Notes

Anticoccidial Derivatives of 6-Azauracil. 5. Potentiation by Benzophenone Side Chains

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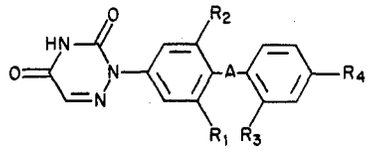
Attachment of *p*-benzophenone side chains at N1 was found to be one of the most effective modifications for enhancing the potency of 6-azauracil against a broad spectrum of coccidia in chickens. Compound **20** was about 1000-fold more potent than 6-azauracil. Structure–activity relationships paralleled those found in a previously reported series of related analogues containing diphenyl sulfide and sulfone side chains. Drug metabolism studies showed the ketones to be reduced rapidly to carbinols, which are the prevalent species in vivo.

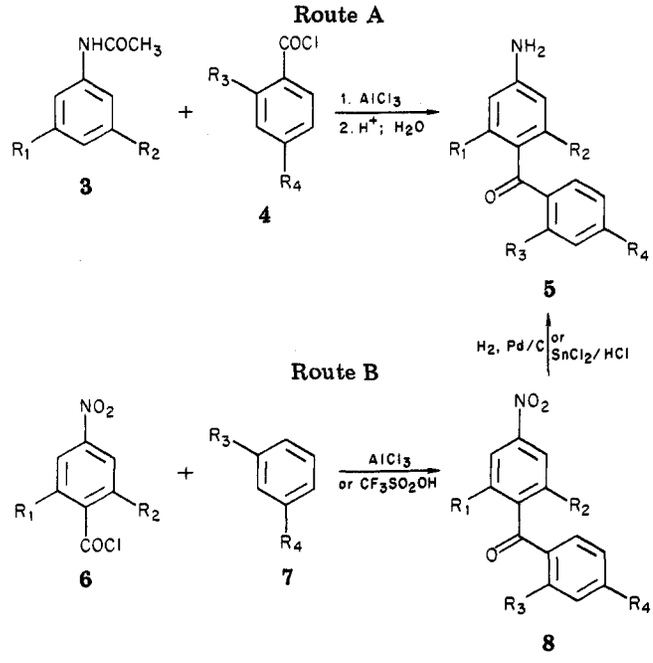
We had previously reported that the anticoccidial activity of 6-azauracil can be increased markedly by attaching, at N-1, phenyl groups containing compact, lipophilic meta substituents.[2] While we were investigating the effect on activity of changing the substituents in the phenyl ring, it appeared for a long time as if bulky substituents were unfavorable for activity and as if substitution in the para position was less favorable than in the meta position. It was then found unexpectedly, however, that the *p*-benzoyl derivative **1** possesses good activity, and this finding stimulated the investigation of similar, bulky para substituents.[3,4] When diphenyl sulfide and diphenyl sulfone side chains were found to be particularly effective for increasing potency, leading to as much as a 4000-fold increase over 6-azauracil,[4] we returned to **1** and introduced additional substituents according to the structure–activity relationships that we had discovered among the sulfides and sulfones (e.g., **2**).



1, A = CO; $R_1 = R_2 = R_3 = R_4 = H$
2, A = SO_2; $R_1 = R_2 = R_4 = Cl$; $R_3 = H$

Chemistry. The 1-aryl-6-azauracils were prepared from substituted anilines according to procedures described in preceding papers of this series.[2,4] The requisite aminobenzophenones were obtained by Friedel-Crafts aroylation routes A or B (Scheme I). The choice of route depended largely on the nature of the desired ketone in relation to orientation in the aroylation. In those instances where either route could be used, our selection was based on the availability and cost of appropriate starting materials. A variation of route B involving use of trifluoromethanesulfonic acid as the catalyst[5] gave purer product.

Scheme I[a]



[a] **3a–8a**, $R_1 = R_4 = Cl$; $R_2 = R_3 = H$. **3b–8b**, $R_1 = Cl$; $R_2 = H$; $R_3 = Me$; $R_4 = Br$.

The aminobenzophenones were then coupled with either ethylcyanoacetylurethane or malonyldiurethane in order to construct an acyclic precursor to the azauracil ring (Scheme II). The sequence using the symmetrical reagent malonyldiurethane was particularly useful, especially in scale-up work; for instance, **14a** could be prepared from **5a** in high overall yield without isolation of intermediates **9a**, **11a**, or **13a**. The resulting 6-azauracils with benzophenone side chains are listed in Table I, together with their pertinent properties. In a few cases, the corresponding carbinol was prepared by reducing the ketone with sodium borohydride (e.g., **20** → **35**).

