ducklings were treated orally with 50–500 μg of II per duckling biweekly for 2 and 4 weeks. None of the ducklings died within the experimental period. In the other experiment, 5 rats were injected ip with 500 μg of II weekly for 6 consecutive weeks. Again, none of the rats died within the period. Histological examination showed no alteration in the liver, kidney, heart, and brain of the ducklings and rats.

Experimental Section

5,7-Dihydroxy-4-(2-methoxycarbonylethyl)coumarin.—A modification of the procedure of Asao, *et al.*,[12] was used. Phloroglucinol·$2H_2O$ (1.6 g) and 2 g of ethyl methyl β-ketoadipate[13] were mixed with 25 ml of AcOH. Dry HCl was bubbled through the mixt until all of the phloroglucinol was dissolved. The soln stood at room temp overnight. The yellowish needles which formed were collected by filtration. The filtrate, after standing several days, yielded additional needles. The crystals were combined, washed with a small amount of H_2O, and dried. Recrystn from MeOH–H_2O gave 2.2 g (84%) of crystals, mp 254–256°. The crude material was used in the next step without further purification.[14]

5,7-Dihydroxycyclopentenone[2,3-*c*]coumarin.—The cyclization was carried out by 2 methods: (a) crude 5,7-dihydroxy-4-(2-methoxycarbonylethyl)coumarin was hydrolyzed with aq NaOH, and the product was pptd by the addition of excess HCl soln; heating of this product in Dowtherm A yielded 5,7-dihydroxycyclopentenone[2,3-*c*]coumarin; (b) crude ester (2 g) was suspended in 50 ml of Dowtherm A. The mixt was heated at 253–255° for 1 hr, and after cooling, a greyish ppt formed. The solid was filtered, washed with cyclohexane, and dried. Recrystn from DMF–H_2O yielded 1.2 g of white plates, mp 318–320° dec. *Anal.* ($C_{12}H_8O_5$) C, H, O.[14] The yield from the cyclization reaction was 68%.

5,7-Dibenzyloxycyclopentenone[2,3-*c*]coumarin (II).—The ketone (2.2 g) was suspended in 22 ml of THF (distd from Na); NaH (1.5 g) was added, and the mixt was stirred at room temp for 24 hr. THF was removed under reduced pressure, and 22 ml of DMF was added to the solid residue. To the soln was added with stirring 2.3 g of $PhCH_2Cl$, and the mixt was stirred at room temp for 36 hr. The resulting soln was mixed with 25 ml of cold H_2O and extd with Et_2O (4 × 5 ml). Evapn of the combined Et_2O soln produced a greenish yellow solid. This was washed with a small amount of MeOH–Et_2O and dried. The residue was chromatographed on alumina eluting with $CHCl_3$. The first 20 ml of eluate was collected and evapd. The residue was recrystd from $CHCl_3$–MeOH and $CHCl_3$–Et_2O until colorless, silky needles were obtained. The yield was 580 mg (15%), mp 111.5–112°. *Anal.* ($C_{26}H_{20}O_5$) C, H.[14]

(13) E. C. Taylor and A. McKillop, *Tetrahedron*, **23**, 897 (1967).

(14) Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Spectral data (ir and uv) were consistent with the proposed structures.

Synthetic Trypanocides. 2. Substituted 5,6-Dihydro[*c*]benzocarbazoles[1]

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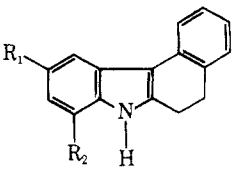
We have previously reported[2] the trypanocidal activity of several substituted 1,2,3,4-tetrahydrocarbazoles. Although the level of *in vitro* activity obtained with some of these compounds was superior to the activity of the dyes[3] clinically used to prevent the infection of the patient by the blood of donors with Chagas-Mazza disease, the search for more active compounds showed that **14** was also more effective than the dyes.

Therefore, a series of substituted 5,6-dihydro[*c*]-benzocarbazoles (DHBC) was prepared (Tables I and II). The DHBC's have been little studied, and none of the substituted compounds in which we are interested have been previously prepared. They fulfill the stability requirement already described,[2] and the acute toxicity is low. No deaths resulted when doses of 1000 mg/kg of the more active compds **29** and **32** were given to white mice either orally or ip. This dose is 10^4-fold more than is usually required in an average blood transfusion.[4] Furthermore, it was established that in compds containing an N-substituted indole nucleus, Cl and MeO substituents in the benzenoid portion of the aromatic ring provide higher activities against *Trypanosoma cruzi*.

