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Studies on the Synthesis of Heterocyclic and Natural Compounds. CMXLV.[1] A Stereoselective Synthesis of Non-Tryptamine Components of Reserpine and Yohimbine from Furfural

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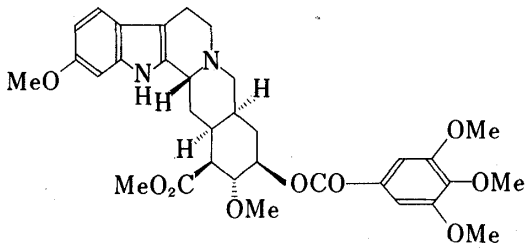
A general method for the stereoselective synthesis of the non-tryptamine components of reserpine and yohimbine *via* the same compound (**6**) is described. This common intermediate was readily obtained by Diels-Alder reaction of the furfural derivative (**10**) with maleic anhydride.

Keywords——synthetic approach to reserpine and yohimbine; non-tryptamine components; Diels-Alder reaction of furfural; halolactonization; reserpine; yohimbine

In the field of the indole alkaloids, reserpine (**1**) and yohimbine (**2**), which involve the basic pentacyclic skeleton, are most familiar because of their remarkable physiological properties.

We have recently reported[2] a stereoselective synthesis of the intermediates (**3**) and (**4**) in the synthesis of *Rauwolfia* alkaloids and cyclization of (**3**) followed by sodium borohydride reduction to form the unexpected lactam (**5**).



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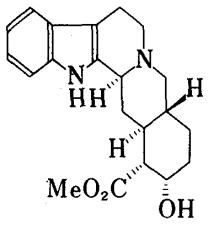

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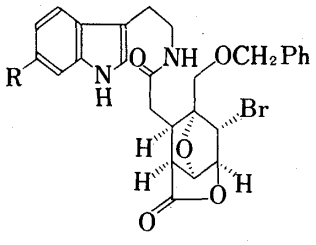

3 : R=H
4 : R=OMe

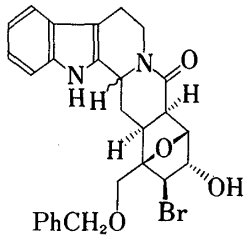

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Chart 1

As a part of our work towards the total synthesis of reserpine (**1**)[3] and yohimbine (**2**),[4] we required a preparative route to the bromolactonic homoester (**7**) and the nitrile (**9**) which were considered to be potential intermediates in the synthesis of *Rauwolfia* alkaloids and yohimbine. It was envisaged that both of these compounds could be derived from the same compound.

Our strategy for the preparation of the homoester (**7**) was basically the same as the procedure previously reported by us,[2] whereas that for the nitrile (**9**) involved sodium borohydride reduction of the Diels-Alder adduct (**6**) followed by catalytic hydrogenation, treatment of the resultant γ-butyrolactone (**8**) with potassium cyanide and finally epimerization.