Biological Screening. The substituted azauracils were tested for anticoccidial activity by determining the minimum effective concentration (MEC) according to Lynch[6] (as modified by Chappel et al.[7]), expressed in parts per

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(2) M. W. Miller, B. L. Mylari, H. L. Howes, Jr., J. E. Lynch, M. J. Lynch, and R. C. Koch, *J. Med. Chem.*, **22**, 1483 (1979).
(3) M. W. Miller, B. L. Mylari, H. L. Howes, Jr., S. K. Figdor, M. J. Lynch, J. E. Lynch, and R. C. Koch, *J. Med. Chem.*, **23**, 1083 (1980).
(4) M. W. Miller, B. L. Mylari, H. L. Howes, Jr., S. K. Figdor, M. J. Lynch, J. E. Lynch, S. K. Gupta, L. R. Chappel, and R. C. Koch, *J. Med. Chem.*, **24**, 1337 (1981).
(5) F. Effenberger and G. Epple, *Angew. Chem.*, **84**, 295 (1972).
(6) J. E. Lynch, *Am. J. Vet. Res.*, **22**, 324 (1961).
(7) L. R. Chappel, H. L. Howes, Jr, and J. E. Lynch, *J. Parasitol.*, **60**, 415 (1974).

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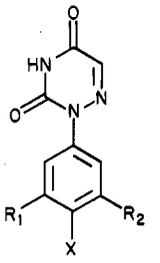
Table I. 2-(4-Benzoylphenyl)-*as*-triazine-3,5(2*H*,4*H*)-diones, Related Structures, and Their Anticoccidial Activities



no.	R_1	R_2	X	formula[a]	mp, °C	$pH_{1/2}$[b]	plasma half-life,[c] h	MEC,[d] ppm
1	H	H	C_6H_5CO	$C_{16}H_{11}N_3O_3$	202-204	7.79		60
15	H	H	4-ClC_6H_4CO	$C_{16}H_{10}ClN_3O_3$[h]	288-290			30
16	H	H	4-MeC_6H_4CO	$C_{17}H_{13}N_3O_3$[h]	241-243			>250
17	H	H	2,4,6-$Me_3C_6H_2CO$	$C_{19}H_{17}N_3O_3$	189-191	7.16		>250
18	H	H	4-$MeCC_6H_4CO$	$C_{17}H_{13}N_3O_4$	247-248			125
19	Cl	H	C_6H_5CO	$C_{16}H_{10}ClN_3O_3$	180-184	7.04		8-15
20	Cl	H	4-ClC_6H_4CO	$C_{16}H_9Cl_2N_3O_3$	206-207	7.16	20	1-2
21	Cl	H	4-$MeSC_6H_4CO$	$C_{17}H_{12}ClN_3O_3S$	279-283			>30[f]
22	Cl	H	4-$MeSO_2C_6H_4CO$	$C_{17}H_{12}ClN_3O_5S$	234-236			>15[g]
23	Cl	H	2,4-$Cl_2C_6H_3CO$	$C_{16}H_8Cl_3N_3O_3$	100			4
24	Cl	H	4-Br-2-MeC_6H_3CO	$C_{17}H_{11}BrClN_3O_3$				8
25	Me	H	C_6H_5CO	$C_{17}H_{13}N_3O_3$	197-199	7.02[e]		8
26	Me	H	4-ClC_6H_4CO	$C_{17}H_{12}ClN_3O_3$	189-190.5	7.60	13	8
27	Me	H	4-CNC_6H_4CO	$C_{18}H_{12}N_4O_3$[h]	100	7.08		125
28	Me	H	2-ClC_6H_4CO	$C_{17}H_{12}ClN_3O_3$[h,i]	147-150	7.08		60
29	Me	H	2,4-$Cl_2C_6H_3CO$	$C_{17}H_{11}Cl_2N_3O_3$	151-154		45	4
30	Me	H	4-Cl-2-MeC_6H_3CO	$C_{18}H_{14}ClN_3O_3$	155-157			15
31	Cl	Me	4-ClC_6H_4CO	$C_{17}H_{11}Cl_2N_3O_3$	130-135		21	8
32	Me	Me	4-ClC_6H_4CO	$C_{18}H_{14}ClN_3O_3$	172-174.5			15
33	C_6H_5CO	H	H	$C_{16}H_{11}N_3O_3$	160-170			>250
34	C_6H_5CO	H	Cl	$C_{16}H_{10}ClN_3O_3$	130			>250
35	Cl	H	4-ClC_6H_4CHOH	$C_{16}H_{11}Cl_2N_3O_3$[h]	179-181			2
36	Me	H	C_6H_5CHOH	$C_{17}H_{15}N_3O_3$	149-152	7.37[e]		30
37	Me	H	4-ClC_6H_4CHOH	$C_{17}H_{14}ClN_3O_3$	100			8-15
38	Me	Me	4-ClC_6H_4CHOH	$C_{18}H_{16}ClN_3O_3$	170			30
39	Me	H	$C_6H_5CH_2$	$C_{17}H_{15}N_3O_2$	117-120			30
40	H	H	(2-thienyl)CO	$C_{17}H_9N_3O_3S$	240			>250
41	H	H	7-Cl-9-oxoxanthen-2-yl	$C_{16}H_8ClN_3O_4$	348-350			>250
42	H	H	CH_3CO	$C_{11}H_9N_3O_3$	263-265	6.53		>250
43	H	H	$CH_3(CH_2)_2CO$	$C_{13}H_{13}N_3O_3$	246-247			>60
44	Cl	H	CH_3CO	$C_{11}H_8ClN_3O_3$	102-110			125

