

Figure 1. The epr spectrum of urazolyl 1 (ca.  $5 \times 10^{-4}$  M) in benzene at ambient temperature.

characterized only by epr spectroscopy and the nature of the decomposition products formed.<sup>10</sup>

In benzene, oxidation of colorless urazole 5, obtained via a modified Ruhkopf procedure,<sup>11-15</sup> (Scheme I) with lead dioxide in the presence of anhydrous sodium sulfate affords, after filtration, a deep orange-brown solution. Chromatography (silica gel, chloroform) of the concentrated solution gives rise to a mobile orange-brown band, collection and evaporation of which affords an air-stable tan solid (mp 108–109°, 66%) identified as the tetrazane dimer of urazolyl 1. Although the solid gives rise to an epr signal, magnetic susceptibility studies indicate it to be essentially diamagnetic. The infrared spectra of both urazolyl 1 (CS<sub>2</sub>) and its tetrazane dimer (KBr) lack the N–H absorption (3.08  $\mu$ ) of urazole precursor 5 (KBr). Urazolyl 1 exhibits carbonyl absorptions at 5.74 and 5.86  $\mu$  rather than at 5.64 and 5.86  $\mu$  (CHCl<sub>3</sub>) as does 5; the solid dimer has carbonyl absorptions at 5.54 and 5.78  $\mu$  as compared to 5.68 and 5.94  $\mu$  (KBr) for 5. The solid dissolves readily in benzene, carbon tetrachloride, or acetonitrile with concomitant dissociation into urazolyl 1. The resultant orange-brown solutions fail to obey Beer's law at higher concentrations. In dilute acetonitrile solution, three ultraviolet absorption bands (206 ( $\epsilon$  11,300), 264 ( $\epsilon$  2410), and 302 nm ( $\epsilon$  2920)) are observed with the latter tailing to ca. 600 nm in the visible region. Owing to paramagnetism, solutions of urazolyl 1 do not afford high resolution nmr spectra but do give rise to very strong epr signals. In carefully degassed benzene solutions, the epr spectrum of 1 (Figure 1) consists of 46 lines from which the hyperfine splitting (hfs) constants have been determined. The hfs constants [ $a_{N-1(2)}$  (1 N) = 7.70,  $a_{N-2(1)}$  (1 N) = 6.25,

(10) For example, one of the more stable hydrazyls of this type, 3-*tert*-butyl-2,3-diazabicyclo[2.2.2]octyl,<sup>6</sup> has been characterized by its epr spectrum which can still be observed after the sample (sealed, degassed, in acetonitrile) has stood 3 months at room temperature. However, this hydrazyl reacts readily with oxygen upon exposure to air.

(11) H. Ruhkopf, *Chem. Ber.*, **73**, 820 (1940).

(12) Addition of an ethereal solution of ethyl chloroformate to a mechanically stirred solution of  $\alpha$ -cumylhydrazine<sup>13</sup> (2) and triethylamine in ether with cooling affords, after vacuum distillation, ethyl 3- $\alpha$ -cumylcarbazate<sup>14</sup> (3, bp 120° (0.05 Torr), 90%). Treatment of carbazate 3 with an excess of methyl isocyanate in refluxing benzene affords 1-carbethoxy-2- $\alpha$ -cumyl-4-methylsemicarbazide<sup>14</sup> (4, mp 144–145.5° (C<sub>6</sub>H<sub>6</sub>), 82%). Heating semicarbazide 4 in 25% aqueous potassium hydroxide produces 1- $\alpha$ -cumyl-4-methylurazole<sup>14</sup> (5, mp 129–131° [EtOH, lit.<sup>15</sup> mp 126.5–127° (sublimation)], 89%).

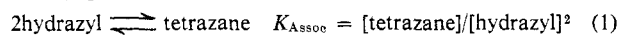
(13) C. G. Overberger and A. V. DiGiulio, *J. Amer. Chem. Soc.*, **80**, 6562 (1958).

(14) Satisfactory ir, nmr, and mass spectra and elemental analyses were obtained for this compound.

(15) J. C. Stickler, Ph.D. Thesis, University of Illinois, Urbana, Ill., 1971, p 76.

