Application of Mannich Reaction to Sulfones I

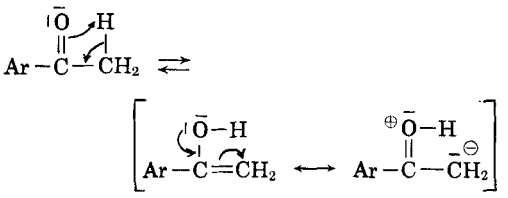
Reactive Methylene Moiety of Sulfones

By W. LEWIS NOBLES and B. BLACKBURN THOMPSON*

The preparation of a series of β-aminosulfones is described. Consideration of sulfone reactivity and mechanism of the condensation are related in this report. These compounds failed to provide significant antibacterial activity.

THE MANNICH REACTION in its simplest form consists of a condensation of ammonia or a primary or secondary amine and formaldehyde with a source of active hydrogen atoms, *e.g.*, alkyl or alkyl aryl ketones, aldehydes, nitroparaffins, phenols, alcohols, thiophenols, or thioalcohols. The reaction has been reviewed extensively (1–4), and the mechanism has been elucidated (5–9).

Mannich bases of acetophenones and propiophenones are readily available (1). Hellmann and Opitz (5) proposed that the active hydrogen compound normally gives rise to a carbanion by ionization of the active methylene group but that certain compound classes, *e.g.*, the acetophenones, could enolize and provide a carbanic center by resonance interaction with another structure—*viz.*, that shown in Scheme I.



Scheme I

Because of the apparent similarity between acetophenones and the alkyl aryl sulfones, several workers (5, 10) have attempted to utilize alkyl aryl sulfones in the Mannich reaction. All such attempts failed. The failure of simple alkyl aryl sulfones to undergo the Mannich reaction may be attributed to an inability to enolize (11). According to Hellmann and Optiz (5), the active hydrogen compound must be able to ionize if enolization is not possible.

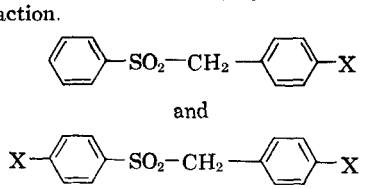
Tröger and Bolte (12) reported that the methylene group in sulfones of the types shown in Scheme II, where X is a strong electron-withdrawing group, do not have hydrogen atoms of sufficient activity to form salts with bases. Where the X group is attached directly to the methylene group, salt formation with strong bases is possible, *e.g.*, in compounds like R—SO_2—CH_2—X.

Compounds capable of ionization are known to undergo the Mannich reaction readily. Thus successful condensations have been reported with arylsulfonylalkanoic acids (10, 13), ethyl benzenesulfonylacetate (14), benzenesulfonylacetonitrile (14), and ω-benzenesulfonylacetophenone (14). Kötz (15) condensed methylenebis(alkylsulfones) with formaldehyde in the presence of a secondary amine as catalyst. The product was 1,1,3,3-tetrakis(alkylsulfonyl)propane. In this case, the nucleophilicity of the carbanion derived from the disulfone is greater than that of the free amine; therefore, formation of the hydroxymethyl derivative of the disulfone would be favored over formation of an aminomethanol. Similarly, a second molecule of the disulfone then would be expected to give a symmetrical methylene derivative of the disulfone (5).

DISCUSSION OF RESULTS

The purpose of this research was to prepare some β-aminosulfones using the Mannich reaction and to test them as potential anti-infectives. Numerous procedures were employed in an attempt to aminomethylate methyl phenyl sulfone (8, 9, 16–20). All such attempts failed. To prove that these results were not attributable to a reverse Mannich reaction (21), some representative β-aminosulfones were prepared by the method of Ufer (22) and subjected to Mannich conditions. No reversal occurred. The properties and data for these β-aminosulfones are given in Table I.

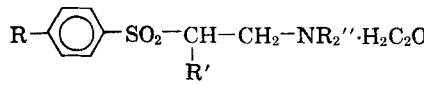
Insufficient lability of hydrogen in the simple alkyl aryl sulfones is evident and, since enolization s not possible (11) in these sulfones, they are unable to undergo the Mannich reaction. Therefore, it was desirable to prepare some sulfones of greater reactivity and to attempt to employ them in the Mannich reaction.



