frared spectrophotometer, Model IR-20, at Matheson Coleman and Bell, Norwood, Ohio. Elementary analyses were made by Galbraith Laboratories, Inc., Knoxville, Tenn.

**δ-Guanidinovaleric Acid (4).** To the solution of *S*-ethylisothiourea dihydrogen sulfate (10.0 g, 0.05 mol) dissolved in 25 ml of 2 *N* NaOH was added 6.0 g (0.05 mol) of δ-aminovaleric acid dissolved in 10 ml of $H_2O$ under ice cooling and vigorous stirring. The mixture stood for 5 hr in the ice bath and was kept overnight at room temperature. The turbid solution was filtered and acidified (pH 4) with concentrated HCl. Absolute EtOH was added to the solution and the precipitate of NaCl was filtered off. The filtrate was concentrated and subjected to ion-exchange chromatography, using a 2.0 × 40 cm column of Amberlite CG-120, 200-400 mesh, pyridine form. For elution, first 500 ml of $H_2O$ and then 0.1 *M* pyridine were used. The peak quantity of 4 appeared in the effluent at approximately 1800 ml. The 4 fractions, 1600-2100 ml, were pooled and concentrated *in vacuo*. The dry residue was treated with $H_2O$-EtOH-$Et_2O$ to produce crystals: yield, 28.0%; mp 267-271°.

**ε-Guanidinohexanoic Acid (5).** *S*-Ethylisothiourea dihydrogen sulfate (10.0 g, 0.05 mol) and 6.5 g (0.05 mol) of ε-aminohexanoic acid were treated in the same way as 4 except for the following modifications. After the reaction was completed the precipitate was filtered and washed with cold $H_2O$. The crystals were then dissolved in 20 ml of 2 *N* HCl. The pH was adjusted to 8.0 by the addition of 2 *N* $NH_4OH$. After standing at 5° overnight, the white crystals were filtered and washed with cold $H_2O$ and EtOH and then dried in a vacuum desiccator: yield, 68.0%; mp 274-275°.

**Guanidinoacetyl-L-histidine Hydrate (6).** The solutions of 1.50 g (0.007 mol) of *S*-ethylisothiourea dihydrogen sulfate in 5 ml of $H_2O$ and 1.74 g (0.007 mol) of Gly-His·HCl in 3 ml of $H_2O$ were adjusted to pH 8-9 with 4 *N* NaOH. They were then mixed and kept at room temperature for a week. The cloudy suspension was filtered and the filtrate concentrated to dryness *in vacuo*. The residue, after addition of a small amount of EtOH, was dried *in vacuo*. A small amount of $H_2O$ was added to dissolve the dry residue and resulting solution was poured onto the column (2.5 cm i.d. × 30 cm Amberlite CG-120, 200-400 mesh, pyridine form). $H_2O$, 1.0 *M* pyridine, 2.0 *M* pyridine, and 1.0 *M* pyridine-0.5 *M* $NH_4OH$ were used as the effluent solutions. Each fraction was tested for ninhydrin, Pauli, and Sakaguchi reactions. The 6 fractions were pooled and concentrated to dryness *in vacuo*: crystals from $H_2O$-EtOH; yield, 69.2%; mp 108-111° dec. Hydrolysis (6 *N* HCl, 110°, 24 hr) gave 1 and His, confirmed by tlc.

**β-Guanidinopropionyl-L-histidine Hydrate (7).** *S*-Ethylisothiourea dihydrogen sulfate (5.0 g, 0.025 mol) and β-Ala-His (5.3 g, 0.025 mol) were treated in the same way as 6: yield, 38.8%; mp 121-124° dec. Hydrolysis as described above gave 2 and His (tlc).

**γ-Guanidinobutyryl-L-histidine Dihydrogen Sulfate (8).** *S*-Ethylisothiourea dihydrogen sulfate (10.0 g, 0.05 mol) and γ-Abu-His (11.0 g, 0.05 mol) were treated in the same way as 6 except for the following changes. For the final crystallization, the aqueous solution was adjusted to pH 5 with 2 *N* $H_2SO_4$ and absolute EtOH was added to form fine white crystals; yield, 51.7%; mp 119-124° dec. Hydrolysis as described gave 3 and His (tlc).

