on nine assays conducted on 3 days. Mean and standard deviation values were 9.66 mg/g ± 0.12 mg for the powder. The relative standard deviation was ±1.3%.

On the basis of this investigation, it is concluded that the proposed method is a superior stability assay of this new pharmaceutically active amine hydrochloride.

REFERENCES

(1) M. R. O. Prudhomme, *Bull. Soc. Pathol. Exot.*, **31**, 929(1938).

(2) M. R. O. Prudhomme, *J. Pharm. Chim.*, **9**, 8(1940).

(3) O. B. Hager, E. M. Young, T. L. Flanagan, and H. B. Walker, *Anal. Chem.*, **19**, 885(1947).

(4) G. Schill, *Acta Pharm. Suec.*, **2**, 13(1965).

(5) V. D. Gupta and D. E. Cadwallader, *J. Pharm. Sci.*, **57**, 112(1968).

ACKNOWLEDGMENTS AND ADDRESSES

Received July 5, 1974, from the *Analytical Research Department, Abbott Laboratories, North Chicago, IL 60064*

Accepted for publication December 15, 1975.

[x] To whom inquiries should be directed.

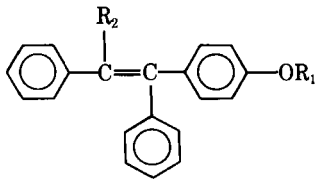
Stereochemistries of Geometric Isomers of 4-(2-Bromo-1,2-diphenylvinyl)phenol, 4-(2-Bromo-1,2-diphenylvinyl)anisole, and 2-[*p*-(2-Bromo-1,2-diphenylvinyl)phenoxy]triethylamine: Corrections of the Literature

A. RICHARDSON, Jr. [*], H. D. BENSON [*], and G. HITE [‡x]

Abstract □ The stereochemistries of geometric isomers of 4-(2-bromo-1,2-diphenylvinyl)phenol, 4-(2-bromo-1,2-diphenylvinyl)anisole, and 2-[*p*-(2-bromo-1,2-diphenylvinyl)phenoxy]triethylamine were determined by conversion of the phenolic analog to the ethers and subsequent comparison of physical properties with those of 2-[*p*-(2-chloro-1,2-diphenylvinyl)phenoxy]triethylamine of known stereochemistry.

Keyphrases □ Stereochemistry—geometric isomers of various substituted 1,2-diphenylvinyl compounds determined, literature correction □ Geometric isomers—various substituted 1,2-diphenylvinyl compounds, stereochemistry determined, literature correction □ Isomers, geometric—various substituted 1,2-diphenylvinyl compounds, stereochemistry determined, literature correction □ 1,2-Diphenylvinyl compounds, substituted—various, stereochemistry of geometric isomers determined, literature correction

The more estrogenic geometric isomers of 2-[*p*-(2-chloro-1,2-diphenylvinyl)phenoxy]triethylamine, clomiphene[1] (I) (1), and of 2-[*p*-(1,2-diphenyl-1-butenyl)phenoxy]-*N,N*-dimethylethylamine (II) (2) were designated *trans-(E)* (3) and *cis-(Z)* (4), respectively. Single-crystal X-ray diffraction studies on isomers of I and II (5) established the *cis*-stereochemistry for the more estrogenic isomers, permitted a consistent correlation of the biological data with structure and stereochemistry, and provided insight into the molecular mechanisms of action (6). Numerous conflicting aspects of the structural determinations of I and II prompted this report, which will review the chemical and physical lines of evidence, place them in perspective, and record the correct stereochemistries and physical properties of 4-(2-bromo-1,2-diphenylvinyl)anisole (III), 2-[*p*-(2-bromo- 1,2- diphenylvinyl)phenoxy]triethylamine (IV), and 4-(2-bromo-1,2-diphenylvinyl)phenol (V), which played the dominant role in the earlier incorrect assignments of stereochemistry to geometric isomers of I (5, 7).



cis-configuration

I: $R_1 = CH_2CH_2N(CH_2CH_3)_2$, $R_2 = Cl$

II: $R_1 = CH_2CH_2N(CH_3)_2$, $R_2 = CH_3CH_2$

III: $R_1 = CH_3$, $R_2 = Br$

IV: $R_1 = CH_2CH_2N(CH_2CH_3)_2$, $R_2 = Br$

V: $R_1 = H$, $R_2 = Br$

EXPERIMENTAL

(*Z*)-4-(2-Bromo-1,2-diphenylvinyl)phenol (V*a*)—This compound was prepared as described by Longfellow and Jackson (8), mp 145–147° [lit. (8) mp 147–149°].

