, the products were **8** (1%), **6** (2%), **4b** (22%), and **3b** (41%). Resolution of the crude product from redn of 1.0 g of **3c** by the same method, except that the system was heptane–MeOH, afforded one main peak. Concn of eluate corresponding to this peak gave 123 mg (12%) of **4c**.

The crude product from redn of 4 mmoles of **3d** was resolved in the same manner. Concn of eluate from the first peak gave 231 mg (25%) of **4d**. The second peak gave 575 mg of starting material.

From 4.0 g of **9a** was obtained 2.32 g (57%) of white solid which was nearly pure (no chromatography required). Recrystn from CH_2Cl_2 gave pure **10a**.

The crude **10b** obtained from redn of 1.5 g of **9b** was an amber oil (0.81 g). It gave a cryst acetate upon treatment with HOAc in Et_2O. These products are described in Tables III and IV.

C. MeOH Not Used.—A suspension of 7.5 mmoles of **3a** in 10 ml of THF and 125 ml of distd NH_3 was treated portionwise with 1.05 g (150 mmoles) of Li. After 4 hr the excess Li was discharged by addn of a small amount of $FeCl_3$. MeOH was then added to neutralize amide ion and the mixt was worked up as described in part A. The products were **5a** (4%), **4a** (6%), **3a** (9%), and **7a** (19%).

7-Oxo-5,6,7,8-tetrahydroharman (5b).—A suspension of 420 mg of **4a** in 37 ml of 1% HCl was stirred at room temp for 1 hr. The resulting soln was basified (pH 11.5) with 20% NaOH and extd with CH_2Cl_2. This ext was washed (H_2O), dried, and concd on a steam bath as hexane was added. Cooling of the soln when the first crystals appeared afforded 206 mg (52%) of **5b** as pale yellow needles; mp 216–218°; ir max 5.85 μ (CO) bright blue fluorescence. *Anal.* ($C_{12}H_{12}N_2O$): C, H, N.

6,9-Dihydroimipramine (12).—A soln of 975 mg (3.5 mmoles of **11** in 20 ml of THF and 4.5 ml of MeOH was added to 20 ml of NH_3. The mixt was stirred and treated with 140 mg (20 mmoles) of Li. When the Li dissolved the NH_3 was evapd and the residue

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TABLE IV

SPECTROSCOPIC DATA FOR REDUCTION PRODUCTS OF HARMAN DERIVATIVES

Compd	uv (mμ) in CH_3OH	δ (ppm), J in Hz[a]
4a[c]	224(ε28,400), 269(5500), 298(5800), 330(1300)	7.95(J = 5), 7.20(J = 5) ortho on pyridine ring; 5.00(m) vinyl; 4.14(4,m) aliphatic[b]
4b[c]	231(ε24,600), 265(4100), 302(5500), 335(1100)	8.10(J = 5), 7.17(J = 5) ortho on pyridine ring; 4.95(m) vinyl; 3.16(4,m) aliphatic
4c[c]	224(ε25,400), 272(5800), 296(6200), 330(1100)	8.02(J = 6), 7.20(J = 6) ortho on pyridine ring; 4.91(m) vinyl; 3.41(4,m) aliphatic[b]
4d[c]	230(ε17,800), 268(4000), 304(3300), 335(2200)	7.92(J = 6), 7.10(J = 6) ortho on pyridine ring; 4.97(m) vinyl; 3.20(4,m) aliphatic
5a	226(ε24,600), 272(5200), 300(5600), 331(1700)	7.90(J = 5), 7.11(J = 5) ortho on pyridine ring; 2.85(2,m), 2.01(2,m,) aliphatic[b]
6[c]	212(ε13,000), 265(5900), 310(2640)	7.97(J = 5), 6.93(J = 5) ortho on pyridine ring; 4.62(m) vinyl; 3.25(3), 2.12(3) aliphatic
7b	212(ε28,900), 250(7400), 300(4600)	6.90, 6.28, 6.18 aromatic; 2.78(5,m) aliphatic; 1.37(3,J = 7) $CHCH_3$
8[c]	210(ε14,800), 257(6300), 302(3000)	8.08(J = 5), 6.97(J = 5) ortho on pyridine ring; 4.72(m) vinyl; 2.43(4,m) aliphatic
10a[c]	Tailing 200–250	5.06(m) vinyl; no aromatic
10b[c]	Tailing 200–250	5.08(m) vinyl; no aromatic