$a_{N-4}$  (1 N) = 1.47, and  $a_H$  (3 H) = 0.56 G] do not vary appreciably with temperature (–80° to +20°, CS<sub>2</sub>). That the radical giving rise to the epr spectrum is in fact a true hydrazyl is indicated by the magnitude of the hfs constants for the hydrazyl nitrogens. Ingold has stated<sup>16</sup> that, in all authentic hydrazyls, “the splitting constants of the two nitrogens are of comparable magnitude and are generally in the range of 6–12 G.” The elemental composition and molecular weight [Calcd for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>: C, 62.06; H, 6.08; N, 18.09; mol wt, 232.1086. Found: C, 62.04; H, 5.98; N, 18.01; mol wt, 232.1080 (mass spec)] are in agreement with the structural assignment and with the observation that the dimer dissociates readily. Finally, reduction of 1 [CH<sub>2</sub>Cl<sub>2</sub>, H<sub>2</sub>O, Na<sub>2</sub>SO<sub>3</sub>, (*n*-Bu)<sub>4</sub>N<sup>+</sup>Br<sup>–</sup>] affords, after sublimation, a white solid (mp 128–129.5°) identical in all respects with authentic urazole 5.

From its failure to obey Beer's law, it is inferred that, in solution, urazolyl 1 is in equilibrium with its tetrazane dimer (eq 1). Association constants for this equilib-



rium have been determined by vapor pressure osmometry at 25.0  $\pm$  0.2° and are 0.58  $\pm$  0.30, 4.5  $\pm$  0.4, and 12  $\pm$  2 for acetonitrile, benzene, and carbon tetrachloride solutions, respectively. Urazolyl 1 appears to be indefinitely stable either as the solid dimer or when dissolved in inert solvents. It is, however, capable of reacting with compounds having more readily abstractable hydrogens, and hydrazyl reagents of this type may conceivably be of some future synthetic utility.

Analogues of 1 have been prepared, and the chemistry of this type of non-arylhydrazyl is currently being pursued.

**Acknowledgments.** This work has been supported in part by funds from the Alfred P. Sloan Research Foundation.

(16) V. Malatesta and K. U. Ingold, *Tetrahedron Lett.*, 3307 (1973).

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## A New, General Synthesis of Tropane Alkaloids<sup>1</sup>

Sir:

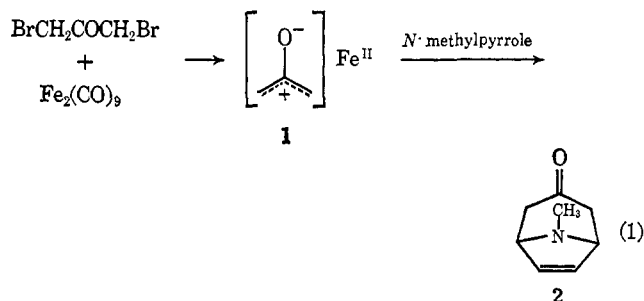
Since the first discovery of the iron carbonyl promoted cyclocoupling reaction between  $\alpha,\alpha'$ -dibromo ketones and 1,3-dienes leading to 4-cycloheptenones,<sup>2</sup> we have been interested in its possible application to the direct synthesis of the tropane alkaloid family.<sup>3</sup> Our original plan outlined in eq 1 suffered from two serious limitations: (1) dibromoacetone, unlike other ordinary dibromo ketones, cannot serve as a precursor of the oxyallyl intermediate 1,<sup>4</sup> and (2) reaction of *N*-methyl-

(1) Carbon–Carbon Bond Formations Promoted by Transition Metal Carbonyls. X. Part IX: R. Noyori, S. Makino, Y. Baba, and Y. Hayakawa, *Tetrahedron Lett.*, 1049 (1974).

(2) R. Noyori, S. Makino, and H. Takaya, *J. Amer. Chem. Soc.*, **93**, 1272 (1971).

(3) Recent reviews: (a) G. Fodor, *Progr. Phytochem.*, **1**, 491 (1968); (b) G. Fodor in “Chemistry of the Alkaloids,” S. W. Pelletier, Ed., Van Nostrand Reinhold, New York, N. Y., 1970, p 431; (c) G. Fodor in “The Alkaloids, Chemistry and Physiology,” Vol. 13, R. H. Manske, Ed., Academic Press, New York, N. Y., 1971, p 351.