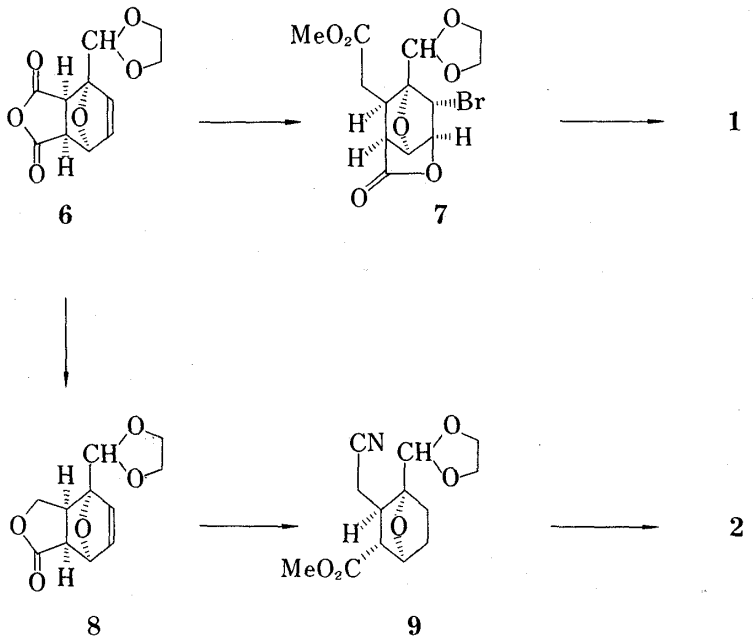


Chart 2

Diels-Alder reaction of maleic anhydride with the protected furfural (**10**) in dry benzene in the presence of a catalytic amount of hydroquinone at room temperature for 17 h gave the desired *endo* adduct (**6**) in 47.9% yield.

Although a problem in the next process is the direction of halolactonization of the dicarboxylic acid derived from the Diels-Alder adduct (**6**), this reaction might proceed in the desired manner because of the steric hindrance of the acetal function at the C_3 position of the adduct (**6**).

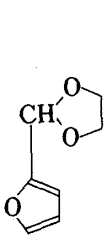
Hydrolysis of the adduct (**6**) with water followed by halolactonization[2] afforded a mixture of the bromolactonic acid (**11**) and its isomer (**15**) in almost quantitative yield. Attempts to separate this mixture at this stage resulted in failure. Thus, this mixture was used in the following reaction without further purification, and was converted, by treatment with excess diazomethane, to a readily separable mixture of the corresponding methyl esters (**12**), mp 149—150°C, and the isomer (**16**), mp 187—189°C, in a ratio of approximately 5.5: 1, as expected.

Transformation of this acid (**11**) to the homomethyl ester (**7**) by means of the Arndt-Eistert reaction[5] was carried out in a usual manner. Treatment of the mixture of the bromolactonic acids (**11** and **15**) with oxalyl chloride in refluxing dry benzene gave the acid chloride (**13**) and its position isomer, which on reaction with diazomethane afforded the diazoketone (**14**) and an isomer. Refluxing the mixture of diazoketones in absolute methanol and dioxane in the presence of freshly prepared silver oxide provided the desired homomethyl ester (**7**), mp 130—132°C, in 52.7% yield after separation and purification by silica gel chromatography.

On the other hand, sodium borohydride reduction[6] of the Diels-Alder adduct (**6**) in dry dimethylformamide followed by acid treatment at room temperature afforded a separable mixture of the desired γ-butyrolactone (**8**), mp 114—116°C, in 35.1% yield and its isomer (**17**), mp 115—116°C, in 35% yield. Attempts to introduce the cyano group at this stage, by treatment of γ-butyrolactone (**8**) with potassium cyanide or sodium cyanide under various

conditions, resulted in the formation of butenolide and the starting furfural derivative (**10**) due to a facile retro Diels-Alder reaction. In order to circumvent this, the double bond was reduced. Catalytic hydrogenation of (**8**) on 5% palladium-carbon in methanol afforded the dihydro-γ-butyrolactone (**18**), mp 83—85°C, in 89.2% yield. Now, introduction of the cyano group proceeded smoothly to give a diastereoisomeric mixture of carboxylic acids (**19**), whose treatment with an excess of diazomethane provided a separable mixture of the corresponding β-methyl ester (**20**), mp 96—98°C, and the desired α-methyl ester (**9**), mp 130—132°C, in 69% overall yield from the dihydro-γ-butyrolactone (**18**), the ratio of the two compounds being approximately 1 : 1. Epimerization of the β-isomer (**20**) to the α-isomer (**9**) using methanolic potassium carbonate solution at room temperature proceeded smoothly in almost quantitative yield.

Thus, we have achieved a stereoselective synthesis of non-tryptamine components (**7**) and (**9**) of reserpine and yohimbine.



