the mixt was concd under reduced pressure. The resulting black semisolid was shaken with cold EtAcO (100 ml) and filtered when a grey powder (6.0 g) was obtd. This solid on crystn from EtAcO gave 3.5 g of **III-1**, mp 151–153°.

The combined EtAcO filtrates on concn under reduced pressure gave 22.2 g of a dark brown solid. This solid was eluted from a silica gel (Fisher, 700 ml) column using $CHCl_3$–EtAcO mixts as eluants. Fractions (500 ml) were collected and monitored from the weight, ir spectrum, and mp of the eluted material in each fraction.

III-10 (3.5 g) was collected in the early fractions, as a light yellow solid, mp 143–147°. The structure was established unequivocally from the spectral (ir and nmr) and elemental anal. data.

Later fractions gave 7.8 g of **III-1** as light yellow crystals, mp 151–153°, identical (mmp, ir and nmr spectra) with the sample obtd previously. In this case also the structure was established from the spectral (ir and nmr) and elemental anal. results.

Acknowledgments.—The authors thank Professor R. U. Lemieux for his advice and encouragement during this investigation, and Messrs. R. A. Fortier, R. R. Thomas, V. Baker, S. Chewonka, and A. Vanson for their capable technical assistance. We also wish to thank Dr. Ken E. Price of Bristol Laboratories, Syracuse, N. Y., for the biological data.

Synthesis of Indoles from 4-Oxo-4,5,6,7-tetrahydroindoles. 4. Tricyclic Heterocycles

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Received December 11, 1970

Condensation of 1-benzoyl-5-bromo-4-oxo-4,5,6,7-tetrahydroindole with substituted thioureas gave 2-amino-4,5-dihydro-6*H*-pyrrolo[3,2-*e*]benzothiazoles, which were dehydrogenated with phenyltrimethylammonium tribromide and debenzoylated. Two of these compds showed good activity in the carrageenin antiinflammatory assay. Examples of the tetrahydropyrrolo[4,3,2-*de*]cinnoline and tetrahydropyridazino[5,4,3-*de*]cinnoline systems were also prepared.

Recently we described a new method of indole synthesis, based upon 4-oxo-4,5,6,7-tetrahydroindoles, which is particularly suitable for fusion of heterocycles to the 4,5-indole positions.[1] The resulting tricyclic systems are intuitively appealing as potential pharmacologically active molecules. When one system of this type, the pyrrolindazole, showed significant activity in standard analgetic and inflammatory assays,[2] we decided to prepare a variety of other tricyclic heterocycles incorporating the indole nucleus.

As previously reported,[1] condensation of 1-benzoyl-5-bromo-4-oxo-4,5,6,7-tetrahydroindole **1a** with substituted thioureas afforded 2-amino-4,5-dihydro-6*H*-pyrrolo[3,2-*e*]benzothiazoles. Preliminary indications of antiinflammatory activity prompted us to prepare a variety of compds of this type (**2a–2e** in Scheme I). For the synthesis of *N*-methylpiperazino derivative **2e** the appropriate thiourea (4-methyl-1-piperazinethiocarboxamide) was required. This compd was conveniently made by condensation of benzoyl isothiocyanate with *N*-methylpiperazine, followed by acid hydrolysis (Experimental Section). Removal of Bz groups from the tricyclic compounds **2a–2e** by alkaline hydrolysis was possible only when there was no H on the 2-amino N (**2d** → **4a** and **2e** → **4b**). Hydrolysis products could not be isolated in the other cases due to their instability.

Dehydrogenation of **4a** with 2,3-dichloro-5,6-dicyanobenzoquinone furnished the fully aromatic derivative **3d** in low yield. However, attempts to dehydrogenate Bz-substituted compounds with this reagent were unsuccessful. After trying some other standard reagents we discovered that phenyltrimethylammonium tribromide was very effective for this type of dehydrogenation. Thus **2b** and **2d** were converted into **3a** and **3b**, resp, in high yields (97% for **3b**). At this time the scope and mechanism of dehydration with $PhN^+Me_3 \cdot Br_3^-$ is not known. However, a bromination–dehydrobromination process seems likely.

In contrast to certain of the dihydro precursors, the fully aromatic compd **3a** was debenzoylated to **3c** which has a H on the 2-amino N. As expected **3b** was readily converted into **3d**.