[a] Elemental analysis or mass spectral analysis and thin-layer chromatography were used to confirm desired product and establish purity. [b] Apparent pK_a measured in 2:1 DMF/H_2O, unless otherwise noted. [c] Determined in 8-week cockerels. Half-lives listed for ketones are actually those of the corresponding carbinols formed by metabolic reduction (see text). [d] Minimum effective concentration in parts per million in feed vs. *Eimeria tenella*, except as noted. [e] Measured in 1:1 DMF/H_2O. [f] Tested against *Eimeria acervulina*. [g] Tested against *Eimeria necatrix*. [h] Hydrates: Compounds **15**, **16**, and **35**, 0.25 mol of H_2O; compound **27**, 1.5 mol; compound **28**, 0.5 mol. [i] N: calcd, 11.98; found, 11.49.

million (ppm) by weight in feed, which controlled infection by *Eimeria tenella* in Leghorn cockerels. Plasma half-life was determined by the method of Rash and Lynch.[8]

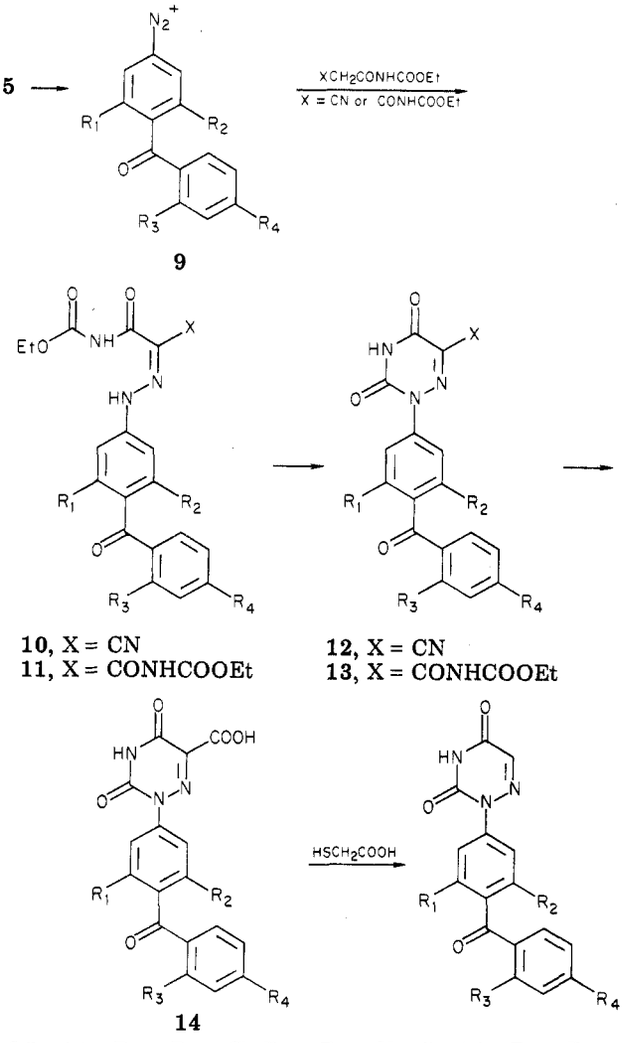
Structure–Activity Relationships. The general structure–activity patterns for the benzophenone derivatives paralleled closely those found earlier in the diphenyl sulfide, sulfoxide, and sulfone series.[4] Activity was increased by substituting the para position of the terminal phenyl ring (R_4) with chlorine but not with more polar substituents or methyl (which in that location might be susceptible to metabolic oxidation). Activity was likewise increased by a compact, lipophilic methyl or chloro substituent in the central phenyl ring at R_1, meta to the azauracil ring and adjacent to the ketone bridge, and it reached a peak when both R_1 and R_4 were chlorine (compound **20**). It usually, however, failed to increase with introduction of an additional substituent ortho to the ketone bridge, such as a methyl or chlorine in the terminal ring at R_3 or in the central ring at R_2. We speculate that these ortho substituents hinder the benzophenone system from assuming the dihedral angle[9] that is most favorable for activity. Analogues derived from *m*- rather than *p*-benzophenones were inactive. Probes into replacing the terminal phenyl group by a heterocycle or a short aliphatic chain gave disappointing results.

Drug metabolism studies were carried out with several of the benzophenone derivatives, and in every case these were found to be reduced rapidly in the chicken to the

(8) J. J. Rash and M. J. Lynch, *Drug Metab. Dispos.*, 4, 59 (1976).