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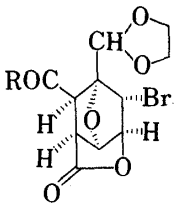
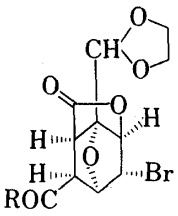
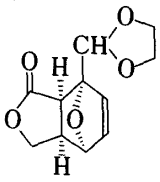


11 : R=OH
12 : R=OMe
13 : R=Cl
14 : R=CHN_2



15 : R=OH
16 : R=OMe



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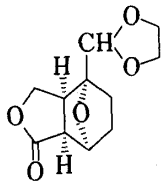

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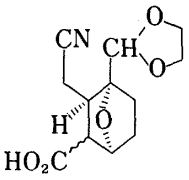

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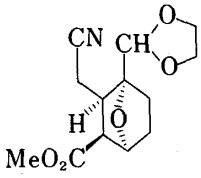

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Chart 3

Experimental[7]

Diels-Alder Reaction of Furfural Ethylene Acetal (10) with Maleic Anhydride——A mixture of maleic anhydride (8 g), furfural ethylene acetal (**10**) (10.8 g) and hydroquinone (100 mg) in dry benzene (30 ml) was stirred for 17 h at room temperature. The precipitate was filtered off and washed with ether to give a solid whose recrystallization from chloroform–benzene afforded the desired *endo* adduct (**6**) (9.3 g, 47.9%), mp 118—120°C. *Anal.* Calcd for $C_{11}H_{10}O_6$: C, 55.64; H, 4.23. Found: C, 55.38; H, 4.27. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1865, 1780 cm^{-1}. NMR ($CDCl_3$) δ: 3.87 (2H, d, J=3 Hz, C_1-H, C_2-H), 3.93—4.13 (4H, m, OCH_2CH_2O), 5.37 (1H, br s, C_6-H), 5.47 (1H, s, $CH\langle^{O}_{O}$), 6.57 (2H, s, olefinic H). MS *m/e*: 140 (M^+-98).

(1*S,2*R**,3*R**,4*S**,5*S**,8*R**)-4-Bromo-3,8-epoxy-3-ethylenedioxymethyl-6-oxa-7-oxobicyclo[3.2.1]octane-2-carboxylic Acid (11) and Its Methyl Ester (12)**——A suspension of the *endo* adduct (**6**) (5 g) in water (150 ml) was stirred for 2 h at room temperature. $NaHCO_3$ (3.3 g) was added in small portions to the above ice-cold solution and Br_2 (9.4 g) was then added. The resulting mixture was stirred for 3 h at room temperature and acidified with 20% H_2SO_4. Afterwards, a small amount of $NaHSO_3$ was added in order to remove excess Br_2. The mixture was extracted with ethyl acetate. The extract was washed with brine and dried over $MgSO_4$. Evaporation of the solvent left a mixture (5.7 g) of bromolactonic acid (**11**) and its position isomer (**15**) as a colorless syrup. Without further purification, the above mixture was treated with an excess of diazomethane in ether. After the usual work-up, the resultant solid was subjected to chromatography on

silica gel. The first elution with chloroform afforded the desired methyl ester (**12**) (322 mg), mp 149—150°C (from chloroform–methanol). *Anal.* Calcd for $C_{12}H_{13}BrO_7$: C, 41.28; H, 3.75. Found: C, 41.17; H, 3.61. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1790, 1735. NMR ($CDCl_3$) δ: 2.97 (1H, d, J=11 Hz, C_2–H), 3.43 (1H, dd, J=4.6 and 11 Hz, C_1–H), 3.72 (3H, s, OCH_3), 4.0 (4H, s, OCH_2CH_2O), 4.65 (1H, s, C_4–H), 4.80 (1H, dd, J=1.4 and 4.6 Hz, C_8–H), 4.92 (1H, d, J=1.4 Hz, C_5–H), 5.32 (1H, s, $CH\langle^{O}_{O}\rangle$). MS m/e: 350, 348 (M^+). The second elution with chloroform gave its isomer (**16**) (59 mg), mp 187—189°C (from chloroform–methanol). *Anal.* Calcd for $C_{12}H_{13}BrO_7$: C, 41.28; H, 3.75. Found: C, 41.28; H, 3.59. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1800, 1740. NMR ($CDCl_3$) δ: 3.09 (1H, dd, J=4 and 13 Hz, C_2–H), 3.21 (1H, d, J=13 Hz, C_1–H), 3.69 (3H, s, OCH_3), 3.82—4.03 (4H, m, OCH_2CH_2O), 4.24 (1H, d, J=1.5 Hz, C_4–H), 4.74 (1H, br s, C_5–H), 5.71 (1H, s, $CH\langle^{O}_{O}\rangle$). MS m/e: 350, 348 (M^+).