It was also possible to prepare a 3,4-fused heterocyclic derivative of indole. Thus, treatment of 4-oxo-4,5,6,7-tetrahydroindole-3-carboxamide (**5**) with hydrazine gave pyrrolo[4,3,2-*de*]cinnoline (**7**). A related pyridazino[5,4,3-*de*]cinnoline (**8**) was obtained when methyl 4-oxo-4,5,6,7-tetrahydrobenzofuran-3-carboxylate (**6**) was heated with hydrazine. This reaction gave a second product, $C_8H_{12}N_4O_2$, which corresponds to the reaction of **6** with 2 molecules of hydrazine followed by one cyclization. We are unable to deduce an unambiguous structure for this product from its spectra (Experimental Section).

Biological Activities.—Many of the compds described in this note showed *in vitro* activity against certain bacteria and fungi (Table I). However, this activity was generally at higher test levels. The most active compd was the *N*-benzenesulfonyl analog **1b**.[1] This compd was especially effective against dermatophytes. It was tested topically as a 1% ointment against *Microsproum canis* ATCC 10214 infection on rats, but was inactive in this assay.

The 2 compds most active in the carrageenin antiinflammatory assay in rats were **4a** and **4b**. They gave the following C/T ratios for the mean edema volume of paws of 8 control rats divided by that of 2

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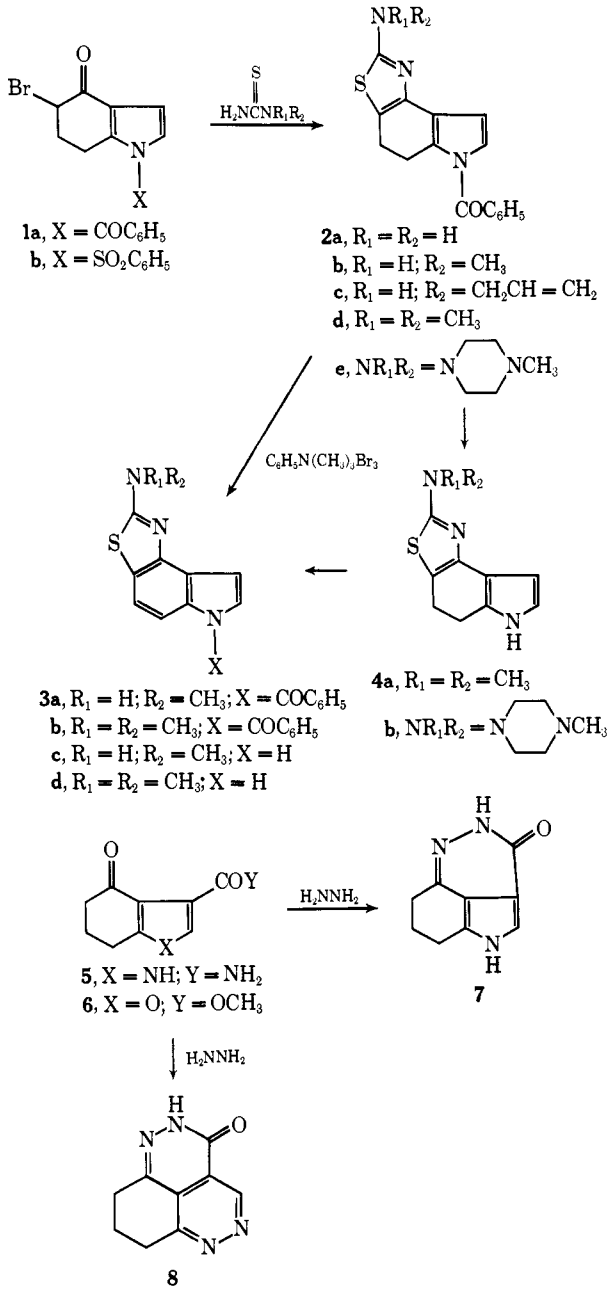
(1) W. A. Remers, R. H. Roth, G. J. Gibs, and M. J. Weiss, *J. Org. Chem.*, **36**, 1232 (1971).

(2) F. J. McEvoy, J. M. Smith, Jr., and D. S. Allen, Jr., U. S. Patent 3,404,157 (1968); see *Chem. Abstr.*, **66**, 20134c (1966).

SCHEME I



treated rats according to the assay procedure of Winter.[3] At 250 mg/kg oral dose these ratios were **4a**: 3.07, 2.46, 4.48, 2.16 in 4 assays. For **4b** they were 2.12, 1.53, 2.69, and 1.29. Neither of these compds was active in the adjuvant-induced polyarthritis assay.