(9) For the effects of ortho substituents on the conformation of benzophenones, see L. Pichat, J. C. Levron, and J. P. Guermont, *Bull. Soc. Chim. Fr.*, 1200 (1969); G. Montaudo, P. Finocchiaro, and P. Maravigna, *J. Am. Chem. Soc.*, **93**, 4214 (1971); G. Montaudo, S. Caccamese, and P. Finocchiaro, *ibid.*, **93**, 4202 (1971); S. K. Dayal, S. Ehrenson, and R. W. Taft, *ibid.*, **94**, 9113 (1972); C. L. Cheng, P. H. Gore, and G. L. D. Ritchie, *Aust. J. Chem.*, **26**, 867 (1973). After we reported the anticoccidial activity of compound **20**,[7] Kluge et al. [*J. Med. Chem.*, **21**, 529 (1978)] prepared 6-azauracils substituted with tricyclic aryl ketones. Apparently, the constrained, nonplanar conformation of their ketone side chains was close enough to optimal that it allowed a moderate degree of activity.

Scheme II[a]



[a] 5a-14a, $R_1 = R_4 = Cl$; $R_2 = R_3 = H$. 5c-14c, $R_1 = R_4 = Cl$; $R_2 = Me$; $R_3 = H$.

corresponding carbinol. The latter was then detectable in plasma for a number of hours and constituted the prevalent form in vivo.[8] When administered in feed, the carbinols showed a potency comparable or slightly inferior to that of the ketones.

Potencies in the benzophenone series ranged up to an MEC of 1–2 ppm for **20** or about 500–1000 times that of 6-azauracil. This compares with the following MEC's for the most potent representatives discovered with other types of substituents in the phenyl ring of phenylazauracils: small substituents,[2] 4 ppm; sulfonamide group,[3] 10 ppm; sulfides and sulfones,[4] 0.25 ppm. The potency of the benzophenone derivatives was achieved without the undesirable persistence in plasma and tissues characteristic of early potent phenylazauracils.[2,8] In our experience, the most effective side chains for potentiating the activity of 6-azauracils are diphenyl ketones (benzophenones), diphenyl sulfides, or diphenyl ether groups (to be published). The same preferred, and more or less interchangeable, side chains can be found among hypolipemic agents,[10] flukicides,[11] and antiinflammatory agents[12] derived from anilines or phenols. Possibly these dihedral, lipophilic but polarizable structures play a common role, such as enhancing binding to receptor proteins, in drugs with different pharmacological actions.

It would be desirable if differences in anticoccidial potency between the present benzophenones and the earlier diphenyl sulfide derivatives could be related to the physical–chemical properties of these compounds. A straightforward comparison would not, however, be meaningful because the two series undergo rapid and different transformations in vivo to active metabolites. Fortunately, in both cases the active metabolites are relatively long-lived and have been identified and tested, so they can be compared. The carbinols are calculated[13] to be about as lipophilic as the sulfones (Hansch relative hydrophobicity: C_6H_5CHOH, 0.69; $C_6H_5SO_2$, 0.62) but less acidic (Hammett substituent constant: C_6H_5CHOH, −0.03; $C_6H_5SO_2$, 0.68); the greater acidity of the sulfones may contribute to their somewhat higher potency.[2]

In extensive testing, compound **20** was shown to control all species of pathogenic coccidia that are commonly encountered in chickens[7] and to possess a wide margin of safety in broilers. During toxicological studies, however, it was found to produce teratogenic effects, and for that reason it was not developed commercially.

Experimental Section

Melting points were determined in capillary tubes on a Thomas-Hoover apparatus and are uncorrected. IR spectra were measured on a Perkin-Elmer Model 21 spectrometer. NMR spectra were recorded on a Varian Model A-60 spectrometer. Mass spectra were determined on a Hitachi Perkin-Elmer Model EU-6 spectrometer. Microanalyses were conducted in these laboratories under the direction of Steve Georgian. Thin-layer chromatography was performed on Eastman silica gel plates 6060 with fluorescent indicator in a system of EtOAc/benzene/HOAc in the ratio of 33:67:5. Visualization was accomplished with UV light, iodine vapor, or modified Ehrlich's spray, alone or in combination.

Synthesis of Aminobenzophenones 5. Method A. The following route is illustrative for aminobenzophenones prepared by route A and is exemplified for the synthesis of the precursor of **25**. A cooled slurry of 2.08 g (0.014 mol) of *m*-acetotoluidide and 7.44 g (0.056 mol) of anhydrous $AlCl_3$ was stirred rapidly under an N_2 atmosphere as 3.92 g (0.028 mol) of benzoyl chloride was added dropwise. The resulting orange solution was stirred at room temperature for 30 min and then heated on a steam bath for 2 h. After cooling, the thick mass was poured onto ice–water layered with EtOAc. The organic solution was washed with H_2O and evaporated to give 5.7 g of a thick gum, which was heated on a steam bath for 1 h with 25 mL of 6 N HCl. The resulting solution was neutralized with excess bicarbonate solution and extracted with CH_2Cl_2. Evaporation of solvent afforded 2.8 g (94%) of yellow crystals, mp 115–121 °C. Recrystallization from CH_2Cl_2–hexane afforded 2.39 g (81%) of product: mp 139–141 °C; IR (KBr) 2.94 (NH), 6.08 (CO), 6.21, 7.55, 11.08, 12.10 μm; NMR ($CDCl_3$) δ 6.2–7.8 (m, 8, ArH), 4.1 (s, 2, NH_2), 2.4 (s, 3, CH_3); mass spectrum, *m/e* (relative intensity) 212 (16), 211 (100), 194 (23), 134 (86). Anal. ($C_{14}H_{13}NO$) C, H, N.

