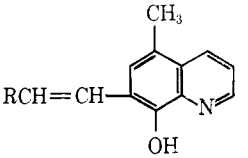
TABLE I

(8-HYDROXY-5-METHYL-7-QUINOLYL)VINYL COMPOUNDS



No.	R	Formula	Mp, °C[a]	Yield, %	—% carbon— Calcd	Found	—% hydrogen— Calcd	Found	—% nitrogen— Calcd	Found
1	1-Methyl-8-hydroxy-2-quinolinium methosulfate[b]	$C_{23}H_{22}N_2O_6S$	193	87					6.16	6.74
2	1-Methyl-5-ethyl-2-pyridinium iodide	$C_{20}H_{21}IN_2O\cdot 0.5H_2O$	250	31	54.43	54.62	5.03	4.87	6.35	6.23
3	1-Methyl-2-quinolinium iodide	$C_{22}H_{19}IN_2O$	242	72	58.16	58.01	4.21	4.20	6.17	6.03
4	3-Methyl-2-benzothiazolium iodide	$C_{20}H_{17}IN_2OS\cdot H_2O$	236	92	50.21	50.70	4.00	4.00	5.86	5.79
5	3-Methyl-2-benzoselenazolium iodide	$C_{20}H_{17}IN_2OSe$	234	81	47.35	47.02	3.38	3.43	5.52	5.50
6	1-Methyl-4-pyridinium iodide	$C_{18}H_{17}IN_2O$	309	57	53.48	53.43	4.24	4.26	6.93	6.97
7	1-Methyl-2-pyridinium iodide	$C_{18}H_{17}IN_2O$	255	43	53.48	53.15	4.24	4.10	6.93	7.01
8	1,6-Dimethyl-2-quinolinium iodide[c]	$C_{23}H_{21}IN_2O$	218	83					5.98	6.39
9	1-Methyl-6-ethoxy-2-quinolinium iodide	$C_{24}H_{23}IN_2O_2$	230	86	57.84	57.80	4.65	4.53	5.62	5.94
10	1-Methyl-4-quinolinium iodide	$C_{22}H_{19}IN_2O\cdot H_2O$	275	61	55.94	55.92	4.48	4.45	5.93	5.89
11	2-Methyl-1-isoquinolinium iodide	$C_{22}H_{19}IN_2O\cdot 0.5H_2O$	232	41	57.03	56.83	4.35	4.19	6.05	5.99

[a] All melting points were with decomposition. [b] The methosulfate was converted to the perchlorate hydroperchlorate, mp above 400°. *Anal.* Calcd for $C_{22}H_{20}Cl_2N_2O_{10}$: N, 5.16. Found: N, 4.95. [c] The iodide was converted to the perchlorate hydroperchlorate, mp 310°, which showed a correct analysis for C, H, and N.

TABLE II

CELL CULTURE TEST RESULTS[a]

No.[b]	ED_{50}, mg/ml	Slope
3	0.63	−0.21
5	4.2	−0.45
8	0.85	−0.79
9	1.40	−0.56
10	0.32	−2.22

[a] Testing by CCNSC on KB 90. [b] Numbers are the same as in Table I.

not even needed. Although full analytical data for 8-hydroxy-1-methyl-2-(8-hydroxy-5-methyl-7-quinolyl)vinylquinolinium methosulfate (**1**, Table I) were not obtained, it is included for comparison with a related compound previously reported.[4]

The Photosensitizing Activity of N,N′-Bis(*p*-formylphenyl)piperazine[1a]

S. N. THAMPI, F. W. SCHUELER,[1b] VERNON B. HAARSTAD,[1c]

Department of Pharmacology, School of Medicine, Tulane University, New Orleans, Louisiana

AND SILAS E. O'QUINN

Department of Dermatology, Louisiana State University School of Medicine, New Orleans, Louisiana