(*Z*)- and (*E*)-4-(2-Bromo-1,2-diphenylvinyl)anisoles (III*a* and III*b*)—These isomers, previously identified incorrectly as *E* and *Z*, respectively, were prepared by the method described by Koelsch (9): (*Z*), mp 117.5–119° [lit. (9) mp 118–120°, lit. (10) mp 118.5–119.5°], and by Curtin *et al.* (10): (*E*), mp 93–94.5° [lit. (10) mp 97–98°]. In addition, III*a* was obtained by treatment of a solution of V*a* with methyl iodide and base.

(*Z*)- and (*E*)-2-[*p*-(2-Bromo-1,2-diphenylvinyl)phenoxy]triethylamines (IV*a* and IV*b*)—These compounds were prepared as described by Palopoli *et al.* (3). Their physical properties are summarized in Table I.

[1] Clomid, Merrell-National Laboratories, Division of Richardson-Merrell Inc., Cincinnati, Ohio.

Table I—Physical Properties of Geometric Isomers of I and III–V[a]

Property	Ia, *cis*-(*Z*)	Ib, *trans*-(*E*)	IIIa, *cis*-(*Z*)	IIIb, *trans*-(*E*)	IVa, *cis*-(*Z*)	IVb, *trans*-(*E*)
Melting point[b]	50–51.5°	73.5–75°	117.5–119°	93–94.5°	51.5–53°	65–66°
λ_{max}[c], nm (CH_3OH)	231 (ε 20,200)	242 (ε 22,100)	233 (ε 23,500)	241 (ε 22,000)	232 (ε 25,400)	240 (ε 23,200)
	246 (ε 15,800) sh	300 (ε 11,400)	257 (ε 11,000) sh	302 (ε 9190)	258 (ε 12,200) sh	302 (ε 9570)
	292 (ε 12,600)		292 (ε 8940)		291 (ε 9860)	
μ[d], D (C_6H_6, 25°)	1.98	2.86	1.92	2.53	1.95	2.85
ν[e], cm^{-1} (KBr)	693, 696 sh	693, 696	690	687, 699	691, 696 sh	690, 696
δf[f], ppm (tetramethylsilane in $CDCl_3$, A_2B_2)	6.82, 7.26	6.52, 6.82	6.87, 7.34	6.53, 6.86	6.82, 7.25	6.53, 6.85

[a] The melting point for Va, which has the *cis*-(*Z*) geometry, is 145–147°. [b] Melting points were determined in a Thomas-Hoover Unimelt apparatus and are uncorrected. [c] UV spectra were determined in 1-cm corex cells with a Cary 118 recording spectrophotometer. Band assignments are believed accurate to within ±1 nm. [d] Dipole moments were measured with a Kahl DM 01 dipolmeter. [e] IR spectra were determined with a Perkin-Elmer model 421 recording spectrophotometer. Band assignments are believed accurate to within ±3 cm^{-1}. [f] PMR spectra were determined on 10% solutions with a Varian model A60-A spectrometer. Band assignments are believed accurate to within ±0.05 ppm. The two entries in each set refer to the *ortho*- and *meta*-protons, respectively, of the disubstituted aromatic ring.

DISCUSSION

The longest wavelength UV maximum appears at a shorter wavelength for Ia (mp 50–51.5°), the more potent estrogenic isomer. Thus, Ia was designated *trans*, since this structure contains the less easily excited *trans*-stilbene chromophore while the more easily excited *trans*-*p*-alkoxystilbene chromophore is a feature of the *cis*-isomer (3). The A_2B_2 PMR pattern occurs at a lower field (0.4 ppm) for the lower melting, more potent estrogenic isomer of II (mp 72–74° and 96–98°). This isomer was designated *cis*. The assignment is consistent with the proposed sandwiching of the disubstituted ring between the monosubstituted rings, a feature unique to the *trans*-structure in which double shielding of the protons of the disubstituted ring by the ring currents of the monosubstituted rings is expected to lead to a higher field A_2B_2 PMR pattern (4).

It was assumed that the three rings exhibit a time-averaged orientation nearly perpendicular to the plane of the vinyl group. Interpreted in the same way, the PMR data for isomers of I contradicted the geometric assignment made on the basis of the UV evidence (*cf.*, Table I) (7). A similar inconsistency exists in the PMR and UV interpretations for II (5). In view of the previously demonstrated inconsistencies in the correlation of UV spectra with geometries of stilbenes (11) and the structural and electronic differences between I and II, the advent of a chemical line of evidence in support of the *trans* assignment for Ia demanded a completely different interpretation of the PMR data for isomers of I (7).

