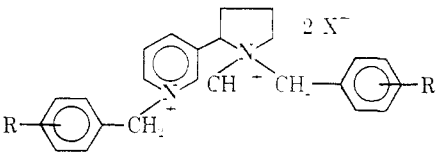
Related bisbenzyl-*S*-(−)-nicotinium dihalides are listed in Table I.

TABLE I
SUBSTITUTED BISBENZYL-*S*-(−)-NICOTINIUM DIHALIDES



No.	R	Mp,[a]	Yield, %	Empirical formula
1	H	213–215	32	$C_{24}H_{28}I_2N_2$
2	*p*-Br	241–242	15	$C_{24}H_{26}Br_2I_2N_2$
3	*p*-Cl	250–251	15	$C_{24}H_{26}Cl_2I_2N_2$
4	*p*-F	255	38	$C_{24}H_{26}F_2I_2N_2$
5	*p*-NO_2	229–232	80	$C_{24}H_{26}Br_2N_4O_4$
6	*p*-CH_3	222–225	48	$C_{26}H_{32}I_2N_2$
7	*o*-CH_3	193–195	58	$C_{26}H_{32}I_2N_2$
8	*m*-CH_3	207–209	39	$C_{26}H_{32}I_2N_2$

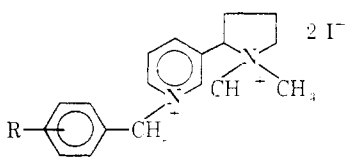
[a] Corrected melting point in °C.

Isomeric *N,N'*-methyl-substituted benzyl derivatives of *S*-(−)-nicotine were synthesized by controlled quaternizations involving reaction first on the pyridine nitrogen (N) and then on the pyrrolidine nitrogen (N'). Quaternizations on the pyridine N were effected by conducting the reactions in AcOH; the N' nitrogen was subsequently quaternized in MeOH.

***N*-*p*-Fluorobenzyl-N'-methyl-*S*-(−)-nicotinium Diiodide.**—A solution of 1.6 g (0.01 mol) of redistilled *S*-(−)-nicotine in 25 ml of glacial AcOH was mixed with 1.5 g of *p*-fluorobenzyl chloride. After 32 hr the solvent was evaporated under vacuum to yield crude and hygroscopic *N*-*p*-fluorobenzyl-*S*-(−)-nicotinium chloride which was extracted with three 25-ml fractions of Et_2O to remove unreacted materials. The crude product was dissolved in MeOH and treated with 4.3 g (0.03 mol) of MeI for 12 hr. It was chromatographed on 50 g of Woelm Activity Grade I neutral Al_2O_3 and eluted with 10–50% of MeOH–C_6H_6 to yield 2.1 g (39%) of product.

The compounds in Table II were prepared similarly.

TABLE II
SUBSTITUTED
N-BENZYL-*N'*-METHYL-*S*-(−)-NICOTINIUM DIIODIDES



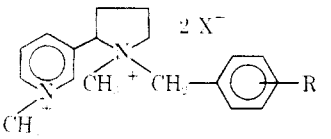
No.	R	Mp,[a]	Yield, %	Empirical formula
9	H	210–212	73	$C_{18}H_{24}I_2N_2$
10	*p*-Br	247–248	41	$C_{18}H_{23}BrI_2N_2$
11	*p*-Cl	235–237	40	$C_{18}H_{23}ClI_2N_2$
12	*p*-F	221–223	39	$C_{18}H_{23}FI_2N_2$
13	*p*-NO_2	225–227	23	$C_{18}H_{23}I_2N_3O_2$
14	*p*-CH_3	225–227	16	$C_{19}H_{26}I_2N_2$
15	*o*-CH_3	205–208	76	$C_{19}H_{26}I_2N_2$
16	*m*-CH_3	170–172	72	$C_{19}H_{26}I_2N_2$

[a] Corrected melting point in °C.

The substituted *N*-methyl-*N'*-benzyl-*S*-(−)-nicotine dihalides (Table III) were prepared in an analogous fashion by conducting the first quaternization with MeI and further treating the product with the appropriate benzyl halide. In those instances where diiodides were obtained the products resulted from halogen exchange.

Acknowledgments.—This research and the related pharmacology have been generously supported by the American Medical Association Education and Research Foundation, Committee for Research on Tobacco and Health, and the A. H. Robins Company, Richmond, Va.