**δ-Guanidinovaleryl-L-histidine Dihydrogen Sulfate Hydrate (9).** *S*-Ethylisothiourea dihydrogen sulfate (0.8 g, 0.0037 mol) and δ-Avl-His (1.0 g, 0.0037 mol) were treated in the same way as 8: yield, 50.6%; mp 80-82° dec. Hydrolysis as above gave 4 and His (tlc).

**ε-Guanidinohexanoyl-L-histidine (10).** *S*-Ethylisothiourea dihydrogen sulfate (1.4 g, 0.0063 mol) and ε-Ahx-His (1.7 g, 0.0063 mol) were treated in the same way as 6: yield, 56.1%; mp 102-103° dec. Hydrolysis as above gave 5 and His (tlc).

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## Synthetic Trypanocides. 3. Structure-Activity Relationships†

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We have previously reported the trypanocidal activity of several substituted 1,2,3,4-tetrahydrocarbazoles[1] (THC) and dihydro[*c*]benzocarbazoles.[2] Continuing with the search for more active compounds and the establishment of a relation between chemical structure and activity, we have prepared several new compounds active against *Trypanosoma cruzi*, the parasite responsible for Chagas's disease.

In the study on structure-activity relationships, the biological effect produced by chemical modification at three regions of the compounds containing an N-substituted indole nucleus was considered, *i.e.*, the benzene ring, the alicyclic ring, and the heterocyclic ring. Previously,[2] we have found that in compounds containing an N-substituted indole nucleus, a methoxy or chlorine substituent in the benzenoid portion of the aromatic ring provides compounds with higher activity. From the several substituents checked on the aromatic nitrogen, the 2-piperidinoethyl has proven to enhance the activity both on the epimastigote and trypomastigote stage of *T. cruzi*.

Maintaining the most active structure, when the alicyclic ring was dehydrogenated, the fully aromatic compounds 6-8, although with good activity on the epimastigote stage, lose completely their activity on the hematic form.

The amount required of the more active compound 4 to prevent the transmission of the disease by an average blood transfusion is slightly below that of Crystal Violet,[3,4] with the advantage of being 20-fold less toxic and colorless. Compounds 9 and 10 and the 8-substituted 5,6-dihydrobenzo[*a*]carbazoles (DHBC) are water insoluble and cannot be checked *in vitro*. Their *in vivo* activity is low even at a high dose.

**Biological Results.** The activities reported in Table I were measured on the epimastigote stage of the Tulahuen strain of *T. cruzi* in a liquid culture medium.[5] When the same test was performed in blood, on the trypomastigote stage, the activity of 4 is 200 μg/ml and therefore only 100 mg will be required for an average transfusion. In the same conditions the activity for Crystal Violet is 250 μg/ml.

The toxicity of 4 was tested on Rockland mice weighing 18-20 g and the $LD_{50}$ was 200-220 mg/kg (ip), whereas

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**Table I**

| Compd | $R_1$ | $R_2$ | $R_3$ | Mp, °C | % yield | Formula[e] | Min[a] useful concn, μg/ml |
|---|---|---|---|---|---|---|---|
| | | | Substituted 1,2,3,4-Tetrahydrocarbazole Fumarates (A) | | | | |
| **1** | $NO_2$ | H | $N(Et)_2$ | 280–282 dec | 50 | $C_{18}H_{25}N_3O_2 \cdot C_4H_4O_4$ | 400 |
| **2** | $NO_2$ | H | $NC_5H_{10}$ | 256–259 dec | 50 | $C_{19}H_{25}N_3O_2 \cdot C_4H_4O_4$ | 250 |
| **3** | H | $OCH_3$ | $N(Me)_2$ | 196–198 | 42 | $C_{17}H_{24}N_2O \cdot C_4H_4O_4$ | 125 |
| **4** | H | $OCH_3$ | $NC_5H_{10}$ | 194–196 | 65 | $C_{20}H_{28}N_2O \cdot C_4H_4O_4$ | 70 |
| **5** | $CF_3$ | H | $NC_5H_{10}$ | 232–233 | 60 | $C_{20}H_{25}F_3N_2 \cdot C_4H_4O_4$ | 500 |
| | | | Substituted Carbazole Fumarates (B) | | | | |
| **6** | | | $N(CH_3)_2$ | 180–182 | 73 | $C_{17}H_{20}N_2O \cdot C_4H_4O_4$ | 100 |
| **7** | | | $N(C_2H_5)_2$ | 170–172 | 62 | $C_{19}H_{24}N_2O \cdot C_4H_4O_4$ | 60 |
| **8** | | | $NC_5H_{10}$ | 194–195 | 77 | $C_{20}H_{24}N_2O \cdot C_4H_4O_4$ | 40 |
| | | | Substituted 1,2,3,4-Tetrahydrocarbazoles (C) | | | | |
| **9**[b] | $CF_3$ | H | | 85–87 | 68 | $C_{13}H_{12}F_3N$ | |
| **10** | H | $CF_3$ | | | 90 | $C_{13}H_{12}F_3N$ | |
| | | | Substituted 5,6-Dihydrobenzo[*a*]carbazoles (D) | | | | |
| **11**[c] | H | | | 158–160 | 95 | $C_{16}H_{13}N$ | |
| **12** | F | | | 138–140 | 95 | $C_{16}H_{12}FN$ | |
| **13** | Cl | | | 156–158 | 90 | $C_{16}H_{12}ClN$ | |
| **14** | Br | | | 157–159 | 80 | $C_{16}H_{12}BrN$ | |
| **15**[d] | I | | | 187–189 dec | 76 | $C_{16}H_{12}IN$ | |
| **16** | $CH_3$ | | | 166–168 | 87 | $C_{17}H_{15}N$ | |
| **17** | $OCH_3$ | | | 186–188 | 84 | $C_{17}H_{15}NO$ | |
| **18** | $NO_2$ | | | 284–285 | 86 | $C_{16}H_{12}N_2O_2$ | |
| **19** | $CF_3$ | | | 278–280 | 82 | $C_{17}H_{12}F_3N$ | |