(1*S,2*R**,3*R**,4*S**,5*S**,8*R**)-4-Bromo-2-diazoacetyl-3,8-epoxy-3-ethylenedioxymethyl-6-oxa-7-oxobicyclo[3.2.1]octane (14)**——Oxalyl chloride (9 ml) was added dropwise to an ice-cold suspension of a mixture (1 g) of the bromolactonic acid (**11**) and its isomer in dry benzene (20 ml) and the mixture was refluxed for 4 h under nitrogen. The solvent and the excess oxalyl chloride were evaporated off *in vacuo* to leave a mixture of the acid chloride (**13**) and its isomer, which on treatment with an excess of diazomethane gave a mixture (1 g) of the diazoketone (**14**) and its isomer, which was used without separation in the following reaction. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2130, 1795, 1735, 1635.

(1*S,2*R**,3*R**,4*S**,5*S**,8*R**)-4-Bromo-3,8-epoxy-3-ethylenedioxymethyl-2-methoxycarbonylmethyl-6-oxa-7-oxobicyclo[3.2.1]octane (7)**——A mixture (100 mg) of diazoketone (**14**) and its isomer and freshly prepared silver oxide (20 mg) in absolute methanol (0.3 ml) and dry dioxane (3 ml) was refluxed for 2 h under nitrogen and then more silver oxide (10 mg) was added. After refluxing for an additional 2 h, the mixture was filtered through a short celite pad and washed with ether. The filtrate was concentrated to leave brown syrup which was subjected to chromatography on silica gel (20 g). Elution with chloroform afforded the desired homomethyl ester (**7**) (44.9 mg), mp 130—132°C (from methanol–chloroform). *Anal.* Calcd for $C_{13}H_{15}BrO_7$: C, 42.85; H, 4.17. Found: C, 42.67; H, 4.19. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1795, 1738. NMR ($CDCl_3$) δ: 2.42—2.63, 2.82—2.99 (each 2H, m, CH_2CO, C_1–H, C_2–H), 3.70 (3H, s, OCH_3), 4.01 (4H, s, OCH_2CH_2O), 4.10 (1H, s, C_4–H), 4.64—4.85 (1H, m, C_8–H), 4.87 (1H, d, J=1 Hz, C_5–H), 5.40 (1H, s, $CH\langle^{O}_{O}\rangle$). MS m/e: 364, 462 (M^+).