This rationale assumed a time-averaged coplanar stilbene with a nearly perpendicular geminal alkoxyphenyl substituent (*trans*-structure) and a time-averaged coplanar alkoxystilbene with a nearly perpendicular geminal phenyl substituent (*cis*-isomer). The A_2B_2 protons in the *cis*-structure were expected to be shielded by the ring currents of the geminal phenyl moiety. Thus, the *trans* assignment to Ia was made on the basis of the less shielded A_2B_2 PMR absorption exhibited by this isomer. The validity of the chemical evidence (and the PMR interpretation for isomers of I) rested on an earlier designation of the *trans*-geometry for IIIa (mp 117.5–119°) (9, 10). This isomer and IVa (mp 51.5–53°) were prepared by conventional methods (phenol, base, RX) (7) from Va (mp 145–147°) (8). Comparisons of dipole moments and UV, IR, and PMR spectra (Table I) (7) established that Ia has the same geometry as IIIa–Va.

The X-ray diffraction analysis (5) of the hydrobromide salt of the *cis*-isomer of II confirmed not only the geometric assignment but also the conformational assumptions made on the basis of the PMR studies (4). The latter point in particular called into question the geometric assignments made for isomers of I on the basis of the chemical evidence and the stereochemistry originally assigned to IIIa and of the PMR spectra and led to the X-ray diffraction studies of both Ib hydrochloride (mp 149–150.5°) and Ia hydroiodide (mp 170–171°). Full accounts of these studies will appear elsewhere. These studies revealed that Ia is *cis*-(*Z*) and not *trans*-(*E*). The disposition of the aromatic rings in I is much the same as that found in the solid state for II. Accordingly, while the UV data for isomers of both I and II are misleading, the PMR data, properly interpreted (4), are not. This proves that the geometries for isomers of III (9, 10), IV, and V (7) were also incorrectly assigned. The correct stereochemistries and the physical properties of geometric isomers of III–V are recorded in Table I.

REFERENCES

(1) L. W. Self, D. E. Holtkamp, and W. L. Kuhn, *Fed. Proc.*, **26**, 534(1967).

(2) M. J. K. Harper and A. L. Walpole, *Nature*, **212**, 87(1966).

(3) F. P. Palopoli, V. L. Feil, R. E. Allen, D. E. Holtkamp, and A. Richardson, Jr., *J. Med. Chem.*, **10**, 84(1967).

(4) G. R. Bedford and D. N. Richardson, *Nature*, **212**, 733(1966).

(5) B. T. Kilbourn and P. G. Owston, *J. Chem. Soc. B*, **1970**, 1.

(6) S. Ernst, G. Hite, J. S. Cantrell, A. Richardson, Jr., and H. D. Benson, *J. Pharm. Sci.*, **65**, 148(1976).

(7) A. Richardson, Jr., and H. D. Benson, "Abstracts of the 153rd Meeting of the American Chemical Society," American Chemical Society, Washington, D.C., 1967, p. M4.

(8) C. F. Longfellow and A. O. Jackson, U.S. pat. 2,429,556 (1947); through *Chem. Abstr.*, **42**, 1029(1948).

(9) C. F. Koelsch, *J. Am. Chem. Soc.*, **54**, 2487(1932).

(10) D. Y. Curtin, E. E. Harris, and E. K. Meislich, *ibid.*, **74**, 2901(1952).

(11) M. Katayama, S. Fujiwara, H. Suzuki, Y. Nagai, and O. Simamura, *J. Mol. Spectrosc.*, **5**, 85(1960).

ACKNOWLEDGMENTS AND ADDRESSES

Received October 20, 1975, from *Merrell-National Laboratories, Division of Richardson-Merrell Inc., Cincinnati, OH 45215, and the ‡Section of Medicinal Chemistry and Pharmacognosy, School of Pharmacy, University of Connecticut, Storrs, CT 06268

Accepted for publication December 17, 1975.

Supported in part by the Department of Health, Education, and Welfare, U.S. Public Health Service, under special Postdoctoral Fellowship GM 49037.

x To whom inquiries should be directed.