TABLE III
SUBSTITUTED
N-METHYL-*N'*-BENZYL-*S*-(−)-NICOTINIUM DIHALIDES



No.	R	Mp,[a]	Yield, %	Empirical formula
17	H	190–193	41	$C_{19}H_{24}BrIN_2 \cdot 0.5H_2O$
18	*p*-Br	175–178	61	$C_{19}H_{23}Br_2IN_2$
19	*p*-Cl	217–219	30	$C_{19}H_{23}ClI_2N_2$
20	*p*-F	226–229	24	$C_{19}H_{23}FI_2N_2$
21	*p*-NO_2	209–211	93	$C_{19}H_{23}BrIN_3O_2 \cdot H_2O$
22	*p*-CH_3	156–161	57	$C_{20}H_{26}BrIN_2 \cdot 2H_2O$
23	*o*-CH_3	188–190	28	$C_{20}H_{26}I_2N_2$
24	*m*-CH_3	219–223	68	$C_{20}H_{26}I_2N_2$

[a] Corrected melting point in °C.

1-Arylsulfonylhydrazides. III. 4-Phenyl-1-arylsulfonylthiosemicarbazides and 2-Arylsulfonylhydrazone-3-phenyl-4-thiazolines[1]

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As a continuation of our investigation of derivatives of the 1-arylsulfonylhydrazides, we now wish to report the preparation of two new series, the 4-phenyl-1-arylsulfonylthiosemicarbazides (Ia–c) and the 2-arylsulfonylhydrazone-3-phenyl-4-thiazolines (IIa–l).

The 1-arylsulfonylthiosemicarbazides have been evaluated as fungicides[2,3] and as bacteriostatic agents.[3,4] Compounds containing the thiazoline ring have been

TABLE I
$ArSO_2NHNHCSNHC_6H_5$

Compd	Ar	Mp, °C,[a] dec	Yield, %[b]	Formula[c]
Ia	*p*-$CH_3OC_6H_4$	170–171	88	$C_{14}H_{15}N_3O_3S_2$
Ib	*p*-$C_2H_5OC_6H_4$	177–178	86	$C_{15}H_{17}N_3O_3S_2$
Ic	*p*-*n*-$C_3H_7OC_6H_4$	162–163	80	$C_{16}H_{19}N_3O_3S_2$

[a] The melting points were determined in open capillary tubes and are uncorrected. [b] The yields are based on the product after the first recrystallization. [c] All analytical results were within ±0.3% of the theoretical values. All compounds were analyzed for C, H, N, S.

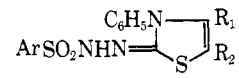
(1) C. Sunkel and M. Sánchez, *J. Med. Chem.*, **12**, 726 (1969).

(2) M. Tamayo, C. Sunkel, and R. Madroñero, *Bull. Soc. Chim. Fr.*, 248 (1964).

(3) N. V. Philips, Belgian Patent 622,688 (March 20, 1963); *Chem. Abstr.*, **64**, 1655*f* (1966).

(4) C. W. Pluijgers and A. Kaars Sijpesteijn, *Ann. Appl. Biol.*, **57**, 465 (1966); *Chem. Abstr.*, **65**, 14354*e* (1966).

TABLE II



Compd	Ar	R_1	R_2	Mp, °C[a]	Yield, %[b]	Formula	Analysis
IIa	p-$CH_3OC_6H_4$	C_6H_5	H	180–182 dec	75	$C_{22}H_{19}N_3O_3S_2$	C, H, N, S
IIb	p-$C_2H_5OC_6H_4$	C_6H_5	H	172–173 dec	77	$C_{23}H_{21}N_3O_3S_2$	C, H, N, S
IIc	p-n-$C_3H_7OC_6H_4$	C_6H_5	H	163–164 dec	88	$C_{24}H_{23}N_3O_3S_2$	C, H, N, S
IId	p-$CH_3OC_6H_4$	Me	COOEt	181–182	72	$C_{20}H_{21}N_3O_3S_2$	N, S
IIe	p-$C_2H_5OC_6H_4$	Me	COOEt	187–188	84	$C_{21}H_{23}N_3O_3S_2$	C, H, N
IIf	p-n-$C_3H_7OC_6H_4$	Me	COOEt	194–195 dec	73	$C_{22}H_{25}N_3O_3S_2$	C, H, N, S

[a–c] See footnotes in Table I.

reported as antituberculous[5,6] and antibacterial[7] agents. Compounds Ia, Ib, Ic, and Id all gave 100% control of *Meloidogne* spp at an application rate corresponding to 29.18 kg/acre.[8] Compound Ib gave 90% control of *Puccinia sorghi* when applied sumultaneously to foliage at 500 ppm and to soil at 14.6 kg/acre.[8]

Experimental Section

1-Arylsulfonyl-4-phenylthiosemicarbazides (I).—The appropriate 1-arylsulfonylhydrazide (4 mmol) was dissolved in 95% EtOH (20 ml), followed by addition of phenyl isocyanate (5.4 g, 4 mmol). Refluxing for 30 min followed by cooling of the solution gave a white, crystalline solid that was recrystallized from MeOH or EtOH.

