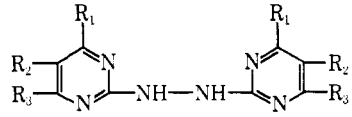
TABLE I
2,2′-HYDRAZOBISPYRIMIDINES



Compd	R_1	R_2	R_3	Method	Mp, °C[c]	Color	Recrystn solvent	Yield, %	Formula[d]
1	H	NO_2	H	B[a]	254–255	Brown	PrOH	33	$C_8H_6N_8O_4$
2	NH_2	NO_2	H	A	>320	Reddish brown	...	57	$C_8H_8N_{10}O_4$
3	$(CH_3)_2N$	NO_2	CH_3	A	224	Yellow	2-PrOH	43	$C_{14}H_{20}N_{10}O_4$
4	$(C_4H_9)_2N$	NO_2	CH_3	A	169–171	Yellow	2-PrOH	30	$C_{26}H_{44}N_{10}O_4$
5	CH_3O	H	H	B[b]	119–120	White	Cyclohexane	47	$C_{10}H_{12}N_6O_2$[e]
6	CH_3O	NO_2	H	C	197	Red	AcOEt	20	$C_{10}H_{10}N_8O_6$

[a] The product was purified by dissolving in DMSO and precipitating with water. [b] The filtered precipitate was dissolved (H_2O) and the free base was precipitated with NH_4OH. [c] All the nitro compounds melted with decomposition. [d] All compounds were analyzed for N. [e] Analyzed for C, H, N.

has led us to prepare a series of 2,2′-hydrazobis(5-nitropyrimidines) as potential antiprotozoal agents. Most of the compounds were obtained by the condensation of the corresponding 2-chloropyrimidines with hydrazine in alcoholic solution (Table I).

Experimental Section[3]

2-Chloro-5-nitropyrimidine,[4] 4-amino-2-chloro-5-nitropyrimidine,[5] 2-chloro-4-dimethylamino-6-methyl-5-nitropyrimidine,[6] and 2-chloro-4-methoxypyrimidine[7] were prepared by procedures described in the literature.

2-Chloro-4-dibutylamino-6-methyl-5-nitropyrimidine.—A solution of 9.7 g (75 mmoles) of dibutylamine and 4.3 ml (75 mmoles) of AcOH in 20 ml of H_2O was added to a solution of 5.2 g (25 mmoles) of 2,4-dichloro-6-methyl-5-nitropyrimidine[8] in 20 ml of dioxane. The mixture was stirred for 2 days and then extracted several times (C_6H_6). The residue, obtained after evaporation of the organic solvent was chromatographed on acid-washed alumina. The fraction eluted with petroleum ether (bp 40–60°) yielded 5.1 g (68%), bp 158° (0.8 mm). *Anal.* ($C_{13}H_{21}ClN_4O_2$) C, H, Cl, N.

2,2′-Hydrazobispyrimidines (Table I). Method A.—A mixture of the corresponding 2-chloropyrimidine (9 mmoles), hydrazine hydrate (4.5 mmoles), and Et_3N (10 mmoles) in *t*-BuOH (35 ml) was refluxed with stirring for 10 hr. The precipitate was filtered, washed (MeOH), dissolved in concentrated HCl, and precipitated with H_2O.

Method B.—One mole of the corresponding 2-chloropyrimidine and 0.5 mole of hydrazine hydrate in absolute EtOH were refluxed with stirring for 10 hr.

Method C.—To a solution of 25 mg of **5** in 2 ml of concentrated H_2SO_4 was added at 0° a solution of 0.12 ml of fuming HNO_3 in 0.6 ml of concentrated H_2SO_4. The mixture was stirred at 0° for 1 hr and poured into ice.

(3) Melting points were taken in capillary tubes and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. All the hydrazopyrimidines were also identified by their molecular weights, determined by mass spectroscopy.

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Synthesis of 5,7-Dioxo-3-methyl-5,6,7,8-tetrahydropyrimido[5,4-*e*]-*as*-triazine[1]

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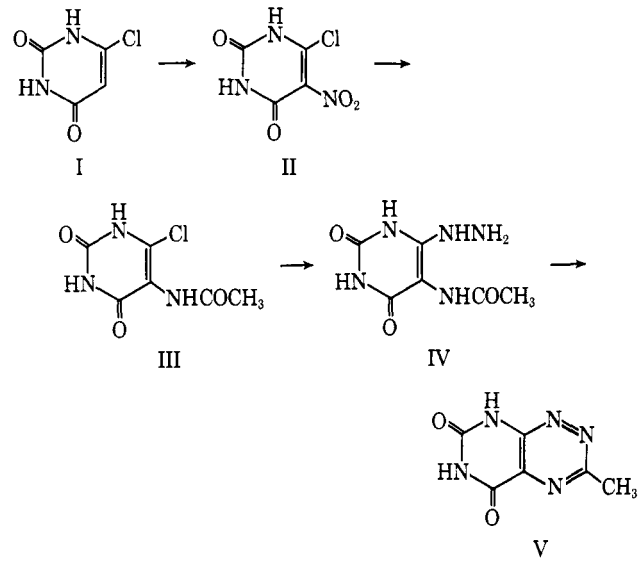
In connection with our investigation of compounds related to a series of pyrimido[5,4-*e*]-*as*-triazine antibiotics [toxoflavin (xanthothricin), fervenulin (planomycin)[2-5]], one of the parent N-unsubstituted derivatives, 5,7-dioxo-3-methyl-5,6,7,8-tetrahydropyrimido[5,4-*e*]-*as*-triazine (V), was synthesized (Scheme I). Compound V is the 7-aza analog of 6-methyllumazine.[6-9]