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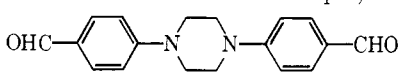
During the course of our continuing program in the polymerization of pharmacophoric moieties, we became interested in the synthesis of a series of piperazines that might be visualized as dimers of *para*-substituted dimethylaminobenzenes. For example, N,N′-bis(*p*-formylphenyl)piperazine (I) might be considered to be a "dimer" of *p*-dimethylaminobenzaldehyde. We proposed to use I as the starting material for the synthesis of this series, utilizing well-known schemes for the preparation of phenethylamines, α-amino acids, *etc.* Bayer[2] ascribes the preparation of I to a procedure patented by Wilson.[3] However, no mention of I was to be found in this patent, in *Chemical Abstracts*, or in Beilstein. Therefore, we decided to attempt its synthesis according to the general procedure described by Wilson.[3] This procedure is a modification of a method originally described by Vilsmier and Haack,[4] for formylation of N,N-disubstituted aromatic amines by a 1:1 complex of N,N-disubstituted formamides and phosphorus oxychloride. However, we found Wilson's conditions to be unsatisfactory. As might be expected, we found it necessary to exclude moisture carefully and to add the $POCl_3$ very slowly to the well-stirred mixture, initially kept at 0° and thereafter not allowed to rise above 20°. The subsequent neutralization step required careful stirring and cooling. Otherwise, a great deal of resinous material was formed. These precautions afforded I in 91% yield.



I

During the course of studies in the synthesis of derivatives of I, it was suspected that one (or all) of

(1) (a) This investigation was supported by a U. S. Public Health Service Research Grant No. CA-03037 from the National Cancer Institute. (b) Deceased. (c) To whom inquiries should be sent.

(2) O. Bayer in "Methoden der Organischen Chemie," Vol VII, E. Müller, Ed., Sauerstoff-Verbindungen II, Teil I, Georg Thieme Verlag, Stuttgart, 1954, p 32.

(3) C. D. Wilson, U. S. Patent 2,437,370 (March 1948); *Chem. Abstr.*, **42**, 5924 (1948).

(4) A. Vilsmier and A. Haack, *Chem. Ber.*, **60**, 119 (1927).

these compounds was causing a very severe photoallergy in one of us (S. N. Thampi). The circumstances which led to the identification of I as a photosensitizing agent are described in the clinical report. These results, plus the fact that persons not directly connected with this phase of our programs were showing signs of photosensitization, prompted us to abandon the study.

Pharmacology.—A 1% ointment of I in petroleum jelly was used for this series of studies. Two male albino rabbits and 2 male albino Sprague-Dawley rats were used. A small amount of the ointment was applied to a portion of the shaved skin of these animals and irradiated for 3 min under a mercury-vapor lamp. Control irradiations were also performed on the same animals treated with plain petroleum jelly. No visible skin reactions were observed in any of these animals given the above treatment daily over a period of 30 days.

Clinical. Case History.—S. N. T., a 31-year old Indian male was seen in the dermatology clinic in August 1963. He had noted the onset of a pruritic skin eruption several months previously. The eruption was limited to the exposed parts of the body and it was noted that exposure to sunshine produced an increase in the pruritus and an exacerbation of the dermatitis. During the preceeding weeks the dermatitis had gradually increased in severity. Physical examination revealed a healthy, well-developed male with a dark, swarthy skin color. An erythematous, papulovesicular dermatitis was present on the exposed areas of the body including the face, ears, neck, "V" area of the chest, extensor aspects of the forearms, and the dorsal surfaces of the hands. The portions of these areas that were protected from the sun such as the body creases and the area beneath the chin were spared. The distribution and the appearance of the skin eruption was suggestive of an allergic contact dermatitis related to photosensitivity.

Investigation.—Patch tests were applied with the following materials: N,N′-bis(*p*-formylphenyl)piperazine (I), 10% in petrolatum; bithionol (2,2′-thiobis-[4,6-dichlorophenol]), 1% in petrolatum; hexachlorophene (2,2′-methylenebis[3,4,6-trichlorophenol]), 1% in petrolatum; and plain petrolatum. At 48 hr, there was a 3+ reaction consisting of erythema, edema, and papulovesicles to I. All other patch tests were negative. Light testing was done according to the technique of Jillson.[5] The light source was a Bausch & Lomb, carbon-arc lamp with therapeutic B carbons. The patient was found to have a normal minimal erythema dose (MED) of 30 sec. A delayed erythema dose (DED) of 4 min was administered, and there was a normal response to the administration of this amount of ultraviolet light.