(4) R. Noyori, Y. Hayakawa, M. Funakura, H. Takaya, S. Murai, R. Kobayashi, and S. Tsutsumi, *J. Amer. Chem. Soc.*, **94**, 7202 (1972).



pyrrole and oxyallyl species leads to electrophilic substitution products rather than the desired  $[\pi 4 + \pi 2]$  cycloadducts of type **2**.<sup>5,6</sup> Fortunately, however, adopting the following modifications, we have developed an effective synthetic entry which is fundamentally based on the initial attempt; the first problem was solved by utilizing  $\alpha, \alpha', \alpha', \alpha'$ -tetrabromoacetone as a starting three-carbon unit,<sup>7</sup> and the second obstacle was removed by the use of *N*-carbomethoxypyrrole in place of *N*-methylpyrrole.

When a mixture of tetrabromoacetone, *N*-carbomethoxypyrrole, and  $\text{Fe}_2(\text{CO})_9$  (3:1:1.5 mol ratio) in benzene was heated at 50° for 72 hr under nitrogen atmosphere and followed by the usual work-up, a 2:1 mixture of the desired adducts **3** and **4** was obtained in 52% yield (based on the starting pyrrole).<sup>8,9</sup> The diastereomers were readily separated by silica gel chromatography using 3:1 *n*-hexane-ethyl acetate as eluent. Stereochemistry of these isomers was verified by nmr analysis. The spectrum of the *cis* isomer **3** [mp 155–157°; ir 1748 (C=O) and 1710  $\text{cm}^{-1}$  (NCOOCH<sub>3</sub>)] exhibited a two-proton doublet at  $\delta$  4.80 ( $J = 4.0$  Hz) due to the  $>\text{CHBr}$  protons, whereas the corresponding signals of the *trans* isomer **4** [mp 112–114°; ir 1740 and 1710  $\text{cm}^{-1}$ ] occurred as *two* one-proton doublets at  $\delta$  4.27 ( $J = 2.0$  Hz) and 5.11 ( $J = 3.5$  Hz).

The adducts **3** and **4** absorbed 1 mol of hydrogen over 10% Pd-C in ethyl acetate (atmospheric pressure, 25°) to give the corresponding saturated products. With ethanol as solvent, further reduction took place to yield the debromination product **5** quantitatively, mp 60–61°, identical with a sample independently prepared from tropinone (**6**) and methyl chloroformate.<sup>10</sup> Exposure of **5** to 10 equiv of diisobutylaluminum hydride (DIBAH) in tetrahydrofuran at –78° for 10 hr and then at 25° for 10 hr gave a 90:10 mixture of tropine (**7**) and  $\psi$ -tropine (**8**) in 96% yield. Both of them were identical with the authentic specimen in all respects.

Even more important is the conversion of **3** or **4** to the unsaturated debromination product **9**. Treatment of **3** or **4** with Zn-Cu couple in methanol containing 5% ammonium chloride at 25° for 10 min afforded **9**, mp 69–70°, in quantitative yield.<sup>11</sup> In actual practice,

(5) R. Noyori, Y. Baba, S. Makino, and H. Takaya, *Tetrahedron Lett.*, 1741 (1973).