Experimental Section

General.—Mps were detd on a Mel-Temp apparat and are cor. Uv spectra were detd in MeOH on a Cary recording spectrophotometer. Solns were dried ($MgSO_4$) and concd under red pressure on a rotary evaporator. Where anal. are indicated only by symbols of the elements, anal. results obtained for those elements were within ±0.4% of the theor values.

2-Substituted-6-benzoyl-4,5-dihydro-6*H*-pyrrolo[3,2-*e*]benzothiazoles (2a-2e).—A mixt of equimolar quants of **1a**,[1] NEt_3, the appropriate thiourea derivative, and THF (10 ml/mmole, except 30 ml/mmole of thiourea) was heated at reflux temp for 20 hr. The mixt was filtered, and the filtrate was concd. Trituration of the residue with Et_2O gave solid which was recrystd from MeOH. In the case of 4-methyl-1-piperazinethiocarboxamide no NEt_3 was used, and the product was isolated as its HBr salt. The prod had uv absorption at 243 mμ (ε 37,000) 310 (8400), and 365 (2400). Other data are in Table II.

(3) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).

TABLE I

In Vitro ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES

	Min inhib concn, μg/ml, against[a]									
	Bacteria			Fungi						
Compd	*Myco.*	*Staph.*	*Strep.*	*M.c.*	*M.g.*	*T.t.*	*T.m.*	*T.r.*	*C.a.*	*C.n.*
1a				5	50	25	25	25		
1b	25	5	50	2.5	10	5	5	10		
2a	62	250	250	16	62	16	16	16	250	62
2b	62			62	250	250	250	250		
2c	62			62	250	250	250	250		
2d	62			250		250	250	250		
2e	62	250	62	25	25	25	25	25	250	50
4a[b]	50	50	50	25	100	100	100	100		100
4b	62	250	62	25	100	100	50	50	250	250

[a] Highest test level was 250 μg/ml. Abbreviations for microorganisms are *Myco*, *Mycobacterium smegmatis* ATCC 606; *Staph.*, *Staphyllococcus aureus* Rose ATCC 14154; *Strep.*, *Streptococcus pyogenes* C203; *M.c.*, *Microsporum canis* ATCC 10214; *M.g.*, *Microsporum gypseum* ATCC 14683; *T.t.*, *Trichophyton tonsurans* NIH 66a; *Trichophyton mentagrophytes*, E11; *T. R. Trichophyton rubrum*, E97; *C.a.*, *Candida albicans*, E83; *C.n.*, *Cryptococcus neoformans*, E138. [b] Active at 250 μg/ml against *Klebsiella pneumonia* AD, *Proteus vulgaris* ATCC 9484, *Pseudomonas aeruginosa* ATCC 10145, and *Salmonella typhosa* ATCC 6539.

4-Methyl-1-piperazinethiocarboxamide.—A suspension of 19.6 g of KSCN in 120 ml of Me_2CO was treated dropwise with 28.8 g of BzCl. The resulting mixt was stirred for 10 min, cooled in an ice bath, and treated with a soln of 20 g of 1-methylpiperazine in 60 ml of Me_2CO. This mixt was stirred at reflux temp for 1 hr, cooled, and dild with 600 ml of H_2O, whereupon the product crystd. Recrystn from $CHCl_3$–hexane gave 24.9 g (66%) of ***N*-benzoyl-4-methyl-1-piperazinethiocarboxamide** as white crystals, mp 166–168°. *Anal.* ($C_{13}H_{14}N_3OS$) C, H, N, S.

A 10-g portion of this Bz deriv was heated on a steam bath with 100 ml of 6 *N* HCl for 30 min. The mixt was cooled and filtered, and the filtrate was chilled in ice and brought to pH 12 with 10 *N* NaOH. Part of the product crystd. Addnl product was obtd by repeatedly extg the filtrate with $CHCl_3$. Recryst from THF–hexane gave 4.5 g (74%) of product with mp 171–173°. *Anal.* ($C_6H_{13}N_3S$) C, H, N, S.

2-Dimethylamino-4,5-dihydro-6*H*-pyrrolo[3,2-*e*]benzothiazole (4a).—A suspension of 3.8 g of **2d** in 75 ml of MeOH was stirred with 2.35 ml of 5 *N* NaOH for 10 min. The cryst product was washed with H_2O, dried, and recrystd from MeOH. This procedure gave **4a** as white cryst: mp 244–247°; uv max 218 mμ (ε 26,000) 242 (15,000), 260 (10,700), 310 (3300). *Anal.* ($C_{11}H_{13}N_3S$) C, H, N, S.