[a]Concentrations were considered to be useful when all epimastigotes were killed after no longer than 16 hr in the liquid media containing the tested compound. [b]Lit.[7] 83–84°. Sublimed (130°, 30 μ). [c]Lit. 163–164°: C. V. Rogers and B. B. Corson, *J. Amer. Chem. Soc.*, **69**, 2910 (1947). [d]It decomposed rapidly and could not be analyzed. [e]All compounds were analyzed for C, H, and N, and the analytical results obtained for these elements were within 0.4% of the theoretical values. The uv, ir, and nmr spectra also were in agreement with the proposed structures. Melting points were taken in capillaries and are uncorrected. All compounds except **9** and **10** were recrystallized from ethanol.

the dose administered to a patient with an average blood transfusion will be around 1 mg/kg. The acute toxic symptoms of 4 were those of central excitation; death occurred with respiratory paralysis. With 0.5 $LD_{50}$ (ip) tachypnea and transitory depression was observed.

Infected blood after treatment with 200 μg/ml of 4 was inoculated into white mice and no infection was detected. Controls died (100%) 15–20 days after inoculation.

The *in vivo* study of **13** was made on mice (18–20 g) infected with the MI strain of *T. cruzi* ($4 \times 10^5$), a dose that kills 90% of the control mice. In mice receiving, 2 days after infection, five daily injections (ip) of 100 mg/kg of 13, the survival increased to 60%.

## Experimental Section

The 6-substituted THC derivatives were prepared by the procedure described by Borsche[6] for 6-nitro-THC. The 6-trifluoromethyl-THC was purified by sublimation (130°, 30 μ) and the 8-methoxy-THC was purified by distillation (190°, 15 mm).

**Trifluoromethylphenylhydrazine Hydrochlorides.** $NaNO_2$ (2.1 g, $3.1 \times 10^{-2}$ mol) in water (10 ml) was added dropwise with stirring to 2-aminobenzotrifluoride (4.27 g, $3.0 \times 10^{-2}$ mol) in concentrated HCl (12 ml) at −5°. After 30 min of stirring, stannous chloride (20 g, $8.9 \times 10^{-2}$ mol) in concentrated HCl (22 ml) was added dropwise. The reaction mixture was kept 16 hr at 0°, water (100 ml) was added, and the solution was made alkaline (pH 8) (concentrated $NH_3$). The suspension was extracted ($Et_2O$, 200 ml); the combined extracts were dried and saturated with dry gaseous HCl, affording 5.8 g (90%) of crystals of mp 216–217° (lit.[7] 218°).

The 4-trifluoromethylphenylhydrazine hydrochloride was obtained in 80% yield by the same procedure: mp 203–204° (lit.[7] 206–207°).