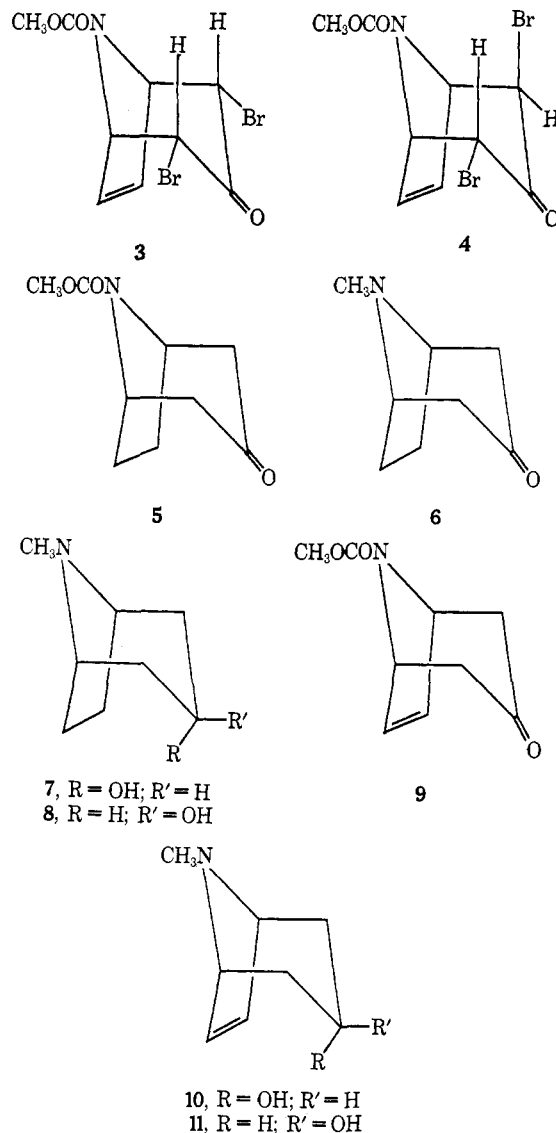
(6) Pyrrole and its *N*-alkylated derivatives are known to undergo Diels-Alder reaction only with difficulty. For example (a) O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **486**, 211 (1931); (b) *ibid.*, **490**, 267 (1931).

(7) Tetrabromoacetone can serve as a synthetic equivalent of *unsubstituted* oxyallyl. Trapping of the reactive three-carbon species by furan and cyclopentadiene as well as the synthetic application will be published elsewhere.

(8) Satisfactory analytical and spectral data were obtained for all new compounds. All ir and nmr spectra were taken in  $\text{CHCl}_3$  and  $\text{CCl}_4$ , respectively.

(9) Zn-Cu couple suspended in dimethoxyethane was also effective as the reducing agent but gave the adducts in lower yield.

(10) G. Kraiss and K. Nádor, *Tetrahedron Lett.*, 57 (1971).



a crude mixture of **3** and **4** without purification could be converted to **9**; yield of the two-step synthesis was *ca.* 60% based on *N*-carbomethoxypyrrole. Reduction of **9** with 10 equiv of DIBAH (tetrahydrofuran, 23 hr at –78° and then 8 hr at 25°) followed by chromatographic separation of the products (alumina, ethyl acetate) gave rise to the alcohols **10** and **11** in pure state (93:7 ratio, 92% yield).<sup>12</sup> Catalytic hydrogenation of **10** and **11** (10% Pd-C, ethanol, 1 atm, 25°) gave **7** and **8**, respectively.

Noteworthy is the stereoselectivity of the reduction of **5** and **9** with DIBAH producing the epimeric alcohols with the desired  $\alpha$  alcohols predominating. Reduction

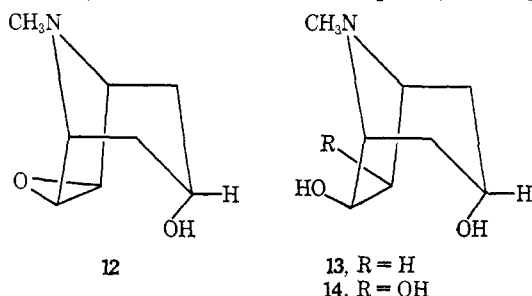
(11) Spectral characteristics were: ir 1710–1700  $\text{cm}^{-1}$  (C=O and NCOOCH<sub>3</sub>); nmr  $\delta$  2.40 (dd,  $J = 16.5$  and 1.5 Hz, 2 H, equatorial protons at C-2 and C-4), 2.80 (dd,  $J = 16.5$  and 4.5 Hz, 2 H, axial protons at C-2 and C-4), 3.84 (s, 3 H, COOCH<sub>3</sub>), 4.8–5.1 (m, 2 H, NCH), and 6.27 (t,  $J = 1.0$  Hz, 2 H, =CH).

