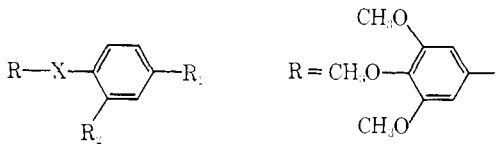
TABLE I



No.	X	R_1	R_2	Yield, %	Crystn solvent	Mp, °C,[a] or bp, °C (mm)	Formula[b]
1	S	NO_2	H	28.0	MeOH	123–124	$C_{15}H_{15}NO_4S$
2	SO_2	NO_2	H	90.0	AcOH–H_2O (80:20)	183–185	$C_{15}H_{15}NO_6S$
3	SO_2	NH_2	H	68.4	MeOH	218–220	$C_{15}H_{17}NO_5S$
4	SO_2	$N(COCH_3)_2$	H		MeOH	170–172	$C_{19}H_{21}NO_7S$
5	S	NO_2	NO_2	41.0	AcOH	203–205	$C_{15}H_{14}N_2O_7S$
6	S	NH_2	NH_2	91.4	MeOH	123–124.5	$C_{15}H_{18}N_2O_3S$
7	SO_2	$NH(COCH_3)$	$N(COCH_3)_2$		EtOH	243–245	$C_{21}H_{24}N_2O_8S$
8	SO_2	NH_2	NH_2	23.6	EtOH	191–192	$C_{15}H_{18}N_2O_5S$
9	C=NH	F	H·HCl	32.0	*i*-PrOH	197.5–199	$C_{16}H_{16}FNO_3$·HCl
10	CO	F	H	81.0	Cyclohexane	87–89	$C_{16}H_{15}FO_4$
11	CO	N_3	H	44.8	Cyclohexane	89–90	$C_{16}H_{15}N_3O_4$
12	CO	NH_2	H	81.0	C_6H_6	155–156	$C_{16}H_{17}NO_4$
13	CH_2	NH_2	H	40.0		155–160 (0.3)	$C_{16}H_{19}NO_3$
14	R———S———S———R				EtOH	141–143	$C_{18}H_{22}O_6S_2$

[a] All melting points are uncorrected. [b] Compounds **1–7**, **9**, **11–13** were analyzed for C, H, N; **8** was analyzed for N; and **10** and **13** were analyzed for C, H. All analyses were within ±0.4% of calculated values except **4**. C: calcd, 56.01; found, 56.43; and **11**, N: calcd, 13.41; found, 12.44; 12.48.

2-Acetylamino-4-diacetylamino-3',4',5'-trimethoxydiphenyl sulfone (**7**) was prepared by acetylating **6** in refluxing Ac_2O, removing Ac_2O under reduced pressure, and oxidizing the residue with H_2O_2 according to the procedure given for **2** except that the reaction mixture was evaporated to dryness under reduced pressure (bath temperature *ca.* 60°), the residue treated with H_2O, and the product removed by filtration and purified by crystallization.

2,4-Diamino-3',4',5'-trimethoxydiphenyl sulfone (**8**) was prepared by the hydrolysis of **7** with 6 *N* HCl.

4-Fluoro-3',4',5'-trimethoxybenzophenone Ketimine Hydrochloride (**9**).—The Grignard reagent of *p*-fluorobromobenzene (73.5 g, 0.42 mol) with 9.2 g (0.4 g-atom) of Mg was prepared in 300 ml of Et_2O. A solution of 3,4,5-trimethoxybenzonitrile (50.0 g, 0.26 mol) in 150 ml of dry THF was added to it slowly. The mixture was then brought to reflux and the solvent was replaced by an equivalent amount of PhMe and refluxed for 16 hr. It was cooled, gassed with NH_3 for **1** hr, and filtered hot, the filtrate concentrated to an oil, and the oil dissolved in Et_2O and converted into the HCl salt.

4-Fluoro-3',4',5'-trimethoxybenzophenone (**10**).—A mixture of **9** (40.0 g, 0.132 mol) and 350 ml of 6 *N* HCl was heated on a steam bath for 4 hr. The mixture was cooled and extracted with Et_2O to obtain the oily product which solidified on standing.

4-Azido-3',4',5'-trimethoxybenzophenone (**11**).—A mixture of **10** (5.8 g, 0.02 mol), NaN_3 (3.3 g, 0.05 mol), 60 ml of DMSO, and 15 ml of H_2O was heated with stirring at 100–110° for 16 hr. The mixture was cooled and diluted with H_2O, the product extracted with Et_2O, and the Et_2O extracts were worked up as usual.