**1-Methoxycarbazole.** A solution of 8-methoxy-THC (602 mg, 2.5 mmol) in xylene (5 ml) and 0.2 g of 30% Pd on charcoal was refluxed for 12 hr. The filtered solution was evaporated and the residue recrystallized (aqueous EtOH): yield 543 mg (90%); mp 66–68° (lit.[8] 69–70°).

**Preparation of 8-Substituted 5,6-Dihydrobenzo[*a*]carbazoles.** A solution of α-tetralone (0.02 mol) in acetic acid (12 ml) was refluxed and the 4-substituted phenylhydrazone (0.02 mol) was added during 1 hr. Heating was maintained for 1 hr longer. After cooling the precipitated DHBC was filtered and worked up as usual.

The 8-nitro-DHBC and 8-trifluoromethyl-DHBC were prepared by this modification. The corresponding 4-substituted phenylhydrazine (0.03 mol) was added to a boiling solution of α-tetralone (0.02 mol) in 10% sulfuric acid in acetic acid (70 ml). The solution was refluxed for 90 min and cooled and the precipitate worked up as usual.

**N-Alkylations.** The alkylation of compounds 1–8 was carried out as previously described.[1]

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## Synthesis of Cephapirin† and Related Cephalosporins from 7-(α-Bromoacetamido)cephalosporanic Acid

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Since the structural elucidation of cephalosporin C (1),[1,2] the discovery of ingenious and remarkably efficient chemical methods[3-6] for its N-deacylation has rendered the novel fused dihydrothiazine-β-lactam nucleus, 7-aminocephalosporanic acid (7-ACA, 2), readily available for the synthesis of semisynthetic cephalosporins which now complement the penicillins in chemotherapeutic interest.[7]

The purpose of this report is to describe a convenient and versatile synthesis of cephapirin (4)[8] and related α-heterosubstituted acetamidocephalosporanic acids by nucleophilic displacement of the bromine atom in 7-(α-bromoacetamido)cephalosporanic acid (3)[9] with mercapto- and aminopyridines[8,10] and various 1,3-disubstituted and trisubstituted thioureas.[11]

Treatment of an aqueous–acetone suspension of 7-ACA (2) with bromoacetyl bromide in the presence of sodium bicarbonate afforded crystalline 7-(α-bromoacetamido)-cephalosporanic acid (3) in 77% yield. The interaction of 3, 4-mercaptopyridine, and triethylamine in methylene chloride at room temperature produced 7-[α-(4-pyridylthio)acetamido]cephalosporanic acid (cephapirin, 4) in 82% yield (Scheme I).

A stirred suspension of 4 and *N,N*-diisopropylethylamine in aqueous acetone reacted with methyl iodide at ambient temperature to provide a fair yield of 7-[α-(1-methyl-4-pyridylthio)acetamido]cephalosporanic acid betaine (5).‡,[12]

3-Mercaptopyridine[13] and commercially available 2-mercaptopyridine were converted by procedures analogous to the one used for the preparation of 4 into the corresponding cephapirin isomers 6 and 7, respectively (Table I). Chemical properties and spectral data observed for cephapirin (4), 6, and 7 were in accord with the assigned structures. However, the remote possibility remained that the tertiary nitrogen atom instead of the thiol function in 4-mercaptopyridine had preferentially undergone reaction with 2 to form 7-[α-(4-thiopyridon-1-yl)acetamido]cephalosporanic acid rather than the thioether 4. This question was definitely settled by the independent synthesis of cephapirin by Silvestri and Johnson.[14] Compound 4 and the product of unequivocal structure which they obtained by coupling 7-ACA (2) with α-(4-pyridylthio)acetyl chloride hydrochloride were identical.

In contrast to the behavior of 4-mercaptopyridine, 4-aminopyridine reacted with 3 to form the betaine 8 as the only product isolated. Since thiols are generally stronger nucleophiles than the corresponding amines, this result was not unexpected. Compound 8 was reported by other investigators[15] after the completion of our work. Their method of synthesis was analogous to our own.

In order to obtain the desired amino analog 9 of cephapirin (4), *N*-(4-pyridyl)glycine[16] was converted into its acid chloride hydrochloride and coupled in an anhydrous medium with silylated 7-ACA to obtain a 59% yield of 9.

7-[α-(1,3-Diethylformamidino-2-thio)acetamido]cephalosporanic acid (10) is a representative of a series of this class of cephalosporins prepared by displacement of the bromine atom in 3 by various acyclic and cyclic 1,3-disubstituted and trisubstituted thioureas in methylene chloride in the presence of a tertiary amine.