(1*S,2*R**,5*S**,6*S**)-2,5-Epoxy-2-ethylenedioxymethyl-8-oxa-7-oxobicyclo[4.3.0]non-3-ene (8)**——A solution of the *endo* adduct (**6**) (1.7 g) in dry dimethylformamide (9 ml) was added dropwise over 1 h to an ice-cold stirred solution of $NaBH_4$ (216 mg) in dry dimethylformamide (3 ml). The temperature for the reaction mixture was kept below 20°C. After 1 h, the mixture was acidified by addition of 2 N H_2SO_4, stirred for 16 h at room temperature, and then extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$ and then evaporated to leave a residue which was subjected to chromatography on silica gel (30 g). Elution with ethyl acetate–*n*-hexane (4: 6 v/v) afforded the desired γ-butyrolactone (**8**) (562 mg), mp 114—116°C (from methanol). *Anal.* Calcd for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found: C, 58.91; H, 5.52. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760. NMR ($CDCl_3$) δ: 3.01—4.13 (4H, m, C_1–H, C_2–H, CH_2OCO), 4.0 (4H, s, OCH_2CH_2O), 5.15 (1H, s, $CH\langle^{O}_{O}\rangle$), 5.26 (1H, d, J=1 Hz, C_6–H), 6.54 (2H, d, J=1 Hz, olefinic H). MS m/e: 140 (M^+-84), and its isomer (**17**) (560 mg), mp 115—116°C (from methanol). *Anal.* Calcd for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found: C, 58.86; H, 5.40. NMR ($CDCl_3$) δ: 3.20—4.18 (4H, m, C_2–H, CH_2OCO), 3.93—4.13 (4H, m, OCH_2-CH_2O), 5.19 (1H, d, J=4 Hz, C_6–H), 5.56 (1H, s, $CH\langle^{O}_{O}\rangle$), 6.57 (2H, s, olefinic H).

(1*S,2*R**,5*S**,6*S**)-2,5-Epoxy-2-ethylenedioxymethyl-8-oxa-7-oxobicyclo[4.3.0]nonane (18)**——A solution of γ-butyrolactone (**8**) (100 mg) in methanol was hydrogenated on 5% Pd-C (100 mg) at room temperature. The catalyst was filtered off and the filtrate was concentrated to leave the desired dihydro-γ-butyrolactone as a crystalline solid (**18**) (90 mg), mp 83—85°C (from methanol). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760. NMR ($CDCl_3$+CD_3OD) δ: 1.93 (4H, s, C_4–H_2, C_5–H_2), 3.13—3.47 (2H, m, C_1–H, C_2–H), 3.93 (4H, s, OCH_2CH_2O), 4.28 (2H, d, J=4 Hz, OCH_2), 4.73 (1H, d, J=5 Hz, C_6–H), 5.07 (1H, s, $CH\langle^{O}_{O}\rangle$). MS m/e: 226 (M^+).

(1*R,2*R**,3*S**,4*S**)-2-Cyanomethyl-1-ethylenedioxymethyl-3-methoxycarbonyl-7-oxabicyclo[2.2.1]heptane (20) and (1*R**,2*R**,3*R**,4*S**)-2-Cyanomethyl-1-ethylenedioxymethyl-3-methoxycarbonyl-7-oxabicyclo[2.2.1]-heptane (9)**——A mixture of γ-butyrolactone (**18**) (156 mg) and KCN (90 mg) in dimethylsulfoxide (2 mg) was heated at 190°C for 7 h under nitrogen. The mixture was acidified with 20% H_2SO_4 to pH 3 and extracted with ether. The extract was washed with brine, dried over $MgSO_4$ and then evaporated to leave the carboxylic acids (**19**) as a diastereoisomeric mixture at C_1 which was treated with an excess of diazomethane in ether for 17 h. The solvent was then evaporated off to leave a residue, which was subjected to chromatography on silica gel (10 g). The first elution with chloroform afforded the β-methyl ester (**20**) (66 mg), mp 96—98°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250, 1725. NMR ($CDCl_3$) δ: 1.49—2.20 (4H, m, C_4–H_2, C_5–H_2), 2.40—3.0 (3H, m, C_1–H, CH_2CN), 3.29 (1H, dd, J=4 and 6 Hz, C_2–H), 3.72 (3H, s, OCH_3), 3.86—4.10 (4H, m, OCH_2CH_2O), 4.70 (1H, t, J=4 Hz, C_6–H), 5.05 (1H, s, $CH\langle^{O}_{O}\rangle$). The second elution with chloroform gave the α-methyl

ester (**9**) (61 mg), mp 130—132°C (from methanol). *Anal.* Calcd for $C_{13}H_{17}O_5N$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.69; H, 6.38; N, 4.90. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250, 1735. NMR ($CDCl_3$) δ: 1.66—1.89 (4H, m, C_4–H_2, C_5–H_2), 2.35—2.97 (4H, m, C_1–H, C_2–H, CH_2CN), 3.74 (3H, s, OCH_3), 3.86—4.08 (4H, m, OCH_2CH_2O), 4.83 (1H, d, J=4 Hz, C_6–H), 5.09 (1H, s, $CH\langle^{O}_{O}\rangle$). MS *m/e*: 267 (M^+).