Method B. Method B is illustrated for the synthesis of **5a**,

(10) S. Renaud, R. Morazain, J. P. Sauvanet, E. Dumont, and P. Drouin, *Haemostasis*, 8, 82 (1979); R. R. Brodie, L. F. Chasseaud, F. F. Elsom, E. R. Franklin, and T. Taylor, *Arzneim.-Forsch.*, **26**, 896 (1976); K. Seri, R. Sato, Y. Hamazaki, T. Yamamoto, and N. Ishiyama, *Atherosclerosis*, **37**, 97 (1980); Carlo Erba, French Patent 2 205 337 (1973); *Unlisted Drugs*, **25**, 188c (1973).

(11) H. J. Kane, C. A. Behm, and C. Bryant, *Mol. Biochem. Parasitol.*, 1, 347 (1980); USAN, "USP Dictionary of Drug Names", 1980, p 288 (salantel); S. E. Knapp and P. J. Presidente, *Am. J. Vet. Res.*, **32**, 1289 (1971).

(12) USAN, "USP Dictionary of Drug Names", 1980, pp 108 (diflumidone) and 332 (triflumidate).

(13) C. Hansch and A. Leo, "Substituent Constants for Correlation Analysis in Chemistry and Biology", Wiley, New York, 1979; W. N. White, R. Schlitt, and D. Gwynn, *J. Org. Chem.*, **26**, 3613 (1961); W. Little, *J. Am. Chem. Soc.*, **86**, 1382 (1964); M. Charton, *Prog. Phys. Org. Chem.*, **13**, 119 (1981). We thank Dr. B. W. Dominy for these calculations.

the precursor of **20**. To 2-chloro-4-nitrobenzoyl chloride (**6a**) [obtained by standard methods from 1300 g (6.4 mol) of 2-chloro-4-nitrobenzoic acid and 640 mL (8.6 mol) of thionyl chloride] under an N_2 atmosphere in 6400 mL of $CHCl_3$ were added 1440 g (12.8 mol) of chlorobenzene and 940 g (7.4 mol) of anhydrous $AlCl_3$. The reaction was stirred at room temperature overnight and then refluxed for 1 h. After cooling, the reaction mixture was quenched with excess ice and 1900 mL of concentrated HCl, and the resulting solid was granulated for 30 min. The product was dissolved in 3200 mL of $CHCl_3$ and washed with 2000 mL of 10% NaOH solution and 2000 mL of brine. The solution was concentrated to an oil, and 2800 mL of MeOH was added. The solution was again concentrated to an oil and diluted with an additional 1000 mL of MeOH. After the solution was stirred overnight at room temperature, a solid separated, which was collected by filtration, washed with 3800 mL of MeOH, and air-dried to give 1602 g (83.5%) of **8a**. This material was used immediately in the hydrogenation step after characterization by TLC analysis.

Alternatively, 3 mL of trifluoromethanesulfonic acid was added to a solution of 72.5 g (0.33 mol) of 2-chloro-4-nitrobenzoyl chloride **6a** in chlorobenzene at room temperature. The resulting dark solution was refluxed for 6 h, and the excess chlorobenzene was removed under vacuum. The brown residue was extracted with 500 mL of CH_2Cl_2 and washed twice with 250 mL of 5% NaOH solution. The organic solution was stirred with Na_2SO_4 and decolorizing carbon and filtered. The filtrate was evaporated to dryness, and the resulting solid was triturated with 200 mL of MeOH and cooled in an ice bath. The precipitated solid was filtered off and washed with 50 mL of cold MeOH, followed by 200 mL of petroleum ether, and the collected solid was air-dried: yield 68.5 g (69.5%); mp 117–118.5 °C.

Hydrogenation of 8a. A 15-gal high-pressure autoclave was charged with 1600 g (5.4 mol) of **8a**, 16 L of tetrahydrofuran (THF), 320 g of 5% palladium on carbon (50% wet with water), and a hydrogen atmosphere of 100 psi. The mixture was agitated at 25 °C until the pressure had fallen to 40 psi. The system was then recharged to 100 psi and agitated for 45 min. The catalyst was filtered and washed with THF. The filtrate was concentrated to 4000 mL, and 12 L of *i*-PrOH was added. The resulting solution was concentrated to 2000 mL, from which a first crop of product was obtained. Concentration of the mother liquor afforded a second crop. The crops were combined and air-dried, affording 997 g (70%) of product: mp 157–160 °C; IR (KBr) 3.00 (NH), 6.02 (CO), 6.22, 7.55, 8.00, 9.20, 10.68, 13.13 μm. Anal. ($C_{13}H_9Cl_2NO$) C, H, Cl, N.