Scheme II

Received August 26, 1964, from the School of Pharmacy, University of Mississippi, University.
Accepted for publication December 15, 1964.
Presented to the Scientific Section, A.PH.A., New York City meeting, August 1964.
* Present address: Department of Pharmaceutical Chemistry, School of Pharmacy, University of Georgia, Athens.

TABLE I.—β-DIALKYLAMINOALKYL ARYL SULFONE OXALATES



Compd.	R	R	R″	Formula	Yield, %	M.p., °C.[a]	Microanalytical Data C, % Calcd.	C, % Found	H, % Calcd.	H, % Found
1	H	H	C_2H_5	$C_{14}H_{21}NO_6S$[b]	27.2	164.5–166.0[c]	49.91	50.12	6.36	6.32
2	H	H	CH_3	$C_{12}H_{17}NO_6S$	10.6	176.0–177.5[c]	47.51	47.69	5.65	5.30
3	H	CH_3	CH_3	$C_{13}H_{19}NO_6S$	20.5	186.0–187.0[c]	49.20	49.34	6.03	5.50
4	CH_3	H	C_2H_5	$C_{15}H_{23}NO_6S$	27.5	165.0–166.0[c,d]	52.15	52.29	6.71	6.51
5	CH_3	H	CH_3	$C_{13}H_{19}NO_6S$	9.5	198.5–200.5[c]	49.20	49.86	6.03	5.64
6	CH_3	CH_3	CH_3	$C_{13}H_{19}NO_6S$	20.8	165.0–173.0[c]	50.74	50.58	6.39	6.22

[a] Uncorrected melting points (Fisher-Johns melting point apparatus). [b] Calculated for 1/4 H_2O of crystallization. [c] Melted with decomposition. [d] Also reported by Üfer (22).

TABLE II.—MISCELLANEOUS COMPOUNDS

Compd.	Name	Formula	Yield, %	M.p., °C.[a]	Microanalytical Data C, % Calcd.	C, % Found	H, % Calcd.	H, % Found
1	Methylenebis(phenylsulfide)[b]	$C_{13}H_{12}S_2$	83.0	34.0–35.0	67.19	67.22	5.21	5.09
2	Methylenebis(phenylsulfone)[c]	$C_{13}H_{12}O_4S_2$	81.5	120.5–122.0	52.68	52.61	4.08	3.97
3	1,1,3,3-Tetrakis(benzenesulfonyl)propane	$C_{27}H_{24}O_8S_4$	66.5	198.5–200.5	53.62	53.42	4.00	4.15
4	ω-Benzenesulfonylacetophenone	$C_{14}H_{12}O_3S$	65.7	93.0–94.0[d]	64.59	64.39	4.65	4.58
5	2,4-Bis(benzenesulfonyl)-1,5-diphenyl-1,5-pentanedione	$C_{29}H_{24}O_6S_2$	59.8	134.0–135.0	65.39	65.29	4.54	4.64
6	ω-Benzenesulfonylacetophenone thiosemicarbazone	$C_{15}H_{15}N_3O_2S_2$	51.6	85.0–86.0	54.03	53.86	4.53	4.61
7	2,4-Bis(benzenesulfonyl)-1,5-diphenyl-1,5-pentanedione dithiosemicarbazone	$C_{31}H_{30}N_6O_4S_4$	69.5	139.0–141.0	54.54	54.62	4.45	4.31

[a] Uncorrected melting points (Fisher-Johns melting point apparatus). [b] Literature melting point is 35°C. (11). [c] Reported to melt at 118–119° (29) and 120–121° (30). [d] Melting point of 95° reported (28).

Methylenebis(phenylsulfide) (compound *1*, Table II), prepared according to the procedure of Shriner *et al.* (11) in 83% yield, was oxidized according to a modification of the procedure of Pomerantz and Connor (23), giving methylenebis(phenylsulfone) (compound *2*, Table II) in 81.5% yield. With amine hydrochloride and paraformaldehyde under the conditions utilized by Mannich and Lammering (24), no reaction with this disulfone was observed. With free amine and formaldehyde only, 1,1,3,3-tetrakis(benzenesulfonyl)propane (compound *3*, Table II) could be isolated. The procedure employed was that of Bodendorf and Koralewski (7). It was also of interest to ascertain if addition of preformed aminomethanols could force the reaction to yield an aminomethyl derivative. Thus formaldehyde and a secondary amine were reacted without solvent at 0° and added gradually to an alcoholic solution of methylenebis(phenylsulfone). A rapid reaction ensued and gave only 1,1,3,3-tetrakis-(benzenesulfonyl)propane. The preparation of the latter compound using sodium hydroxide as catalyst is described under *Experimental*. The results are quite similar to those observed when a secondary amine was used as the catalyst.