4,5-Dihydro-2-(4-methyl-1-piperazinyl)-6*H*-pyrrolo[3,2-*e*]benzothiazole (4b) was prepd as described for **4a**. From 1.84 g of **2e** was obtd 811 mg (75%) of **4b** as colorless crystals, mp 189–195°. *Anal.* ($C_{14}H_{18}N_4S$) C, H, N, S.

6-Benzoyl-2-dimethylamino-6*H*-pyrrolo[3,2-*e*]benzothiazole (3b).—A soln of 305 mg of **2d** in 2 ml of THF was treated with 355 mg of $PhN^+Me_3 \cdot Br_3$ in 1 ml of THF. After 2 hr the mixt was treated with 5 ml of H_2O, whereupon the product crystd. Recrystn from Me_2CO–hexane gave **3b** as white needles: mp 184–185°; uv max 220 mμ (ε 48,000), 250 (34,000), 270 (38,000), 290 (30,500), 338 (18,300). *Anal.* ($C_{18}H_{15}N_3OS$) C, H, N, S.

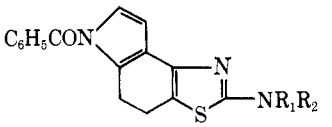
6-Benzoyl-2-methylamino-6*H*-pyrrolo[3,2-*e*]benzothiazole (3a) was prepd as described for **3b**. From 927 mg of **2b** was obtd 654 mg (72%) of **3a** as white crystals, mp 184–188° after recrystn from CH_2Cl_2–hexane. *Anal.* ($C_{17}H_{13}N_3OS$) C, H, N, S.

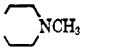
2-Dimethylamino-6*H*-pyrrolo[3,2-*e*]benzothiazole (3d). A. From 3b.—A suspension of 155 mg of **3b** in 4 ml of MeOH was stirred with 0.1 ml of 5 *N* NaOH for 10 min. The cryst product was washed with MeOH (yield 53 mg, 51%). Recrystn from MeOH gave **3d** with mp 276–280°; uv max 228 mμ (ε 31,000), 294 (13,200), 304 (14,700), 315 (15,600). *Anal.* ($C_{11}H_{11}N_3S$) C, H, N, S.

B. From 4a.—To a suspension of 1.03 g of **4a** in 10 ml of dioxane was added a soln of 1.02 g of 2,3-dichloro-5,6-dicyanobenzoquinone in 2 ml of dioxane. The mixt was stirred 2 hr and

TABLE II

2-SUBSTITUTED-6-BENZOYL-4,5-DIHYDRO-6*H*-PYRROLO[3,2-*e*]BENZOTHIAZOLES



Compd	R_1R_2	Yield, %	Mp, °C	Formula	Analysis
2a	H, H	79	190–193	$C_{16}H_{13}N_3OS$	C, H, N, S
b	H, CH_3	92	171–174	$C_{17}H_{15}N_3OS$	C, H, N, S
c	H, $CH_2CH{=}CH_2$	95	138–141	$C_{19}H_{17}N_3OS$	C, H, N, S
d	CH_3, CH_3	75	117–120	$C_{18}H_{17}N_3OS$	C, H, S
e·HBr		68	255–257	$C_{21}H_{22}N_4OS \cdot HBr$	C, H, N, S, Br

filtered. The solids were extd with dil HCl, and the ext was brought to pH 7 with NaOH, whereupon a ppt formed. This ppt of **3d** (153 mg, 16%) was washed with H_2O and dried in air. It has an ir spectrum superimposable with that of the same product prepd from **3b**.

2-Methylamino-6*H*-pyrrolo[3,2-*e*]benzothiazole (3c) was prepd as described for **3d** from **3b**. From 454 mg of **3a** was obtd, after recrystn from MeOH, 158 mg (53%) of **3c** of yellow cryst, mp 195–196°. *Anal.* ($C_{10}H_9N_3S$) C, H, N, S.