Epimerization of (20) to (9)——A mixture of β-methyl ester (**20**) (11 mg) and K_2CO_3 (11 mg) in absolute methanol (0.5 ml) was stirred for 6 h at room temperature under nitrogen. The mixture was diluted with ether, washed with brine and then dried over $MgSO_4$. Removal of the solvent gave the practically pure α-methyl ester (**9**) (10 mg). The IR and NMR spectra and TLC behavior were identical with those of an authentic sample.

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References and Notes

1) Part CMXLIV: T. Kametani, T. Honda, K. Fukumoto, M. Toyota, and M. Ihara, *Heterocycles*, **16**, 1673 (1981).
2) T. Suzuki, A. Tomino, S. Kagaya, K. Unno, and T. Kametani, *Heterocycles*, **13**, 203 (1979); T. Suzuki, A. Tomino, K. Unno, and T. Kametani, *Chem. Pharm. Bull.*, **29**, 76 (1981).
3) T. Suzuki, S. Kagaya, A. Tomino, K. Unno, T. Kametani, T. Takahashi, and Y. Tanaka, *Heterocycles*, **9**, 1749 (1978); T. Suzuki, S. Kagaya, A. Tomino, K. Unno, and T. Kametani, *J. Chem. Soc. Perkin I*, **1980**, 2801. Total synthesis, see R.B. Woodward, F.E. Bader, H. Bickel, A.J. Frey, and R.W. Kierstead, *J. Am. Chem. Soc.*, **78**, 2023 (1956); B.A. Pearlman *J. Am. Chem. Soc.*, **101**, 6404 (1979); P.A. Wender, J.M. Schaus, and A.W. White, *J. Am. Chem. Soc.*, **102**, 6159 (1980).
4) T. Suzuki, A. Tomino, K. Unno, and T. Kametani, *Heterocycles*, **13**, 301 (1979). Total synthesis, see E. van Tamelen, M. Shamma, A. Burgstahler, J. Wolinsky, R. Tamm, and P. Aldrich, *J. Am. Chem. Soc.*, **80**, 5006 (1958); L. Töke, K. Honty, and Cs. Szántay, *Chem. Ber.*, **102**, 3248 (1969); G. Stork and R.N. Buthikonda, *J. Am. Chem. Soc.*, **94**, 5109 (1972); T. Kametani, Y. Hirai, M. Kajiwara, T. Takahashi, and K. Fukumoto, *Chem. Pharm. Bull.*, **24**, 2500 (1976); E. Wenkert, T.D.J. Hall, G. Kunesch, K. Orito, and R.S. Yadav, *J. Am. Chem. Soc.*, **101**, 5370 (1979); R.T. Brown and S.B. Pratt, *J. Chem. Soc. Chem. Comm.*, **1980**, 165.
5) W.E. Backman and W.S. Struve, *Org. Reactions*, **1**, 38 (1942).
6) B. Belleau and J. Puranen, *Can. J. Chem.*, **43**, 2551 (1965); J.J. Bloomfield and S.L. Lee, *J. Org. Chem.*, **32**, 3919 (1967).
7) Melting points are not corrected and were determined with a Yazawa microapparatus. IR spectra were recorded with a Shimadzu IR-400 spectrophotometer. Mass spectra were obtained with Hitachi M-52G and JEOL MJS-OISG-2 spectrometers. NMR spectra were taken in solution in deuteriochloroform and deuteriomethanol (tetramethylsilane as an internal standard) with a JEOL JNM-PMX-60 or JEOL PS-100 instrument.