Barney (25) converted methylenebis(ethylsulfone) into vinylene-1,1-bis(ethylsulfone). To study the stability of Mannich bases derived from methylenebis(phenylsulfone), an attempt to prepare vinylene-1,1-bis(phenylsulfone) by Barney's procedure was made. Addition of a secondary amine across the double bond would be expected to yield a typical Mannich derivative. The attempted synthesis of vinylene-1,1-bis(phenylsulfone) gave only a carbonaceous mass. No further attempts to obtain a Mannich base have been made to date.

When ω-benzenesulfonylacetophenone (compound *4*, Table II) was subjected to conditions similar to those employed with methylenebis(phenylsulfone), similar results were obtained. For example, basic conditions provided only 2,4-(benzenesulfonyl)-1,5-diphenyl-1,5-pentanedione (compound *5*, Table II). No reaction occurred under acidic conditions. Sample preparative methods are given under *Experimental*, while data for these compounds and related derivatives (compounds *6* and *7*, Table II) are given in Table II.

Balasubramanian and Baliah (14) were able to obtain Mannich bases derived from ω-benzenesulfonylacetophenone when aromatic aldehydes and ammonium acetate were employed with ethanol as the solvent. Additional studies are anticipated to ascertain the reasons for failure in the present study.

Baliah and co-workers also prepared Mannich

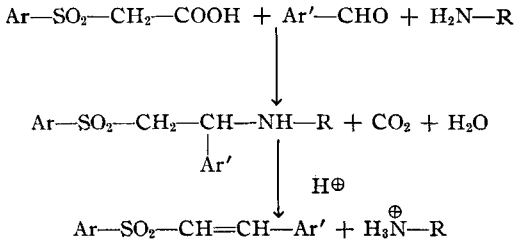


Fig. 1.—Mannich reaction in arylsulfonylacetic acid series.

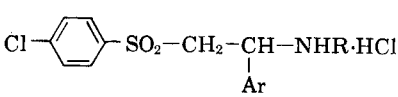
derivatives of arylsulfonylalkanoic acids (10, 13), arylsulfonylacetonitrile (14), and ethyl arylsulfonylacetate (14) employing aromatic aldehydes and ammonium acetate. Additional condensations involving arylsufonylacetic acids were investigated in this research.

Thus, *p*-chlorophenylthioacetic acid was prepared in 78.5% yield according to a modification of the procedure of Uyeda (26). Oxidation of this acid with potassium permanganate, according to the method of Backlund (27), gave a 76.8% yield of *p*-chlorobenzenesulfonylacetic acid. Employing the procedure of Baliah and co-workers (10, 13), *p*-chlorobenzenesulfonylacetic acid was condensed with various aromatic aldehydes and ammonium acetate or benzylamine (see Fig. 1). Results similar to those recorded by Baliah and co-workers (10, 13) were observed. For example, prolonged heating decreased the yield of Mannich base and increased the yield of the α,β-unsaturated sulfones, by-products of the condensation. Prolonged treatment with hydrogen chloride gave colored products which could not be purified easily. In general, the reactions required 8–15 min. and gave completely decarboxylated products. Further studies on the application of the Mannich reaction to arylsulfonylacetic acids are being compiled currently as Part II of this series. All relevant data for the Mannich bases and α,β-unsaturated sulfones prepared in this study are given in Tables III and IV, respectively.