Duplicate patch tests of the following compounds were then applied: I, N,N′-bis(*p*-phenethylamine)-piperazine (II), N,N′-bis(*p*-nitrostyrenyl)piperazine (III), N,N′-bis(*p*-phenylalanyl)piperazine (IV), N,N′-bis(*p*-methanolylphenyl)piperazine (V), Schiff base of I with 3,4,5,-trimethoxyaniline (VI), N,N-diethylamino-ethylenediamino derivative of the azlactone of I (VII), oxime of I (VIII), 3,4,5-trimethoxyhippurylazlactone of I (IX), bithionol, and hexachlorophene. All compounds were prepared in 1% concentration in petrolatum. The patch tests were removed at 24 hr and 2+ reactions consisting of erythema and edema were present at all sites except with compounds IV, VIII, bithionol, and hexachlorophene. One of each duplicate patch-test site was then exposed to ultraviolet light from the previously mentioned light source for a period of 20 sec. Twenty-four hours later, there was more marked erythema and edema in the patch-test sites exposed to ultraviolet light than in the patch-test sites that were not exposed. Compounds IV, VIII, hexachlorophene, and bithionol remained negative. The patch-test sites were then examined 24 hr later. At this time the areas which were not exposed to ultraviolet light were almost completely clear while those patch-test areas receiving exposure to ultraviolet light continued to show marked erythema and edema.

Course.—The patient was instructed to avoid contact with I and related compounds and to avoid undue exposure to ultraviolet light. During the next few weeks the dermatitis completely cleared. Several months later there was a brief recurrence of the dermatitis when the patient was again exposed to the above-mentioned compounds for a short period of time.

Discussion. It is known that photosensitivity may be produced in man or animals by exposure to many chemical substances. Coal tar and petroleum products, sulfonamides, sulfonylureas, chlorothiazides, phenothiazines, tetracyclines, griseofulvin, furocoumarins, hexachlorophene, bithionol, and the halogenated salicylanilides are some of the agents which may induce sensitivity to light. To our knowledge this is the first reported occurrence of photosensitivity in man secondary to skin contact with piperazine compounds. It was possible to identify the photosensitizing compounds through the use of patch-testing and photopatch-testing techniques. Further investigation is warranted to ascertain the photosensitizing potential of other piperazine derivatives.

Experimental Section

N,N′-Bis(phenyl)piperazine was prepared by the procedure of Pratt and Young.[6]

N,N′-Bis(*p*-formylphenyl)piperazine (I).—A mixture of 45 g (0.19 mole) of N,N′-bis(phenyl)piperazine and 90 g (1.23 moles) of N,N-dimethylformamide was stirred thoroughly and cooled in an ice bath. $POCl_3$ (225 g, 1.45 moles) was added dropwise from a dropping funnel during 90 min. The temperature of the mixture was not allowed to rise above 20°. The resulting, orange mixture was heated with stirring on a steam bath for another 90 min, then poured over crushed ice. This mixture was stirred and neutralized carefully with cold, 20% NaOH. The yellow product was filtered, washed (neutral to litmus) with cold water, and dried. Recrystallization from ethanol gave 51 g (91%) of white, feathery crystals mp 205°(uncor) (Fisher-Johns).

Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.46; H, 6.12; N, 9.53. Found: C, 72.91; H, 6.22; N, 9.63.

The **oxime** of I was prepared by refluxing a mixture of 3.5 g (0.025 mole) of hydroxylamine hydrochloride, 5 g (0.021 mole) of I, 15 ml of pyridine, and 25 ml of commercial absolute ethanol for 1 hr. The solvents were removed by evaporation in a current of air under a hood. The crude oxime, on recrystallization from ethanol, yielded 5 g (90%) of white crystals, mp 255° (uncor).

Anal. Calcd for $C_{18}H_{20}N_4O_2$: C, 66.7; H, 6.18; N, 17.28. Found: C, 67.07; H, 6.32; N, 17.46.

As mentioned above, the toxicity of I prompted us to abandon the project. Therefore, purification and analysis of several derivatives were not attempted.

(5) O. F. Jillson and W. L. Curwen, *Arch. Dermatol.*, **80**, 678 (1959).

(6) D. S. Pratt and C. O. Young, *J. Am. Chem. Soc.*, **40**, 1428 (1918).