Reduction of 8 with Stannous Chloride. Alternatively, amino ketones **5** could be prepared from nitrobenzophenones by reduction with $SnCl_2$ as in the following example for the precursor of **24**. To 15.9 g (0.045 mol) of **8b** in 120 mL of dimethoxyethane and 150 mL of 95% EtOH was added a solution of 31.5 g (0.14 mol) of $SnCl_2 \cdot 2H_2O$ in 125 mL of concentrated HCl at such a rate that the temperature did not exceed 40 °C. After stirring several hours at room temperature, the reaction mixture was quenched with excess ice–water layered with CH_2Cl_2. The reaction mixture was adjusted to pH 11 with 10% NaOH solution, and the organic layer was washed with H_2O and brine and dried over Na_2SO_4. Concentration of solvent afforded an oily solid, which was converted in ether with HCl gas to 11.0 g (68%) of the hydrochloride salt: mp >290 °C dec; IR (KBr) 5.99 (CO), 6.19, 7.68, 7.96, 10.70 μm; NMR (D_2O) δ 6.8–7.7 (m, 6, ArH), 2.5 (s, 3, CH_3). A satisfactory analysis was not obtained for this intermediate, but it was transformed to **24**, which was adequately characterized.

Synthesis of 6-Azauracils from 5 and Cyanoacetylurethane. The following procedure is typical for the cyanoacetylurethane route and is exemplified for the preparation of **31**. To a solution of 12.8 g (0.040 mol) of **5c**·HCl in 500 mL of H_2O was added 80 mL of concentrated HCl. The solution was maintained at −5 to 0 °C as a solution of 4.03 g (0.044 mol) of $NaNO_2$ in 8 mL of H_2O was added slowly beneath the surface. After about 15 min, the solution of **9c** was filtered to remove small amounts of separated solid. It was maintained at 0 °C as it was added slowly to a solution of 6.6 g (0.044 mol) of cyanoacetylurethane in 250 mL of pyridine and 700 mL of H_2O, which was also maintained at 0 °C. A yellow solid (**10c**) began to crystallize almost immediately. After 30–40 min, the product was collected, washed well with H_2O, and air-dried to give 18.9 g of crude product. This was recrystallized from HOAc–H_2O to give 14.7 g (82%) of product: mp 155–175 °C; IR (KBr) 3.10 (NH), 4.51 (CN), 5.63 (CO), 5.84 (CO), 5.95, 6.25, 6.70, 7.77, 8.36, 9.78, 10.88 μm; mass spectrum, *m/e* 447. This material was not characterized further but used directly in the next step.

Preparation of the Nitrile. A slurry of 14.65 g (0.032 mol) of **10c**, 2.6 g (0.032 mol) of anhydrous NaOAc, and 250 mL of glacial HOAc was stirred at reflux for 3 h. The resulting yellow solution was concentrated to 50 mL and cooled. Water was added dropwise with stirring as a solid separated. This was filtered, washed with H_2O, and air-dried to give 8.0 g (62%) of the cyclized nitrile **12c**. The material was characterized by TLC analysis and carried on immediately to the next step.

Conversion of the Nitrile to the Carboxylic Acid. A slurry of 7.5 g (0.018 mol) of **12c** in 175 mL of glacial HOAc and 20 mL of concentrated HCl was refluxed overnight. The resulting clear solution was concentrated to a dark foam, which was triturated with H_2O to give, after filtration and drying, 6.9 g (91%) of crude **14c**. The material was purified by triturating with CH_2Cl_2 and then crystallizing from MeOH–H_2O. There was obtained 2.76 g (30%) of pure **14c**: mp 188–190 °C dec; IR (KBr) 2.90–3.15 (broad OH and NH), 5.70–5.85 (broad CO), 6.28, 6.45, 7.13, 7.55, 7.93, 10.75 μm; mass spectrum, *m/e* 419 to 375. This material exhibited one spot on TLC analysis and was used directly in the next step.

Preparation of 31. To 2.14 mL of mercaptoacetic acid heated to 100 °C under an N_2 atmosphere was added 2.14 g (5.0 mmol) of **14c**. The resulting slurry was stirred rapidly and heated to 170 °C as a solution formed and CO_2 was evolved. After 1.3 h, the solution was cooled as crystallization commenced. About 20 mL of H_2O was added, and the product was collected, washed with H_2O, and dried to give 2.05 g of yellow crystals. Recrystallization from hot MeOH afforded 830 mg (44%) of pure **31**: mp 130–135 °C; IR (KBr) 2.95 (NH), 5.77–5.93 (broad CO), 6.28, 7.17, 7.49, 7.89, 9.18, 10.77 μm; NMR ($CDCl_3$ + Me_2SO-d_6) δ 7.2–7.9 (m, 7, ArH), 2.20 (s, 3, CH_3); mass spectrum, *m/e* (relative intensity) 375 (42), 304 (17), 264 (68), 139 (100). Anal. ($C_{17}H_{11}Cl_2N_3O_3$) C, H, N.