Other investigators have reported[17] that 7-[(α-formamidinothio)acetamido]cephalosporanic acid was not obtained from the reaction of 7-(α-chloroacetamido)-cephalosporanic acid with thiourea in aqueous solution. The products isolated were 7-ACA and pseudothiohydantoin formed by intramolecular displacement of the *N*-chloroacetyl group by thiourea.

**Structure–Activity Relationships.** Microbiological reports relating to cephapirin (4),†,[18] its 1-methyl betaine 5,‡,[19] and the class of substituted formamidinothioacetamidocephalosporanic acids[20] exemplified by 10 have disclosed the potent antimicrobial properties of these semisynthetic cephalosporins, some of which compare favorably with commercially important cephalothin (11).[21,22]

Some comparative minimal inhibitory concentrations (MIC's) data, expressed in μg/ml, are given in Table I. The MIC's were determined by the standard twofold broth dilution method after overnight incubation at 37°. Although all of the compounds shown have broad-spectrum activity, 10 and 5 stand out in overall activity. Crystalline 10 is unstable in aqueous solutions and, to a lesser degree, in the dry state. In general, these compounds derived from the substituted thioureas had good resistance toward β-lactamases produced by cephalothin-sensitive strains of *Klebsiella pneumoniae* and *Escherichia coli* but were found to be somewhat more toxic to animals than the other cephalosporins reported in this paper.[20]

### Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. The elemental analyses are within ±0.4% of theoretical values unless stated. The ir spectra were recorded on a Beckman IR-9 spectrometer. The nmr spectra were run on a Varian A-60 spectrometer at a sweep width of 500 Hz with Silanor-$D_2O$-TSP as the internal standard.

**7-(α-Bromoacetamido)cephalosporanic Acid** (3). To a vigorously stirred suspension of 200 g (0.731 mol) of 7-aminocephalosporanic acid (7-ACA, 2) in 2 l. of water and 750 ml of acetone was added 200 g (2.38 mol) of $NaHCO_3$, in portions, to prevent excessive foaming. The resulting solution was cooled to 3° and 200 g (0.99 mol) of bromoacetyl bromide was added in portions over a 10-min period. After 1 hr of stirring with the cooling bath removed, the pH was adjusted to 4 with 40% $H_3PO_4$. Decolorizing carbon (40 g, Darko-KB) was added and after 15 min the slurry was filtered through a Celite pad, with suction, and the pad washed with 600 ml of water. The combined filtrates were then brought to pH 2 with 40% $H_3PO_4$ and after stirring for 1 hr in an ice bath the crystalline product was filtered, washed well with cold water, and air-dried. The yield was 200 g (77%). An analytical sample was obtained by recrystallization from acetone-water, mp 173°. *Anal.* ($C_{12}H_{13}BrN_2O_6S$) C, H, N, Br.

**7-[α-(4-Pyridylthio)acetamido]cephalosporanic Acid** (4).[8] To a stirred suspension of 39.3 g (0.1 mol) of 3 in 500 ml of $CH_2Cl_2$ was added 14 ml (0.1 mol) of triethylamine. To the resulting solution was added 11.1 g (0.1 mol) of 4-mercaptopyridine. A nearly clear solution resulted with precipitation of the product beginning after a few minutes. After stirring 4 hr the crystalline product was filtered off, washed well with $CH_2Cl_2$, and air-dried. The white product weighed 35 g (82%). Recrystallization from boiling acetone-water (1:1) gave an analytical sample, mp 155°. Nmr indicated 0.5 mol of acetone of solvation: nmr ($D_2O$ + $KHCO_3$) δ 7.7-8.6 (m, 4, $-C_6H_4N$), 4.2 (s, 2, $-CH_2-$). *Anal.* ($C_{17}H_{17}N_3O_6S_2 \cdot 0.5C_3H_6O$) C, H, N.

**7-[α-(1-Methyl-4-pyridylthio)acetamido]cephalosporanic Acid Betaine** (5).[12] To a stirred suspension of 42.3 g (0.1 mol) of 4 in 50 ml of water and 600 ml of acetone at 22° was added 12.9 g

†Cephapirin is the nonproprietary name for 7-[α-(4-pyridylthio)acetamido]cephalosporanic acid (4), code number BL-P1322; CEFADYL is the trade name of Bristol Laboratories for this compound.

‡The code number for 5 is BL-S217.