EXPERIMENTAL

β-Dialkylaminoalkyl Aryl Sulfones (Table I).—A modification of the procedure of Ufer (22) was utilized to prepare β-dialkylaminoalkyl aryl sulfones. Thus, 0.1 mole of sodium hydroxide and 0.1 mole of sodium arylsulfinate were heated in 90 Gm. of absolute ethanol. To this solution, contained in a 1-L. three-necked flask equipped with stirrer and condenser, was added a hot solution of 0.1 mole of a β-dialkylaminoalkylchloride hydrochloride dissolved in 30 Gm. of absolute ethanol. The resultant mixture was refluxed for 2 hr. and filtered hot. The hot filtrate was treated with 1–2 ml. of a saturated solution of oxalic acid in absolute ethanol and filtered. Finally, a calculated molar quantity of saturated oxalic acid solution (absolute ethanol) was added and the mixture allowed to stand 30 min. The amine oxalate then was filtered and purified by recrystallization from ethanol or aqueous ethanol. The products, which decomposed at their melting points, are reported in Table I.

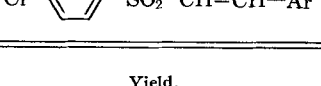
TABLE III.—SUBSTITUTED β-AMINOETHYL *p*-CHLOROPHENYL SULFONE HYDROCHLORIDES



Compd.	Ar	R	Formula	Yield, %	M.p., °C.[a]	Microanalytical Data — C, % Calcd.	C, % Found	H, % Calcd.	H, % Found
1	2-Thienyl	Benzyl	$C_{19}H_{20}Cl_2NO_2S_2$	23.3	247.0–248.0[b]	53.14	53.14	4.69	4.56
2	Phenyl	H—	$C_{14}H_{15}Cl_2NO_2S$	18.1	221.0–222.0[b]	50.61	50.46	4.55	4.39
3	Phenyl	Benzyl	$C_{21}H_{21}Cl_2NO_2S$	29.1	248.0–249.0[b]	59.71	60.11	5.01	5.14
4	*p*-Dimethylaminophenyl	Benzyl	$C_{23}H_{26}Cl_2N_2O_2S$	15.2	144.5–146.0[b]	59.35	59.27	5.63	5.64
5	2-Phenylethenyl	Benzyl	$C_{23}H_{23}Cl_2NO_2S$[c]	18.0	157.0–158.0[b]	60.99[c]	60.92	5.17[c]	4.82

[a] Uncorrected melting points (Fisher-Johns melting point apparatus). [b] Melted with decomposition. [c] Calculated for $\frac{1}{4}$ H_2O of crystallization.

TABLE IV.—α,β-UNSATURATED SULFONES



Compd.	Ar	Formula	Yield, %	M.p., °C.[a]	Microanalytical Data — C, % Calcd.	C, % Found	H, % Calcd.	H, % Found
1	2-Thienyl	$C_{12}H_{10}ClO_2S_2$	8.3	177.0–178.0	50.43	50.19	3.53	3.04
2	Phenyl	$C_{14}H_{11}ClO_2S$	15.2	127.0–128.0	60.32	60.16	3.98	3.84
3	*p*-Dimethylaminophenyl	$C_{16}H_{16}ClNO_2S$	1.8	162.0–164.0	59.71	59.65	5.01	4.74
4	2-Phenylethenyl	$C_{16}H_{13}ClO_2S$	4.2	153.5–155.0[b]	63.05	62.84	4.30	4.13

[a] Uncorrected melting points (Fisher-Johns melting point apparatus). [b] Melted with decomposition.

Methylenebis(phenylsulfide) (Compound 1, Table II).—Following the procedure of Shriner *et al.* (11), 1 mole of benzenethiol, 1 Gm. atom of sodium, and 0.5 mole of methylenebromide gave an 83% yield of methylenebis(phenylsulfide), melting at 34.0–35.0° on purification from ethanol. Shriner *et al.* reported 35° as the melting point.

Methylenebis(phenylsulfone) (Compound 2, Table II).—A modification of the procedure of Pomerantz and Connor (23) was used to oxidize methylenebis(phenylsulfide). Thus, 0.5 mole (116 Gm.) of methylenebis(phenylsulfide) was dissolved in 500 ml. of a glacial acetic acid–acetic anhydride mixture (1:1 by volume). To this solution, cooled to 0°, was added 270 ml. of 30% hydrogen peroxide over a period of 1 hr. After 3 hr. in an ice bath, the mixture was allowed to come to room temperature as the ice melted. After standing 3 days at room temperature, a small amount of manganese dioxide was added to destroy the peroxide. The solvent was evaporated and the residue taken up in hot ethanol and purified with charcoal. On cooling and filtering, crystals were obtained. A yield of 81.5% of colorless crystals, m.p. 120.5–122.0° was obtained on further purification from hot ethanol.