Chemical Constituents of Gentianaceae XIX: CNS-Depressant Effects of Swertiamarin

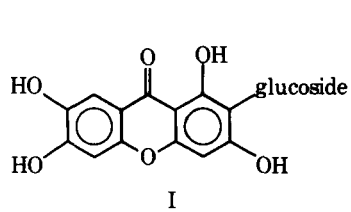
S. K. BHATTACHARYA *, P. K. S. P. REDDY *, S. GHOSAL‡x, A. K. SINGH ‡, and P. V. SHARMA ‡

Abstract □ CNS activity of swertiamarin, a secoiridoid glucoside from *Swertia chirata*, was evaluated. An apparent anomaly, associated with the unanticipated finding that the alcoholic extracts (excluding mangiferin) of *S. chirata* significantly reversed the mangiferin-induced CNS-stimulating effects in albino mice and rats, was resolved. The results indicate that swertiamarin and mangiferin antagonize each other *in vivo* and thereby reverse their CNS effects.

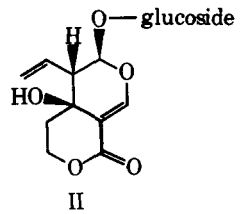
Keyphrases □ Gentianaceae—*Swertia chirata*, CNS activity of swertiamarin evaluated □ Swertiamarin—CNS activity evaluated, interaction with mangiferin □ CNS activity—swertiamarin evaluated □ Mangiferin—CNS activity, effect of swertiamarin

One result of a prior study, dealing with the active principles of *Swertia chirata* (Gentianaceae) (1), was the unanticipated finding that the alcoholic extracts, containing xanthones (excluding mangiferin) and secoiridoid glucosides, in doses of 50–100 mg/kg ip, significantly reversed the mangiferin-induced hyperactivity in albino mice and rats and also the potentiating effect of mangiferin on amphetamine toxicity in aggregated mice. Mangiferin (I), isolated in appreciable quantities from *S. chirata* (1.2 g/kg of whole plant) (1) and from *Canscora decussata* (30 g/kg of whole plant) (2), was earlier shown to produce significant pharmacological actions on the central nervous system (CNS) of laboratory animals (3, 4). In doses of 50–100 mg/kg ip, it produced definite signs of CNS stimulation in albino mice and rats as evidenced by hyperactivity, fine tremors, piloerection, increased spontaneous motility, reversal of reserpine-induced ptosis and sedation, potentiation of the analgesic effect of subanalgesic doses of morphine, and potentiation of amphetamine toxicity in aggregated mice.

The actions of mangiferin were subsequently found to be mediated *via* monoamine oxidase inhibition (5). Also, it was shown recently (6) that mangiferin-induced potentiation of the antinociceptive effect of morphine, like that of nialamide, was 5-hydroxytryptamine mediated. This paper describes findings that indicate that the reversal of mangiferin-induced pharmacological effects by the alcoholic extracts of *S. chirata* is due to the presence of an appreciable quantity (about 4 g/kg of whole plant) (5) of a CNS depressant swertiamarin (II).



I



II

EXPERIMENTAL

The isolation and purification of swertiamarin from *S. chirata* were reported previously (5). Pharmacological studies were conducted on albino mice (18–25 g) and albino rats[1] (80–120 g). The animals were fed a standard pellet diet[2]. All experiments were conducted at ambient temperature of 24 ± 2°.

The drug was tested in doses of 25–100 mg/kg ip. Unless stated otherwise, the data given indicate the effect of swertiamarin in doses of 50 mg/kg ip and a pretreatment time of 1 hr. In experiments where combined effects of mangiferin and swertiamarin were investigated, mangiferin was administered at 100 mg/kg ip and the pretreatment time was 2 hr.

In all experiments, 10 animals were used for the drug-treated and control groups; controls received only the vehicle, distilled water. Statistical analyses were done by the Student t test and χ-square test at appropriate places.

RESULTS AND DISCUSSION

In primary observational tests (7), swertiamarin produced a transient stimulation followed by signs of marked central depression in albino mice. The initial stimulation was absent in albino rats. The depressant activity was characterized by considerably diminished spontaneous motility, grouping of animals on one side of the cage, and ptosis. However, reflexes were intact, and the animals responded to external stimuli.

With higher doses (75–100 mg/kg ip), normal activities of the mice such as grooming were further reduced, the gait became abnormal, and the animals lost their ability to remain on an inclined plane. They responded to painful stimuli, although the righting reflex was sluggish. In these doses, swertiamarin produced significant hypothermia in albino rats as recorded by a rectal thermister probe (Table I). Since these observations were indicative of CNS depressant activity, swertiamarin was subjected to further pharmacological screening as follows.

The effects of swertiamarin on hexobarbital hypnosis (8) and amphetamine toxicity in aggregated and isolated mice (9) were evaluated

[1] The animals were supplied by Messrs B. N. Ghosh & Co., Calcutta, India.

[2] Hindusthan Levers, Calcutta, India.