Chemistry.—The DHBC's were prepared by the Fisher indole synthesis and by a modified procedure described in the Experimental Section. The unsubstituted DHBC has been previously prepared by Ghigi[5] in low yield and purity; however, under our conditions the yield was 80%. A series of 10-substituted DHBC's were prepared in good yields from 4-substituted phenylhydrazines; under the same conditions, the 2-substituted phenylhydrazines gave a poor yield or none of the desired DHBC. Such a difference in reactivity in the Fisher reaction between 4- and 2-substituted phenylhydrazines has been previously reported by

TABLE I

SUBSTITUTED 5,6-DIHYDRO[*c*]BENZOCARBAZOLES[a]



No.	R_1	R_2	% yield	Mp, °C	Formula
1[b]	H	H	80	102–103	$C_{16}H_{13}N$
2	F	H	50	148–150	$C_{16}H_{12}FN$
3	Cl	H	85	135–136	$C_{16}H_{12}ClN$
4	Br	H	60	158–160	$C_{16}H_{12}BrN$
5	I	H	60	142–144	$C_{16}H_{12}IN$
6	CH_3	H	60	143–145	$C_{17}H_{15}N$
7	OCH_3	H	96	154–155	$C_{17}H_{15}NO$
8[c]	H	F	45	143–145	$C_{16}H_{12}FN \cdot C_6H_3N_3O_7$
9	H	Cl	50	105–106	$C_{16}H_{12}ClN$
10[d]	H	Br	40	142–144	$C_{16}H_{12}BrN$
11	H	I	50	161–163	$C_{16}H_{12}IN$
12[e]	H	CH_3	60	146–147	$C_{17}H_{15}N$
13[f]	H	OCH_3	50	140–142	$C_{17}H_{16}NO$

[a] All compds were analyzed for C, H, N, and the anal. results obtained for these elements were within 0.3% of the theoretical values. The uv, ir, nmr, and mass spectra also were in agreement with the proposed structures. Melting points were taken in capillaries and are uncorrected. All compds except **10**, **12**, and **13** were recrystd from EtOH. [b] Lit. 97–98°; see E. Ghigi, *Gazz. Chim. Ital.*, **60**, 194 (1930). [c] This was an oil and was analyzed as the picrate which was recrystd from EtOH. [d] Sublimed (135°, 100 μ). [e] Sublimed (120°, 50 μ). [f] Sublimed (100°, 50 μ).

(1) This investigation was supported by grants from the Instituto Nacional de Farmacologia y Bromatologia and C.N.I.C.T. (Argentina).

(2) J. Gallo Pecca and S. M. Albonico, *J. Med. Chem.*, **13**, 327 (1970).

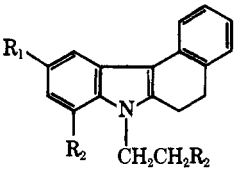
(3) J. Kloetzel, *Rev. Inst. Med. Trop. Sao Paulo*, **3**, 254 (1961).

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

(5) E. Ghigi, *Gazz. Chim. Ital.*, **60**, 194 (1930).

TABLE II

SUBSTITUTED 5,6-DIHYDRO[c]BENZOCARBAZOLE FUMARATES[a]



No.	R_1	R_2	R_3	Mp, °C	% yield	Formula	Minimal useful[b] concentration, μg/ml
14	H	H	$N(Et)_2$	164–166	60	$C_{22}H_{26}N_2 \cdot C_4H_4O_4$	160
15	F	H	$N(Et)_2$	158–160	70	$C_{22}H_{25}FN_2 \cdot C_4H_4O_4$	40
16	Cl	H	$N(Et)_2$	170–172	75	$C_{22}H_{25}ClN_2 \cdot C_4H_4O_4$	300
17	Br	H	$N(Et)_2$	156–158	75	$C_{22}H_{25}BrN_2 \cdot C_4H_4O_4$	c
18	I	H	$N(Et)_2$	160–162	60	$C_{22}H_{25}IN_2 \cdot C_4H_4O_4$	c
19	CH_3	H	$N(Et)_2$	169–171	65	$C_{23}H_{28}N_2 \cdot C_4H_4O_4$	150
20	OCH_3	H	$N(Et)_2$	148–150	60	$C_{23}H_{28}N_2O \cdot C_4H_4O_4$	30
21	H	F	$N(Et)_2$	156–158	55	$C_{22}H_{25}FN_2 \cdot C_4H_4O_4$	80
22	H	Cl	$N(Et)_2$	176–178	80	$C_{22}H_{25}ClN_2 \cdot C_4H_4O_4$	40
23	H	Br	$N(Et)_2$	182–183	50	$C_{22}H_{25}BrN_2 \cdot C_4H_4O_4$	350
24	H	I	$N(Et)_2$	158–160	60	$C_{22}H_{28}N_2 \cdot C_4H_4O_4$	c
25	H	CH_3	$N(Et)_2$	180–182	60	$C_{23}H_{28}N_2 \cdot C_4H_4O_4$	80
26	H	OCH_3	$N(Et)_2$	182–183	70	$C_{23}H_{28}N_2O \cdot C_4H_4O_4$	160
27	F	H	$N(Me)_2$	188–189	60	$C_{20}H_{21}FN_2 \cdot C_4H_4O_4$	40
28	F	H	NC_5H_{10}[d]	226–228	50	$C_{23}H_{25}FN_2 \cdot C_4H_4O_4$	140
29	H	Cl	$N(Me)_2$	184–186	60	$C_{20}H_{21}ClN_2 \cdot C_4H_4O_4$	20
30	H	Cl	NC_5H_{10}[d]	190–192	75	$C_{23}H_{25}ClN_2 \cdot C_4H_4O_4$	80
31	OCH_3	H	$N(Me)_2$	160–162	50	$C_{21}H_{24}N_2O \cdot C_4H_4O_4$	80
32	OCH_3	H	NC_5H_{10}[d]	156–158	50	$C_{24}H_{28}N_2O \cdot C_4H_4O_4$	20