1,1,3,3-Tetrakis(phenylsulfonyl)propane (Compound 3, Table II).—According to the procedure reported by Barney (25), 0.05 mole (15.8 Gm.) of methylenebis(phenylsulfone) was mixed with 4.0 Gm. of 30% formaldehyde solution and 19.8 Gm. of methanol. The resultant mixture then was heated to 50–60°, and 0.13 Gm. of sodium hydroxide was added to the mixture. After the initial vigorous reaction, the mixture was heated to 70–80° for 5–10 min., then cooled. The precipitate was removed by filtration and dried. Recrystallization gave colorless crystals, m.p. 198.5–200.5°, in 66.5% yield.

ω-Benzenesulfonylacetophenone (Compound 4, Table II).—As described by Troger and Beck (28), 0.27 mole of sodium benzenesulfinate, 0.25 mole of phenacyl chloride, and 400 ml. of ethanol gave 65.7% of colorless crystals, melting at 93.0–94.0°.

2,4 - Bis(benzenesulfonyl) - 1,5 - diphenyl - 1,5-pentanedione (Compound 5, Table II).—Following the procedure of Barney (25), described above in the preparation of 1,1,3,3-tetrakis(benzenesulfonyl)propane, ω-benzenesulfonylacetophenone (0.056 mole) was condensed with formaldehyde (4.2 Gm. of 30% formalin), 14 Gm. of sodium hydroxide, and 22 ml. of methanol to give 59.8% of a product, melting at 134.0–135.0°.

ω-Benzenesulfonylacetophenone Thiosemicarbazone (Compound 6, Table II).—Following a modification of the procedure of Bernstein *et al.* (31), 5.0 Gm. (0.02 mole) of ω-benzenesulfonylacetophenone, dissolved in 300 ml. of warm 95% ethanol, was mixed with a solution of 1.7 Gm. (0.02 mole) of thiosemicarbazide in 300 ml. of warm water. The mixture was heated for 20 min. and cooled. The product was collected by filtration and recrystallized from 50 ml. of 50% ethanol to give 51.6% of crystals melting in the range 86.0–87.0°.

2,4 - Bis(benzenesulfonyl) - 1,5 - diphenyl - 1,5-pentanedione Dithiosemicarbazone (Compound 7, Table II).—According to the above procedure, 2,4-bis(benzenesulfonyl) - 1,5 - diphenyl - 1,5 - pentanedione (5.0 Gm., 0.01 mole) and 1.70 Gm. (0.02 mole) of thiosemicarbazide gave 69.5% of the dithiosemicarbazone, m.p. 139.0–141.0°.

***p*-Chlorophenylthioacetic Acid.**—The procedure of Uyeda (26) was modified by using equal molar amounts of each of the ingredients and by changing the purification procedure. Thus, 72.0 Gm. (0.76 mole) of α-chloroacetic acid, 40.0 Gm. of sodium bicarbonate, and 2 L. of water were placed in a 4-L. beaker, and 110 Gm. (0.76 mole) of *p*-chlorobenzenethiol and 30 Gm. of sodium hydroxide in 200 ml. of water were added. After 0.5 to 2 hr. on a steam bath, the mixture was cooled, filtered, and the filtrate treated with 41 ml. of sulfuric acid (previously diluted to 100 ml.). The product was collected on a Büchner funnel and purified by dissolving in dilute aqueous sodium hydroxide, treated with charcoal, filtered, and acidified. There was obtained in this manner 78.5% of a product, melting at 105.5–106.0°.

***p*-Chlorobenzenesulfonylacetic Acid.**—Oxidation of the above acid by the procedure of Backlund (27) gave 76.8% of the theoretical yield of product, melting at 125.0–127.0°.

Anal.—Calcd. for C, 40.94; H, 2.99. Found: C, 40.83; H, 3.11.