Synthesis of 6-Azauracils from 5 and Malonyldiurethane. The following example for **14a** is illustrative of the "combined-step" synthesis **5** → **9** → **11** → **13** → **14**. A slurry of 1380 g (5.2 mol) of **5a** in 18.5 L of HOAc and 1.455 L of concentrated HCl was stirred under an N_2 atmosphere for 30 min at room temperature. A solution of 400 g (4.7 mol) of $NaNO_2$ in 1.04 L of H_2O was added while maintaining the reaction temperature between 10 and 15 °C. After 30 min at 10 °C, the solution of **9a** was treated with 1050 g of NaOAc and 1400 g of malonyldiurethane. An exotherm resulted, which was controlled by external cooling. After 1 h at room temperature, the solution of **11a** was treated with 424 g of NaOAc and heated at 106 °C for 2 h. The resulting solution, which contained **13a**, was diluted with 5.6 L of 50% aqueous H_2SO_4, and heating was continued for 2 h. The stirring rate was increased, and 26 L of H_2O was added to induce crystallization. After granulation for 30 min, the crystals were collected by suction filtration and washed well with H_2O to give a wet cake of **14a**. The cake was stirred with 30 L of saturated $NaHCO_3$ solution. After 30 min, 8 L of EtOAc was added, and stirring was continued rapidly for 30 min. The resulting solids were collected, and the layers in the filtrate were allowed to separate. The aqueous layer and solids were combined and adjusted to pH 1.0 during rapid stirring with 4 L of concentrated HCl. The resulting crystals were collected by suction filtration, washed with H_2O, and air-dried at 50 °C to give 1355 g (65%) of product, mp 295–297 °C dec. Anal. ($C_{17}H_9Cl_2N_3O_5 \cdot H_2O$) C, H, N.

Synthesis of 20. A procedure similar to that for **31** was followed. From 1350 g (3.3 mol) of **14a**, 2700 mL (35 mol) of propionic acid, and 270 mL (3.6 mol) of mercaptoacetic acid there was obtained crude **20**. Recrystallization from acetone/*i*-PrOH afforded 850 g (71%) of pure product: mp 206–207 °C; IR (KBr) 5.70–5.80 (CO), 5.98 (CO), 6.24, 7.12, 7.73, 8.94, 9.15, 10.69, 11.74 μm; NMR [$CDCl_3$ + $(CD_3)_2SO$] δ 12.50 (broad s, 1, NH), 7.55–7.95 (m, 8, ArH); mass spectrum, *m/e* (relative intensity) 363 (29), 361 (43), 250 (41), 139 (100). Anal. ($C_{16}H_9Cl_2N_3O_3$) C, H, N.

Synthesis of Alcohol 35. The following example is illustrative for the method of synthesis of alcohols. To a slurry of 2.0 g (5.6

mmol) of **20** in 300 mL of H_2O and 60 mL of 10% aqueous NaOH was added 216 mg (5.6 mmol) of $NaBH_4$. The resulting slurry was stirred for 18 h as a light yellow solution gradually developed. The product was precipitated by the slow addition of 10% aqueous HCl to pH 2.0. The crystals were collected, washed with H_2O, and dried to give 1.8 g (88%) of product: mp 179–181 °C (acetone/*i*-PrOH); IR (KBr) 2.90 (broad NH and OH), 5.76 and 5.87 (CO), 6.68, 7.16, 7.46, 9.01, 9.16, 11.50 μm; mass spectrum, *m/e* 363. Anal. ($C_{16}H_{11}Cl_2N_3O_3 \cdot 0.25H_2O$) C, H, N.

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Registry No. 1, 83437-12-1; **5a**, 50274-85-6; **5b**·HCl, 83437-13-2; **5c**·HCl, 83437-14-3; **6a**, 7073-36-1; **8a**, 50274-64-1; **10c**, 83437-15-4; **11a**, 53334-38-6; **12c**, 83437-16-5; **13a**, 53266-65-2; **14a**, 83437-29-0; **14c**, 40913-56-2; **15**, 38571-25-4; **16**, 38571-18-5; **17**, 83437-17-6; **18**, 38571-18-5; **19**, 38571-27-6; **20**, 38571-19-6; **21**, 83437-18-7; **22**, 83437-19-8; **23**, 38571-37-8; **24**, 57715-86-3; **25**, 38571-26-5; **26**, 38571-28-7; **27**, 38571-35-6; **28**, 38571-34-5; **29**, 38571-36-7; **30**, 38571-38-9; **31**, 38560-82-6; **32**, 83437-20-1; **33**, 83437-21-2; **34**, 83437-22-3; **35**, 38561-06-7; **36**, 38561-08-9; **37**, 38561-07-8; **38**, 83437-23-4; **39**, 83437-24-5; **40**, 83437-25-6; **41**, 83437-26-7; **42**, 83437-27-8; **43**, 83437-28-9; **44**, 38560-76-8; *m*-acetotoluidide, 537-92-8; benzoyl chloride, 98-88-4; 4-amino-2-methylbenzophenone, 30086-89-6; chlorobenzene, 108-90-7; cyanoacetylurethane, 6629-04-5; malonyldiurethane, 49754-15-6.