(12) Major isomer **10**: mp  $\sim 36^\circ$ ; picrate mp 273° (lit.<sup>13</sup> 278°); ir 3600 (OH) and 3060  $\text{cm}^{-1}$  (=C–H); nmr  $\delta$  1.69 (br d,  $J = 14$  Hz, 2 H, equatorial protons at C-2 and C-4), 1.8–2.5 (m, 3 H, OH and axial protons at C-2 and C-4), 2.18 (s, 3 H, NCH<sub>3</sub>), 3.33 (m, 2 H, NCH), 3.71 (t,  $J = 6.3$  Hz, 1 H, CHOH), and 6.17 (narrow m, 2 H, =CH). Minor isomer **11**: ir 3600 (OH) and 3060  $\text{cm}^{-1}$  (=C–H); nmr  $\delta$  1.47 (ddd,  $J = 12, 9.5$ , and 3.0 Hz, 2 H, equatorial protons at C-2 and C-4), 1.84 (ddd,  $J = 12, 6.5$ , and 2.5 Hz, 2 H, axial protons at C-2 and C-4), 2.14 (s, 3 H, NCH<sub>3</sub>), 2.30 (br s, 1 H, OH), 3.40 (m, 2 H, NCH), 3.56 (dd,  $J = 9.5$  and 6.5 Hz, 1 H, CHOH), and 5.82 (s, 2 H, =CH).

(13) P. Dobó, G. Fodor, G. Jancsó, I. Koczor, J. Tóth, and I. Vincze, *J. Chem. Soc.*, 3461 (1959).

of tropinone (6) with either ordinary hydride reagents ( $\text{LiAlH}_4$ ,  $\text{NaBH}_4$ , etc.) or dissolving metals is known to give the  $\beta$  epimer **8** preferentially.<sup>14</sup> Equilibrium conditions also lead to the thermodynamically more stable isomer **8**.<sup>14</sup> Only the catalytic reduction has been employed for the selective production of the  $\alpha$  epimer **7**.<sup>15, 16</sup>

Synthetic methods for converting the key intermediate **10** to a variety of naturally occurring alkaloids have already been established.<sup>3</sup> Scopine (**12**), tropane-



diol (**13**), and telodine (**14**) which bear an oxygen function(s) at the C-6 (and C-7) position have become readily accessible. Thus the present method marks the realization of a novel, general synthesis of tropane family. Attractive features of the route outlined herein include (1) the directness, (2) the ready, economical availability of the starting materials, (3) the efficiency of the general synthesis of various alkaloids *via* a single, common intermediate,<sup>17</sup> and (4) the flexibility which allows the preparation of a number of artificial analogs not occurring in plant tissues.<sup>18</sup> Further refinements of the procedure are in progress.

**Acknowledgment.** Partial financial support from the Takeda Science Foundation is acknowledged.

(14) (a) R. Mirza, *Nature (London)*, **170**, 630 (1952); (b) A. H. Beckett, N. J. Harper, A. D. J. Balon, and T. H. E. Watts, *Tetrahedron*, **6**, 319 (1959).

(15) L. C. Keagle and W. H. Hartung, *J. Amer. Chem. Soc.*, **68**, 1608 (1946).

(16) Reduction of **6** with DIBAH under the comparable conditions gave a 97:3 mixture of **7** and **8**.

(17) The well-known Robinson procedure failed to prepare **2**: J. Kebrle and P. Karrer, *Helv. Chim. Acta*, **37**, 484 (1954); A. Stoll and E. Jucker, *Chimia*, **9**, 25 (1955). Direct synthesis of scopinone by this method was also unsuccessful.

(18) For instance, tropanes having alkyl groups at C-2 and C-4 positions are easily obtainable by the use of dibromo ketones having long alkyls.<sup>1</sup>

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## A Novel Isoquinoline Alkaloid Group. The Aporphine-Pavine Dimers<sup>1</sup>