[a] All compds were analyzed for C, H, N, and the anal. results obtained for these elements were within 0.3% of theoretical values. All compds were recrystd from EtOH. The uv, ir, nmr, and mass spectra (of the bases) are in agreement with the proposed structures. Melting points were taken in capillaries and are uncorrected. [b] J. Gallo Pecca and S. M. Albonico, *J. Med. Chem.*, **13**, 327 (1970); these tests were performed by Dr. M. Alvarez, Instituto de Investigaciones de la Enfermedad de Chagas. [c] Not resistant to sterilization; see footnote *b*. [d] Piperidino.

several workers.[1,6,7] Electronic effects are not of major importance, since this difference is observed irrespective of the nature of the substituents. Hence the relatively low reactivity of the 2-substituted compounds has to be attributed to the position and not to the nature of the substituents.

Experimental Section

5,6-Dihydrobenzo[c]carbazole and 10-Substituted DHBC.—A soln of the 4-substituted phenylhydrazine (0.01 mole) and β-tetralone (0.01 mole) in 15 ml of EtOH and 0.5 ml of HOAc was kept at 20° for 1 hr. The cryst solid was filtered, dissolved in 10 ml of HOAc satd with HCl, and refluxed for 15 min. The pptd 10-substituted DHBC was filtered and worked up as usual.

8-Substituted 5,6-Dihydrobenzo[c]carbazoles.—A soln of 2-substituted phenylhydrazine (0.01 mole) and β-tetralone (0.01 mole) in EtOH–HOAc (20 ml, 3:1) was heated to 60° for 15 min. On cooling, the phenylhydrazine crystd out. The solid was filtered and dissolved in 10 ml of HOAc with 10 mg of di-*tert*-butyl-*p*-cresol. The soln was satd with HCl and heated to 140° in a sealed ampoule under N_2 for 1 hr, cooled, poured into 100 ml of 25% NH_4OH, and extd (BzH, 200 ml). The combined exts were dried ($MgSO_4$) and evapd under vacuum, leaving an oil; the oil was dissolved in C_6H_6–MeOH (19:1) and filtered through a column with 50 g of silica gel. The eluent was worked up as usual.

8-Fluor-DHBC was purified through the picrate from which the base was removed as described by Bobbitt.[8]

Preparation of Compounds in Table II.—A mixt of 0.005 mole of the respective DHBC and 0.25 g of $NaNH_2$ in 10 ml of xylene was stirred at 140° (bath temp) for 2 hr. The 0.25 g of $NaNH_2$ and 0.01 mole of 2-diethylaminoethyl chloride·HCl (or the corresponding 2-substituted ethyl chloride·HCl for compounds **27–32**) were added. The mixt was refluxed for 1 hr under the same conditions and, after cooling, was poured into H_2O (10 ml), and HOAc was added to pH 3. The aq phase was made alk (Na_2CO_3) and extd (Et_2O, 200 ml). The combined exts were dried and evapd. The oily residue was dissolved in hot EtOH (1.5 ml), and 0.58 g of fumaric acid was added. After cooling, the crystalline fumarates were filtered and worked up as usual.

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(6) B. M. Barclay and N. Campbell, *J. Chem. Soc.*, 530 (1945).
(7) C. E. Dalgliesh and F. G. Mann, *ibid.*, 653 (1947).
(8) J. M. Bobbitt, *J. Org. Chem.*, **22**, 1729 (1957).

Nitrofuryl Heterocyclics. 2

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In the previous paper of this series[1] it was shown that nitrofurans containing partial structure Ia possessed marked antibacterial activity. This note is concerned with the synthesis and biological evaluation of some [5-(5-nitro-2-furyl)-1,3,4-thiadiazol-2-yl]amides and -ureas (II) (*i.e.*, containing partial structure Ib).

Chemistry.—The preparation of intermediate urea **1** and the alkylation of this compound and 2-acetamido-

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(1) For the previous paper in this series see M. D. Closier and P. J. Islip, *J. Med. Chem.*, **13**, 638 (1970).