SCHEME I



As expected, the uv absorption spectra (pH 1 and 11) of V resembled more closely those of 1-demethyltoxoflavin[5] rather than those of toxoflavin[2,4] or fervenulin.[3]

Experimental Section

4-Chloro-5-nitrouracil (II).—The reported procedure gave low yields.[10] The following is a modified procedure. 4-Chlorouracil[10] (11.5 g, 0.08 mole) was added in small portions to 36 ml of concentrated H_2SO_4 at 15° with stirring. To the solution at 0–5° was added, dropwise, 12 ml of fuming HNO_3 (90%). After addition, the mixture was stirred for 30 min at 10°. The resulting yellow solution was poured, with vigorous stirring, into 60 g of

(1) This investigation was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute, of the National Institutes of Health, U. S. Public Health Service, Contract No. PH-43-65-94.

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flaked ice (the beaker was immersed in a Dry Ice–acetone bath). White solid separated on scratching of the beaker. The product was immediately filtered through a medium-coarse sintered-glass funnel and washed twice with ice water. It was then dried overnight *in vacuo* (P_2O_5) to give 10.5 g (70% yield) of II: mp 244–246° (lit.[10] 220–222°); $\lambda_{max}^{pH\ 1}$ 276 mμ (ε 6600); $\lambda_{max}^{pH\ 1}$ 226 mμ (ε 11,800), 331 mμ (ε 6300). *Anal.* Calcd for $C_4H_2ClN_3O_4$: C, 25.08; H, 1.05; N, 21.93. Found: C, 24.80; H, 1.20; N, 21.60.

5-Acetamido-4-chlorouracil (III).—A solution of freshly prepared II (8.0 g, 0.04 mole) in 200 ml of AcOH and 30 ml of Ac_2O was hydrogenated at 4.2 kg/cm² in the presence of 5% Pt–C at room temperature. Theoretical amount of H_2 was absorbed in 3 hr. The catalyst was removed by filtration; the filtrate was heated on a steam bath for 30 min and evaporated *in vacuo* to dryness. To the cool syrup was added EtOH (20 ml). The product slowly solidified on standing. It was isolated by filtration giving 5.29 g (61% yield) of III, mp 238–242°. Recrystallization from AcOH–EtOAc gave an analytically pure sample as a white solid: mp 241–242°; $\lambda_{max}^{pH\ 1}$ 267 mμ (ε 12,200); $\lambda_{max}^{pH\ 11}$ 228 mμ (ε 7200), 286 mμ (ε 16,300). *Anal.* Calcd for $C_6H_6ClN_3O_3$: C, 35.40; H, 2.97; N, 20.64. Found: C, 35.67; H, 3.10; N, 20.60.

5-Acetamido-4-hydrazinouracil (IV).—A mixture of 2.0 g (0.01 mole) of III, 0.32 g of hydrazine, and 1.0 g of Et_3N in 120 ml of EtOH was refluxed on a steam bath for 3 hr. After the mixture was cooled, the solid product was collected by filtration and washed (EtOH, Et_2O) to give 2.2 g of IV, mp 230–232°. The product was identified as its acetone derivative (prepared from 0.2 g of IV, 2 ml of acetone, 20 ml of H_2O, and 5 drops of AcOH), white crystals (0.15 g), mp 324–325°. *Anal.* Calcd for $C_9H_{13}N_5O_3$: C, 45.18; H, 5.47; N, 29.28. Found: C, 44.80; H, 5.50; N, 29.10.