[a] Me groups, NH's, and picrate absorption omitted. Spectrum in $CDCl_3$ unless otherwise noted. [b] Determined in DMSO-d_6 [c] The ir spectrum showed a sharp peak at 6.0 μ (KBr) due to the vinyl ether group.

was taken up in water and CH_2Cl_2. The org layer was resolved by liquid–liquid partition chromatography on diatomaceous earth with a heptane–methyl cellosolve solvent system. A ratio of 1:5 lower phase:diatomaceous earth was used and the recording spectrophotometer was set at 250 mμ. Concn of eluate from the second major peak (0.5 hold-back volume) afforded **12** as a colorless oil, which was unstable to air and heat, but could be stored for at least a month under N_2 at 5°. It had uv max 250 mμ (ε 5650), 290 (2820) sh, 340 (705); nmr δ 7.10 (m, 4, arom), 5.84 (broadened apparent s, 2, vinyl) ppm. Isomeric nonconjugated diene structures are ruled out for **12** because they would require 3 vinyl protons. *Anal.* ($C_{19}H_{26}N_2$): C, H, N.

Acknowledgment.—We wish to thank Mr. L. Brancone and staff for microanalyses, Mr. W. Fulmor and staff for spectra, and Mr. C. Pidacks and staff for partition chromatographic separations. We also thank Mr. R. Vessey and Mr. E. Markely for conducting the biological assays.

Synthesis of Some s-Triazoles with Potential Analgetic and Antiinflammatory Activities[1]

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Received August 19, 1970

A series of 5-alkyl-4-amino-s-triazole-3-thiols have been prepared. 4-Amino-5-ethyl-s-triazole-3-thiol showed moderate analgetic and antiinflammatory activities and a few derivatives showed weak analgetic and/or antiinflammatory activities, but of a lower order than the parent compound.

The chemistry of s-triazoles has been described by Kröger, *et al.*[2] In recent years there has been a growing interest in the pharmacology of s-triazole derivatives. Yale and Piala[3] have reported that 5-(*p*-aminophenyl)-s-triazole-3-thiol shows diuretic and natriuretic activity in rats when administered intraperitoneally. In connection with synthesis of condensed s-triazole heterocycles described elsewhere[4] we prepared a series of 5-alkyl(aryl)-4-amino-s-triazole-3-thiols. The zwitterionic character of this series of compounds prompted us to study their pharmacological properties.

Chemistry.—4-Amino-5-alkyl(aryl)-s-triazole-3-thiols were prepared according to published procedures.[2a,5] Most of the N- and S-substituted derivatives were synthesized starting from the Et analog **2**. Arylidene and alkylidene derivatives were obtained by condensing **2** with carbonyl compounds according to conventional methods.[2a,6] Compound **24** obtained by condensation of **2** with 2-methyl-2-thiocyanato-4-pentanone[7] according to the procedure of Mathes[8] gave on alkylation the monoalkyl derivative **37** showing that the mercapto group of the pyrimidine nucleus was unaffected.

S-Alkylations of **2** were carried out by treating with a wide variety of alkylating agents in the presence of calcd amounts of methanolic alkali or NaOEt. A Mannich reaction was carried out on the *N*-formyl derivative of **2** using piperidine to furnish the *S*-piperidinomethyl derivative **28**. Reaction with aromatic acid chlorides at low temperatures and an optimum pH value (6.5) gave *S*-aroyl derivatives. Performing the acylations at higher temperatures and lower pH gave exclusively the

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