5,6,7,8-Tetrahydropyrrolo[4,3,2-*de*]cinnolin-3-2*H*-one (7).—A mixt of 890 mg of 4-oxo-4,5,6,7-tetrahydroindole-3-carboxamide (**5**)[4] and 7 ml of hydrazine hydrate heated at reflux temp for 2 hr, cooled, and filtered. Recrystn of the product from MeOH gave 431 mg (65%) of **7** as white solid which did not melt at < 350°; uv max 233 mμ (ε 10,000), 267 (5700), 276 (6100), 298 (4700); ir 3.1–3.45 μ (NH), 6.15 (CONH); nmr (CF_3CO_2H) δ 11.6 (broad, pyrrole NH), 7.98 (d, J = 2.5 Hz, pyrrole, deshielded by CO), 2.7–2.4 (m, 6, $CH_2CH_2CH_2$) ppm. *Anal.* ($C_9H_9N_3O$) H, N; C: calcd, 61.70; found, 62.28.

(4) H. Stetter and R. Lauterbach, *Justus Liebigs Ann. Chem.*, **655**, 120 (1962).

2,7,8,9-Tetrahydro-3*H*-pyridazino[5,4,3-*de*]cinnolin-3-one (8).—A mixt of **6** (7.66 g) and hydrazine hydrate (20 ml) was stirred at room temp for 1 hr, cooled in ice, and filtered. The solids were extd with cold MeOH. The sol portion, after recryst from Me_2CO–hexane, gave 2.53 g (34%) of **8** as yellow needles: mp 251–255° dec; uv max 253 mμ (ε 4400), 261 (5000), 294–300 (4200); ir 3.1–3.4 μ (NH), no unconj CO, 6.15 (NCOC=C); nmr (CF_3CO_2H) δ 10.23 (s, proton in pyrazine ring deshielded by CO), 3.65 and 3.45 (each is t, 2, J = 6 Hz, $CH_2CH_2CH_2$), 2.51 (m, 2, $CH_2CH_2CH_2$) ppm. *Anal.* ($C_9H_8N_4O$) C, H, N.

The insol portion (1.31 g), after recryst from boiling MeOH, gave golden needles: mp 188–190°; uv max 256 mμ (ε 8500); ir 2.94–3.45 μ, no unconj CO, 6.15; nmr (DMSO-d_6) δ 12.0 (broad, s), 8.08 (s), 6.23 (broad, 2), 2.95–2.5 (m, 4, CH_2CH_2), 1.93 (m, 2, $CH_2CH_2CH_2$) ppm. *Anal.* ($C_9H_{12}N_4O_2$) C, H, N.

Acknowledgment.—We thank Mr. L. Brancone and staff for microanalyses, Mr. W. Fulmor and staff for spectra data, Dr. A. E. Sloboda for antiinflammatory assays, and Mr. A. C. Dornbush for antibacterial and antifungal assays.

Antimalarial Activity of Guanylhydrazone Salts of Aromatic Ketones. 2. Development of Active Polyhalo Derivatives[1a,b]

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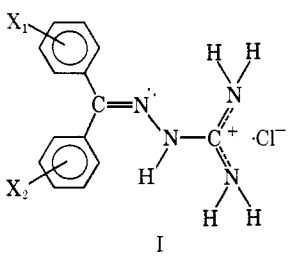
Received January 22, 1971

Twenty-four guanylhydrazones of polyhalo-substituted benzophenones were synthesized and tested in the primary antimalarial screen in mice infected with *Plasmodium berghei*. All compds but one bore halo or halogen-containing substituents on both rings. The minimum requirement for activity within this context is the presence of a CF_3 group in the 3 or 4 position or a F_3CO group in the 4 position on one ring and halo or CF_3 in the 3 or 4 positions on the second ring. Eighteen of these compds were active and 16 were at least partially curative at one or more dose levels. Twelve compds produced 100% cures at one or more dose levels. One compd (3,4-dichloro-4′-trifluoromethylbenzophenone guanylhydrazone·HCl) was outstanding and yielded 100% cures over the dose range 80–640 mg/kg. Replacement of H by Me in the guanidine moiety abolished antimalarial activity.

In the first paper in this series[2] the syntheses and antimalarial activities of 30 compds were presented. The generic type is represented by structure I. It became apparent that optimal activity resided in benzophenone guanylhydrazones wherein both rings bore halo or halo-



I

gen-containing substituents. It was found that the presence of a CF_3 group on one ring was essential for

(1) (a) This investigation was conducted under Contract DA-49-193-MD-3016 from the U. S. Army Research and Development Command. This is Contribution No. 885 to the Army Research Program on Malaria. (b) Presented in part at the 169th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, Abstract MEDI-57. (c) Department of Psychiatry, Stanford University School of Medicine, Palo Alto, Calif.

(2) J. R. DoAmaral, E. J. Blanz, Jr., and F. A. French, *J. Med. Chem.*, **12**, 21 (1969).