5,7-Dioxo-3-methyl-5,6,7,8-tetrahydropyrimido[5,4-*e*]-*as*-triazine (V).—A suspension of 500 mg (2.5 mmoles) of IV in 50 ml of Ph_2O was heated at 220–230° with stirring for 30 min. The hot reaction mixture was filtered and to the cold filtrate was added 20 ml of Et_2O. There was obtained a bright yellow solid, which was collected by filtration and washed [twice with 10 ml of petroleum ether (bp 35–60°), Et_2O (20 ml)] to give 100 mg (22% yield) of V, mp 281–282°. Recrystallization from PrOH yielded an analytical sample, mp 281–282°. The product was soluble in H_2O and MeOH. The nmr spectrum (D_2O) showed one singlet at τ 7.18 (CH_3); $\lambda_{max}^{pH\ 1}$ 231 mμ (ε 17,200); $\lambda_{sh}^{pH\ 1}$ 270 mμ (ε 3100); $\lambda_{max}^{pH\ 1}$ 338 mμ (ε 4900); $\lambda_{max}^{pH\ 11}$ 252 mμ (ε 17,400), 390 mμ (ε 4100). *Anal.* Calcd for $C_6H_5N_5O_2$: C, 40.23; H, 2.81; N, 39.10. Found: C, 40.00; H, 2.65; N, 38.90.

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Book Reviews

Mechanisms of Reactions of Sulfur Compounds. Volume 1. 1966. By N. KHARASCH, B. S. THYAGARAJAN, and A. I. KHODAIR. Intra-Science Research Foundation, Santa Monica, Calif. 1967. 286 pp. 17.5 × 25.5 cm. $12.00.

This book surveys the literature for the period 1965–1966 of reactions of organic sulfur compounds which are interesting in respect to reaction mechanisms although many of the reactions reported are of more synthetic than theoretical interest. In many cases the reaction mechanisms proposed are speculative with little or no experimental tests of their validity. The book is extremely interesting, however, in that it brings together a great variety of much stimulating chemistry and can serve two distinct purposes, generating research ideas in the mind of the reader or as a convenient source of abstracts and references for the person planning or already carrying out work in a particular area. I enjoyed the book very much.

The references cited are treated in either of two ways, as a simple literature citation with no details, or as a summary describing the work in detail. The authors state in the introduction that "the importance of a paper should by no means be judged by whether or not a summary has been included in the report." This is the weakest aspect of the book. I have found that generally the papers abstracted were those which appeared in English in readily available journals, mainly the *Journal of the American Chemical Society* and the *Journal of Organic Chemistry*, while the papers cited but not summarized were those written in foreign languages and/or in journals less accessible. For example, a rough count gave the following: out of *ca.* 34 references to papers in Russian journals only one was summarized, none out of 14 in French, two out of 30 in German, and one out of 13 in Italian. Further, some of the papers which appeared in the *Journal of the American Chemical Society* were summarized twice. The value of this annual report could be increased many times if a greater effort were made to summarize the important papers in the foreign (non-English) literature.

The coverage is also spotty. None of Middleton's work on thiocarbonyl compounds (*J. Org. Chem.*, 1956) is even cited while every paper dealing with thiocarbonyl S-oxides is summarized. Only one of Cram's papers dealing with stereochemistry of sulfonyl-stabilized carbanions and none of Corey's is summarized even though this is one of the most important areas of current research and one which is subject to different interpretations.

I am confident that the editors will take measures to correct the weaknesses in a generally well-conceived and well-executed book and that future volumes will become increasingly valuable to those doing research in sulfur chemistry and organic chemists generally.

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Reviews of Pharmacological Topics. I. **Advances in Pharmacology. Volume 5.** Edited by SILVIO GARATINI and PARKHURST A. SHORE. Academic Press Inc., New York and London. 1967. ix + 318 pp. 23.5 × 16 cm. $15.00.

The seven reviews of Volume 5 are as follows: Molecular forces in anesthesia (B. P. Schoenborn and R. M. Featherstone), The effect of endotoxin on resistance to infection and disease (F. M. Berger), Effect of drugs on mast cells (A. Goth), Drugs and aggressiveness (L. Valzelli), Pharmacologic and endocrine aspects of carcinoid syndrome (J. A. Oates and T. C. Butler), Drug actions on thermoregulatory mechanisms (H. L. Borison and W. G. Clark), and Pharmacology of benzodiazepines: laboratory and clinical correlations (G. Zbinden and L. O. Randall). One can see readily that with the exceptions of the first and last of the chapters which have been reviewed well in similar volumes under different sponsorship, the topics are of considerable timeliness and reviews of them are welcome. One is impressed with the versatility of one contributor (F. M. Berger) who after much notable work on muscle relaxants and antianxiety agents has now turned to endotoxin and resistance to disease. The chapter on drugs and aggressiveness (in animals) will provide much correlation of hitherto separated observations in the psychopharmacological laboratory.

All reviews are written well and lucidly, and the book is printed with unusual clarity and pictorial pleasantness. It will be received as one of the better educational efforts and surveys in contemporary professional pharmacology.

II. **Annual Review of Pharmacology. Volume 8.** Edited by H. W. ELLIOTT, W. C. CUTTING, and R. H. DREISBACH. Annual Reviews, Inc., Palo Alto, Calif. 1968. vii + 594 pp. 23 × 16.5 cm. $8.50.

This annual volume contains thirty reviews, some of them on repeatedly presented topics (SAR, metabolic fate of drugs, review