2-Arylsulfonylhydrazone-3-phenyl-4-thiazolines (II).—The appropriate I (5 mmol) was dissolved in DMF (25 ml), and 5 mmol of α-bromoacetophenone (1 g) or ethyl α-chloroacetoacetate (0.82 g) was added. The solution was heated 30 min on a steam bath, the dark red liquid was chilled, and 3 N NH_4OH was added to bring it to pH 8. Addition of H_2O (100 ml) gave the product as a greenish powder which was washed several times with H_2O and recrystallized from EtOH.

Acknowledgment.—We thank Dr. Juan Estevan of the University of Barcelona for elemental analyses and also the Diamond Shamrock Corp. for generous supplies of several reagents.

(5) P. C. Eisman, E. A. Konopka, T. Gisi, R. H. Mizzoni, and R. L. Meyer, *Ann. Rev. Tuberc. Pulmonary Dis.*, **77**, 703 (1958); *Chem. Abstr.*, **53**, 5494*i* (1959).

(6) R. H. Mizzoni and P. C. Eisman, *J. Amer. Chem. Soc.*, **80**, 3471 (1958).

(7) I. Ishii, M. Katagiri, M. Sakazume, and T. Misato, *Nippon Nogei Kagaku Kaishi*, **40**, 437 (1968); *Chem. Abstr.*, **66**, 9270w (1967).

(8) Personal communication from Mr. Norman M. Pollack, Diamond Shamrock Corp.

An Aminopyrimidine Steroid[1]

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Thus far, only two steroids where ring A is a pyrimidine ring capable of tautomeric forms have been reported.[3] This work describes the first amino analog of this type.

Experimental Section[4]

17β-Acetoxy-2,4-diaza-1-hydroxy-3-methylamino-1,3,5(10)-estratriene.—A solution of 50 mg of methyl 17β-acetoxy-1,5-seco-2,3,4-trisnorestran-5-on-1-oate,[3,5] 100 mg of methylguanidine sulfate, and 150 mg of anhydrous NaOAc in 5 ml of anhydrous EtOH was refluxed 96 hr. The steroids were recovered from the H_2O-diluted mixture with $CHCl_3$, then dissolved in 2 ml of glacial HOAc and refluxed for 16 hr. The material was again recovered with $CHCl_3$ after H_2O dilution of the reaction. Chromatography of the resultant mixture of starting material and product on a silica tlc plate (50% EtOAc–$CHCl_3$) gave 16 mg of product. Recrystallization from EtOAc gave pure material, mp 290 dec; ν_{max} 3460, 3340, 3230, 1720, 1635, 1610, 1570, 1515 cm^{-1}; λ_{max} 234, 290 mμ; λ_{max} (acid) 230, 261 mμ. *Anal.* ($C_{19}H_{27}N_3O_3$) N.

(3) D. M. Piatak and E. Caspi, *Steroids*, **3**, 631 (1964); E. Caspi and D. M. Piatak, *Experientia*, **19**, 465 (1963).

(4) Melting points are corrected. When analyses are indicated by the symbol for the element, analytical results obtained for those elements were within ±0.4% of the theoretical values. Uv spectra were taken in MeOH or MeOH with 2 N HCl added (0.1 ml/5 ml).

(5) E. Caspi, P. K. Grover, D. M. Piatak, and Y. Shimizu, *J. Chem. Soc.*, 3052 (1965).

Antituberculous Schiff Bases

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Schiff's bases formed by the condensation of isoniazide [I] with various benzaldehydes are reported to possess antituberculous activity.[1] We have prepared additional Schiff's bases (benzylideneisonicotinoyl hydrazones) which were tested for antituberculous activity by the technique of Doub and Youmans.[2]

Experimental Section

Preparation of Schiff's bases.—Isoniazide (1 g) was dissolved in EtOH (30 ml) and to it was added aldehyde[3] (1.3 g) in 20 ml of EtOH. The mixture was refluxed on a steam bath. In some cases, the compound separated while hot, in others on cooling or on dilution with H_2O. Most of the compounds were pale yellow and crystallized from EtOH.

(1) This work was supported by Public Health Service Grants A-5326 and CA-07137 and Niv Deans Fund.

(2) Recipient of Career Program Award CA-K3-16614 from the National Cancer Institute.

(1) M. Negwer, "Organisch-Chemische, Arzneimittel und ihre Synonyma," Akademie Verlag, Berlin, 1959, pp 199–200.

(2) L. Doub and G. P. Youmans, *Amer. Rev. Tuberc.*, **61**, 407 (1950).

(3) S. R. Agrawal, V. B. Desai, H. C. Kaushik, M. S. Khan, and J. R. Merchant, *J. Indian Chem. Soc.*, **39**, 759 (1962).