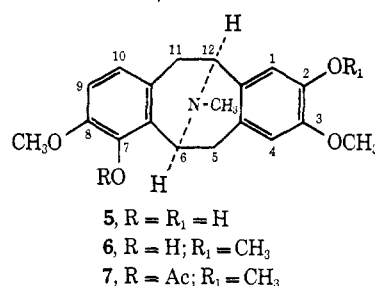
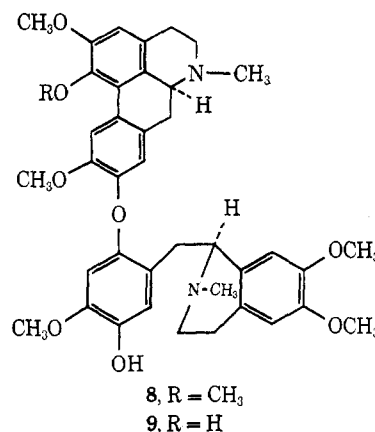
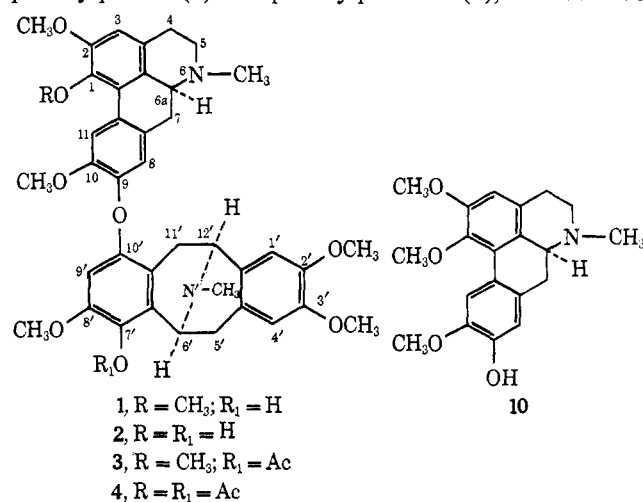
Sir:

Within the complex skein of isoquinoline alkaloids, the aporphine-benzylisoquinoline dimers have so far been considered representatives of a terminal stage of development in the biogenetic tree.<sup>2</sup> We now wish to

(1) This research was supported by Grant CA-11450 from the National Institutes of Health. The authors are grateful to Professors J. Slavik and F. R. Stermitz for alkaloidal samples. All compounds were analyzed by high and low resolution mass spectroscopy. Nmr spectra were obtained in  $\text{CDCl}_3$ , CD curves in MeOH.

(2) For a discussion of the chemistry of isoquinoline alkaloids see M. Shamma, "The Isoquinoline Alkaloids," Academic Press, New York, N. Y., 1972.

report the isolation and structural elucidation of pennsylvavine (**1**) and pennsylvavoline (**2**), the first two



examples of a new group of dimeric alkaloids, the aporphine-pavines, probably derived from aporphine-benzylisoquinolines and thus extending the biogenetic locus.

The giant meadow rue, *Thalictrum polygamum* Muhl. (Ranunculaceae), endemic throughout Pennsylvania, yielded the weakly basic and monophenolic pennsylvavine (**1**), mp 122–123° (ether),  $[\alpha]^{25}_D -174^\circ$  (c 0.6, MeOH). The uv spectrum,  $\lambda_{\text{max}}^{\text{EtOH}}$  230, 280 sh, 288, 308 sh, and 320 sh nm (log  $\epsilon$  4.62, 4.38, 4.40, 4.23, and 4.15), was essentially that of a 1,2,9,10-tetrasubstituted aporphine (280, 308, and 320 nm) superimposed on that of a pavine or isopavine (288 nm).<sup>3</sup>

The mass spectrum of **1** (Scheme I) revealed a parent peak,  $M^+$  (R = CH<sub>3</sub>, R<sub>1</sub> = H,  $m/e$  680, 36%,  $\text{C}_{40}\text{H}_{44}\text{N}_2\text{O}_8$ ),<sup>4</sup> and a base peak E ( $m/e$  204, 100%,  $\text{C}_{12}\text{H}_{14}\text{NO}_2$ ).

(3) Among monomeric isoquinoline alkaloids, only pavines and isopavines show strong and selective absorption near 288 nm, see ref 2, p 112.

(4) The parent peak,  $M^+$ , for a monophenolic aporphine-benzylisoquinoline dimer of the thalicarpine series is  $m/e$  682; cf. M. Shamma, S. S. Salgar, and J. L. Moniot, *Tetrahedron Lett.*, 1859 (1973).