β-Aminoethyl *p*-Chlorophenyl Sulfone Hydrochlorides (Table III).—Using the appropriate aldehyde (0.02 mole), benzyl amine or ammonium acetate (0.02 mole), *p*-chlorobenzenesulfonylacetic acid (0.02 mole), and glacial acetic acid (4 ml.), the mixture was refluxed 8–15 min. and treated with ether. The ether extract was treated with hydrogen chloride in ether and the amine hydrochloride collected on a Büchner funnel. The products, purified from ethanol, are given in Table III. The procedure is that of Balasubramanian and Baliah (10, 13).

α,β-Unsaturated Sulfones (Table IV).—The filtrate from the above procedure was evaporated and treated with a small amount of methanol, according to the procedure of Baliah *et al.* (10, 13). The unsaturated sulfones which separated were recrystallized from 95% alcohol. The pertinent data are reported in Table IV.

REFERENCES

(1) Blicke, F. F., in "Organic Reactions," vol. 1, John Wiley & Sons, Inc., New York, N. Y., 1942, pp. 303–341.
(2) Karbe, H., *Arch. Pharm.*, **283**, 38(1950).
(3) Reichert, B., "Die Mannich Reaktion," Springer-Verlag, Berlin, Germany, 1959.
(4) Hellmann, H., and Opitz, G., "α-Aminoalkylierung," Verlag Chemie, Weinheim, Germany, 1960.
(5) Hellmann, H., and Optiz, G., *Angew. Chem.*, **68**, 265 (1959); *Chem. Ber.*, **89**, 81(1956); **90**, 8, 15(1957); *Ann.*, **604**, 214(1957); **605**, 141(1957).
(6) Cummings, T. F., and Shelton, J. R., *J Org. Chem.*, **25**, 419(1960).
(7) Bodendorf, K., and Koralewski, G., *Arch. Pharm.*, **271**, 101(1933).
(8) Liebermann, S. V., and Wagner, E. C., *J. Org. Chem.*, **14**, 1001(1949).
(9) Alexander, E. R., and Underhill, E. J., *J. Am. Chem. Soc.*, **71**, 4014(1949).
(10) Balasubramanian, M., and Baliah, V., *J. Chem. Soc.*, **1954**, 1844.
(11) Shriner, R. L., Struck, H. C., and Jorison, W. T., *J. Am. Chem. Soc.*, **52**, 2060(1930).
(12) Tröger, J., and Bolte, F., *J. Prakt. Chem.*, **103** (No. 2), 163(1921).
(13) Balasubramanian, M., Baliah, V., and Rangarajan, T., *J. Chem. Soc.*, **1955**, 3296.
(14) Balasubramanian, M., and Baliah, V., *J. Indian Chem. Soc.*, **32**, 493(1955); through *Chem. Abstr.*, **50**, 10042(1956).
(15) Kötz, A., *Ber.*, **33**, 1120(1900).
(16) Szmant, H. H., and Henley, W. O., *J. Org. Chem.*, **19**, 1(1954).
(17) Dalgiesh, C. E., *J. Am. Chem. Soc.*, **71**, 1697(1949).
(18) Senkus, M., *ibid.*, **68**, 10(1946).
(19) Mannich, C., and Ganz, E., *Ber.*, **55**, 3486(1922).
(20) Maxwell, C., *Org. Syn.*, **23**, 30(1943).

(21) Snyder, H. R., *et al.*, *J. Am. Chem. Soc.*, **75**, 4672 (1953).
(22) Üfer, H., Ger. pat. 702,064(Jan. 2, 1941); through *Chem. Abstr.*, **36**, 98(1942).
(23) Pomerantz, A., and Connor, R., *J. Am. Chem. Soc.*, **61**, 3386(1939).
(24) Mannich, C., and Lammering, D., *Ber.*, **55**, 3510 (1922).
(25) Barney, A. L., U. S. pat. 2,641,594(June 1953); through *Chem. Abstr.*, **47**, 11805(1953).
(26) Uyeda, Y., *J. Chem. Soc. Japan*, **52**, 410(1931); through *Chem. Abstr.*, **26**, 5082(1932).
(27) Backlund, D., *Arkiv. Kemi, Mineral. Geol.*, **1A** (No. 1), (1940); through *Chem. Abstr.*, **34**, 7860(1940).
(28) Tröger, J., and Beck, O., *J. Prakt. Chem.*, **87**, 289 (1913).
(29) Fromm, A., *Ann.*, **253**, 161(1889).
(30) Otto, R., and Tröger, J., *Ber.*, **25**, 3428(1892).
(31) Bernstein, J., *et al.*, *J. Am. Chem. Soc.*, **73**, 906(1951).