2-Benzazepines. 2.[1,2] Thiazolo[5,4-*d*][2]benzazepines

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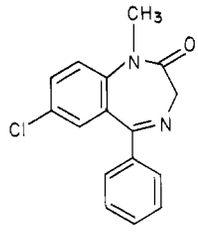
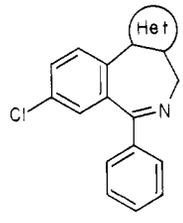
As part of a program in the area of annelated 2-benzazepines, several thiazolo[5,4-*d*][2]benzazepines were prepared. Treatment of the bromo ketones **7–9** with various thio amides gave the thiazoles **10–15**, which when treated with methylamine gave the title compounds. The preliminary pharmacology of these compounds showed that they had central nervous system activity similar to the 1,4-benzodiazepines, such as diazepam. The thiazolo[5,4-*d*][2]benzazepines were also found to bind to the benzodiazepine–receptor complex, indicating that their pharmacological actions are probably related to the 1,4-benzodiazepines.

Although an extensive amount of work has been done in the area of 1,4-benzodiazepines, such as diazepam (**1**), especially in regards to their use as anxiolytic agents,[3] very little information exists on the chemistry and/or pharmacology of the corresponding 1-carbon isoteres, the 2-benzazepines, especially 4,5-heterocyclic-fused compounds, **2**.[4]



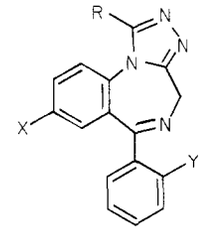
1 (diazepam)



2 (4,5-fused 2-benzazepine)

A further impetus toward preparing compounds of general structure **2** was provided by the triazolo-1,4-benzodiazepines, **3**, discovered by Upjohn.[5] These triazolo-1,4-benzodiazepines, depending on the substituents, have pharmacological profiles ranging from anxiolytics to hypnotics.

One generalization about the activity of the 1,4-benzodiazepines is that along with anxiolytic properties, there is always various degrees of sedation, muscle relaxation, and anticonvulsant, ataxia, and ethanol potentiating effects. Therefore, a program in the area of 4,5-heterocyclo-2-benzazepines was undertaken in an attempt to prepare compounds that might show anxiolytic activity with possibly a different profile than the 1,4-benzodiazepines.



3

The following is an account of the synthesis and pharmacological activity of novel thiazolo[5,4-*d*][2]benzazepines.

Chemistry. The starting materials for the preparation of thiazolo[5,4-*d*][2]benzazepines were the acetylenic compounds **1–3** described by Trybulski et al.[2] Hydration of **1–3** with formic acid/water in the presence of mercuric sulfate gave the ketones **4–6**. Bromination of **4–6** with cupric bromide yielded the bromo ketones **7–9**, which condensed readily with thiourea or thioacetamide to give the thiazoles **10–15**. Removal of the phthaloyl group by treatment of **10–15** with methylamine gave the thiazolo[5,4-*d*][2]benzazepines **16–21**; see Scheme I. The melting points and yields for compounds **4–21** are listed in Tables I–III.

A less efficient synthesis of compound **17** started with the alcohol **22** and is outlined in Scheme II. Oxidation of **22** with pyridinium chlorochromate gave the aldehyde **23**, which was further oxidized by the method of Corey et al.[6] and gave the methyl ester **24**. Condensation of **24** with the anion of acetonitrile gave the keto nitrile **25**. Treatment of **25** with cupric bromide gave the bromo ketone **26**, which, without purification, was condensed with thiourea to give the thiazole **27**. Treatment of **27** with acetic an-

(1) Dedicated to the memory of Dr. Willy Leimgruber who died July 8, 1981.
(2) Paper 1: Trybulski, E. J.; Reeder, E.; Blount, J. F.; Walser, A.; Fryer, R. I. *J. Org. Chem.* **1982**, *47*, 2441.
(3) Sternbach, L. H. "The Benzodiazepines"; Garattini, S.; Mussini, E.; Randall, L. O., Eds.; Raven Press: New York, 1973; pp 1–26. Gschwend, H. W. "Anxiolytics"; Fielding, S.; Lal, H., Eds; Futura Publishing Co.: Mt. Kisco, NY, 1979; pp 1–40.
(4) During the course of this work, a patent appeared describing the synthesis of pyrazolo-2-benzazepines: Gschwend, H. U.S. Patent 3 947 585, 1976.
(5) Rudzik, A. D.; Hester, J. B.; Tang, A. H.; Straw, R. N.; Friis, W. In ref 3, pp 285–297.
(6) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.

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