4-Amino-3',4',5'-trimethoxybenzophenone (**12**).—A mixture of **11** (3.13 g, 0.01 mol), 0.4 g of 5% Pd–C, and 75 ml of Me_2CO was hydrogenated at room temperature and atmospheric pressure. After 3 hr the mixture was filtered and concentrated to give a solid product.

4-Amino-3',4',5'-trimethoxydiphenylmethane (**13**).—A mixture of **12**·HCl (5.0 g, 0.0155 mol), 0.4 g of 5% Pd–C, 100 ml of MeOH, and 10 ml of AcOH was hydrogenated at 5 kg/cm² for 5 hr at room temperature. The mixture was filtered and the filtrate was concentrated to a solid, treated with NaOH solution, and extracted with CH_2Cl_2. The CH_2Cl_2 extract, on the usual work-up, gave a syrup which was purified by distillation.

Acknowledgment.—This work was supported by U. S. Army Medical Research and Development Command under Research Contract No. DA-49-193-MD-2869, and is Contribution No. 718 from the Army Research Program on Malaria.

Synthetic Trypanocides. I. Substituted 1,2,3,4-Tetrahydrocarbazoles[1]

JORGE GALLO PECCA AND SEM M. ALBONICO

Department of Organic Chemistry, School of Pharmacy and Biochemistry, University of Buenos Aires, Argentina

Received October 6, 1969

The high incidence of the Chagas–Mazza disease (South American trypanosomiasis) among blood donors in some places makes it difficult to reject infected blood.[2] Therefore it is necessary to add to the blood a trypanocidal substance that must be water soluble, compatible with the anticoagulant solution, and resistent to sterilization, and which prevents infection of the patient by the blood. So far only colorants[3] have been used for this purpose, but these have many disadvantages.[4]

Since some substituted 1,2,3,4-tetrahydrocarbazoles are active against *Trypanosoma cruzi*,[5] a series of related new compounds fulfilling the above requirements were prepared in order to test their trypanocidal activity (Table I).

Chemistry.—The 1,2,3,4-tetrahydrocarbazole (THC) and the 6-substituted THC (I) were prepared by the Fisher indole synthesis[6] with the modification described in the Experimental Section for 6-iodo-THC.

(1) This investigation was supported by grants from the Instituto Nacional de Farmacología y Bromatología and CNICT.

(2) J. A. Cerisola and J. O. Lazzari, Abstracts, Segundas Jornadas Entoepidemiológicas Argentinas, 1967, p 203.

(3) J. Kloetzel, *Rev. Inst. Med. Trop. Sao Paulo*, **3**, 254 (1961).

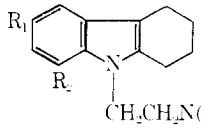
(4) G. C. Vilaseca, J. A. Cerisola, J. A. Olarte, and A. Zothner, *Vox Sanguinis*, **11**, 711 (1966).

(5) U. Hörlein, German Patent 930,988 (1955); *Chem. Abstr.*, **52**, 17288 (1958).

(6) C. U. Rogers and B. B. Corson, "Organic Synthesis," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 884.

TABLE I

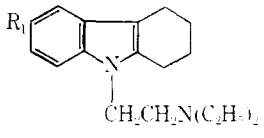
SUBSTITUTED 1,2,3,4-TETRAHYDROCARBAZOLE FUMARATES



II

No.	R_1	R_2	Yield, %	Mp, °C	Formula[a]	Minimal oseid[b] concentration, μg/ml
1[c]	H	H	42	183–184	$C_{18}H_{26}N_2 \cdot C_4H_4O_4$	350
2	F	H	36	168–170	$C_{18}H_{25}FN_2 \cdot C_4H_4O_4$	350
3[d]	Cl	H	38	182–184	$C_{18}H_{25}ClN_2 \cdot C_4H_4O_4$	320
4	Br	H	37	184–185	$C_{18}H_{25}BrN_2 \cdot C_4H_4O_4$	360
5	I	H	41	192–194	$C_{18}H_{25}IN_2 \cdot C_4H_4O_4$	700
6	CH_3	H	38	188–189	$C_{19}H_{28}N_2 \cdot C_4H_4O_4$	370
7	OCH_3	H	35	158–170	$C_{19}H_{28}N_2O \cdot C_4H_4O_4$	360
8	H	F	30	165–167	$C_{18}H_{25}FN_2 \cdot C_4H_4O_4$	710
9	H	Cl	41	154–155	$C_{18}H_{25}ClN_2 \cdot C_4H_4O_4$	80
10	H	Br	35	143–144	$C_{18}H_{25}ClN_2 \cdot C_4H_4O_4$	175
11	H	I	41	153–154	$C_{18}H_{25}IN_2 \cdot C_4H_4O_4$	340
12	H	CH_3	30	163–165	$C_{19}H_{28}N_2 \cdot C_4H_4O_4$	320
13	H	OCH_3	35	153–154	$C_{19}H_{28}N_2O \cdot C_4H_4O_4$	730