Tumor Inhibitors VI

Cissampareine, New Cytotoxic Alkaloid from *Cissampelos pareira*. Cytotoxicity of Bisbenzylisoquinoline Alkaloids

By S. MORRIS KUPCHAN, A. C. PATEL, and EIICHI FUJITA

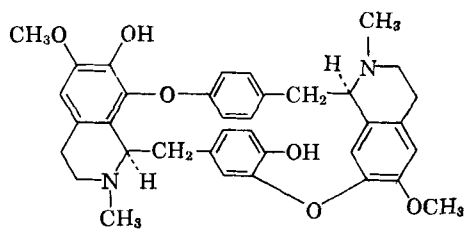
A preliminary study of *Cissampelos pareira* Linn. from Peru yielded a new alkaloid, cissampareine. Evidence is presented for assignment to cissampareine of the empirical formula, $C_{37}H_{38}N_2O_6$. Cissampareine and four other bisbenzylisoquinoline alkaloids isolated from menispermaceous plants were found to show significant and reproducible inhibitory activity against human carcinoma of the nasopharynx carried in cell culture (KB).

CISSAMPELOS PAREIRA Linn. is a climbing shrub distributed throughout warm parts of Asia, East Africa, and America. The roots are reported to have found use as a diuretic, febrifuge, remedy for heart trouble, and against dysentery and sores (1).

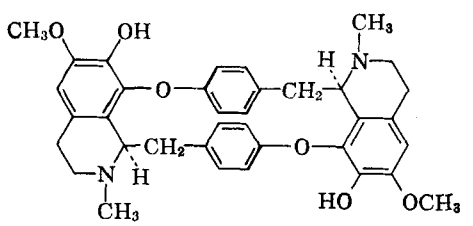
In 1840, Wiggers (2) isolated an amorphous alkaloid from the roots of a South American *C. pareira* sample, and the name pelosine was assigned to the alkaloid. Scholtz (3, 4) showed that pelosine is identical to *l*-curine (I). Bhattacharji *et al.* reported in 1956 (5) that *C. pareira* Linn. from Kashmir yielded two new alkaloids, hayatine and hayatinine, and that the same species from Pilibhit yielded hayatine and *l*-curine but no hayatinine. The methiodide of hayatine was shown to possess powerful neuromuscular blocking activity comparable to that of *d*-tubocurarine chloride (6, 7). Structural studies of hayatine (8) and hayatinine (9) indicate that both are alkaloids of the bisbenzylisoquinoline type.

DISCUSSION

An earlier study led to isolation from the roots and vines of *C. pareira* Linn. from Madras, India, of *l*-curine (I),[1] *d*-isochondrodendrine (II),[1] and hayatine (10). Preliminary pharmacological evaluation of the methanol-extractable alkaloids, of the methiodide prepared from the latter mixture, and



I



II

of the quaternary alkaloids, showed that all had curarelike activity (10).

The present report describes a preliminary study of the alkaloids of a sample of *C. pareira* Linn. from Department Huanuco, Peru,[2] and the isolation and characterization of cissampareine, a new cytotoxic alkaloid. Coarsely ground whole plant was extracted successively with petroleum ether, methanol, and 1.5% hydrochloric acid solution. Each extract was processed for alkaloid

Received November 7, 1964, from the Department of Pharmaceutical Chemistry, School of Pharmacy, University of Wisconsin, Madison.
Accepted for publication December 9, 1964.
This investigation was supported in part by grants HE-02952 and CA-04500 from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md.

[1] Absolute configurations indicated for I–IV are those assigned by Tomita, M., and Kunimoto, J., *J. Pharm. Soc. Japan*, **82**, 734, 741(1962).

[2] The plant sample (whole plant) was procured by the Ciba Pharmaceutical Co., Summit, N. J. (acquisition number C-974), and identified by the late Professor Robert E. Woodson, Jr., Department of Botany, Washington University, St. Louis, Mo. The authors thank Dr. E. Schlittler and Dr. H. B. MacPhillamy for the plant material.