[a] All compounds were analyzed for C, H, N and analytical results obtained for those elements are within 0.5% of theoretical values. The compounds were recrystallized from EtOH, except **6** from absolute EtOH. The uv, ir, and nmr spectra are in agreement with the proposed structures. Melting points were taken in capillary and are uncorrected. [b] Concentrations were considered to be useful when all trypanosomes were killed after no longer than 16 hr. These tests[8] were performed by Dr. M. Alvarez, Instituto de Investigacion de la Enfermedad de Chagas. [c] The base has been reported by J. W. Cusic and C. A. Dornfeld, U. S. Patent 2,541,213 (1951). [d] The base has been reported. See ref 5.



I

The 8-substituted-THC's (II) which are more difficult to prepare were obtained by the Borsche synthesis as modified by Perkin and Plant.[7]

The procedure described by Barnes, *et al.*,[8] for preparing 8-bromo-THC did not yield substantial quantities of pure material, and therefore other reaction conditions were used to prevent oxidation. These are described in the Experimental Section.

Experimental Section

8-Methoxy-THC was purified through the picrate from which the base was recovered as described by Bobbitt.[9]

6-Iodo-1,2,3,4-tetrahydrocarbazole.—To a stirred solution of 0.5 ml (0.005 mol) of cyclohexanone in 2 ml of AcOH heated to reflux, 1.1 g (0.005 mol) of 4-iodophenylhydrazine was added during 1 hr. After being refluxed with stirring for 1 hr, the product was collected on a filter and washed with 5% $NaHSO_3$ soln. Recrystallization from MeOH–H_2O gave 0.84 g (70%) of cream-colored needles, mp 155–156°. *Anal.* ($C_{12}H_{12}IN$) C, H, N.

8-Iodo-1,2,3,4-tetrahydrocarbazole. To a stirred solution of 2.7 g (0.01 mol) of 2-iodophenylhydrazine·HCl in 25 ml of H_2O 1 ml (0.01 mol) of cyclohexanone and 1.25 ml of saturated solution of NaAcO were added. After being stirred for 15 min, the solution was extracted (Et_2O, 100 ml). The solvent was dried and evaporated under vacuum. The solid residue was dissolved in 20 ml of AcOH, and the soln was heated to 100° in a sealed ampoule under N_2 for 2 hr, poured into 150 ml of 25% NH_4OH, cooled, and extracted (Et_2O, 200 ml). The combined extracts were dried ($MgSO_4$) and evaporated under vacuum leaving an oily residue that was sublimed (170°, 4 μ) yielding 1.52 g (51%) of off-white crystals, mp 56–60°. *Anal.* ($C_{12}H_{12}IN$) C, H, N.

By the same procedure 8-bromo-1,2,3,4-tetrahydrocarbazole was obtained: yield 50% of white crystals: mp 63–64° (lit.[9] mp 57°). *Anal.* ($C_{12}H_{12}BrN$) C, N, H.

Preparation of the Compounds in Table I.—A mixture of 0.01 mol of the respective substituted 1,2,3,4-tetrahydrocarbazole and 0.5 g of $NaNH_2$ in 20 ml of xylene was stirred at 140° bath temperature for 2 hr. Then 0.5 g of $NaNH_2$ and 0.01 mol of 2-diethylaminoethyl chloride·HCl were added. The mixture was refluxed for 1 hr under the same conditions and, after cooling, was poured into H_2O (25 ml), and 1 *N* HCl was added to pH 1. The aqueous phase was made alkaline (Na_2CO_3) and extracted (Et_2O, 200 ml). The combined extracts were dried and evaporated. The oily residue was dissolved in hot EtOH (5 ml) and 1.16 g (0.01 mol) of fumaric acid was added. After cooling the crystalline fumarates were filtered and worked up as usual.

The alkylation of the unsubstituted THC proceeds better using potassium *t*-butoxide in DMSO (55% yield).

Acknowledgment.—The authors wish to thank Drs. J. A. Cerisola, M. J. Vernengo, and E. A. Ruveda for helpful discussions of this work.

(7) W. H. Perkin and S. G. P. Plant, *J. Chem. Soc.*, 1825 (1921).
(8) C. S. Barnes, K. H. Pausacker, and W. E. Badcock, *ibid.*, 730 (1951).
(9) J. M. Bobbitt, *J. Org. Chem.*, **22**, 1729 (1957).