solution of NaOMe in MeOH (7.69 mL of 3.11 N solution, 0.024 mol) was added to a solution of 3 (8.03 g, 0.024 mol) in EtOH (500 mL). The solution was evaporated under reduced pressure, and the residue was washed with ether and dried in vacuo to give 8.28 g (97%) of 4 as a yellow solid: mp 231 °C dec. Anal. ($C_{17}H_{14}ClFNO_3Na$ with 1.95% of H_2O) C, H, Cl N, Na.

4-[[(4-Chlorophenyl)(5-fluoro-2-hydroxyphenyl)-methylene]amino]butanamide (5). The ketone 2 (15 g, 0.06 mol) was added to a solution of 4-aminobutanamide hydrochloride (9 g, 0.065 mol) and NaOMe (3.25 g, 0.06 mol) in MeOH (0.6 L). The mixture was evaporated to near dryness at 60 °C under reduced pressure. EtOH (0.4 L) was added and the solvent evaporated as before. The yellow residue obtained was dissolved in $CHCl_3$, washed (H_2O), dried ($MgSO_4$), and evaporated to dryness under reduced pressure to give a solid. Recrystallization from light petroleum (bp 60–80 °C) gave 18 g (90%) of 5 as a bright yellow solid: mp 137–140 °C. A further recrystallization from AcOEt gave 16 g (80%) of 5, mp 139–141 °C.

DTA suggested that 5 existed in two crystalline forms: A, mp 136 °C; B, mp 142.5 °C. IR (KBr) 3400, 3200 (ν NH_2), 1655 (ν C=O), 1620 (ν C=N), 1580, 1490 (ν aromatic C=C) cm^{-1}; UV λ_{max} (MeOH) 332 (ϵ 4200), 250 (10 800), 210 (24 000); ^1H NMR (80 MHz, Me_2SO-d_6) δ 15.1 (s, 1, O*H*), 7.2–7.8 (m, 4, $H_{2'}$, $H_{3'}$, $H_{5'}$, $H_{6'}$), 7.1–7.4 (3 d, 1, $^3J_{H_4F}$ = 8 Hz, $^3J_{H_4H_3}$ = 9 Hz, $^4J_{H_4H_6}$ = 3 Hz, H_4), 6.8–7.1 (2 d, 1, $^3J_{H_3H_4}$ = 9 Hz, $^3J_{H_3F}$ = 5 Hz, H_3), 6.7 (br, 2, CON*H*$_2$), 6.25–6.60 (2 d, 1, $^3J_{H_6F}$ = 10 Hz, $^4J_{H_6H_4}$ = 3 Hz, H_6), 3.3 (t, 2, $^3J_{HH}$ = 6.5 Hz, NC*H*$_2$CH$_2$–), 1.6–2.4 (m, 4, –C*H*$_2$C*H*$_2$CONH$_2$); ^{13}C NMR ($CDCl_3$, 50.29 MHz) proton noise decoupled δ 26.3 (s, $CH_2CH_2CH_2$), 33.0 (s, *C*H$_2$CONH$_2$), 51.0 (s, =NCH$_2$), 116.5 (d, $^2J_{CF}$ = 24.5 Hz, C-6), 199.0 (d, $^3J_{CF}$ = 8 Hz, C-3), 119.4 (d, $^3J_{CF}$ = 7.0 Hz, C-1), 119.9 (d, $^2J_{CF}$ = 23.5 Hz, C-4), 128.8 (s, C-3′ and C-5′), 129.5 (s, C-2′ and C-6′), 131.8 (s, C-1′), 135.8 (s, C-4′), 154.6 (d, $^1J_{CF}$ = 235.3 Hz, C-5), 159.3 (br s, C-2), 172.8 (d, $^4J_{CF}$ = 3.0 Hz, *C*=NCH–), 174.7 (s, *C*ONH$_2$). Anal. ($C_{17}H_{16}ClFN_2O_2$) C, H, Cl, F, N.

Pharmacology. Acute Lethality in Mice. Compounds were administered by either the intraperitoneal or oral route to male albino mice (CD_1, Charles River, France, weighing 18–22 g), which were then returned to their home cages (10 mice per cage). The number of dead mice from each dose were noted 48 h or 7 days after intraperitoneal or oral administration, respectively. LD_{50} values (dose inducing death in 50% of the mice) were determined, by use of log-probit paper.[17]

Antagonism of Bicuculline-Induced Lethality in Mice. Compounds were injected intraperitoneally, at predetermined serial doses, 30 min before bicuculline (0.9 mg/kg, iv). The percentage of mice dead (10 mice per drug per dose and per experiment) were noted 3 h after the injection of bicuculline (controls: 100% mortality). The ED_{50} (dose protecting 50% of the mice against the lethal effect of bicuculline) was obtained for each compound by the use of log-probit paper.[17]

Antagonism of Bicuculline-Induced Clonic Convulsions in Mice. Compounds were injected intraperitoneally, at increasing doses, 30 min before bicuculline (0.45 mg/kg, iv). The percentage of mice convulsing were noted during 1 h after bicuculline (controls: 100% clonic convulsions and 10–20% tonic convulsions and death). The ED_{50} (dose protecting 50% of the animals against bicuculline clonic convulsions) was calculated for each compound using log-probit paper.[17]

Displacement of [^{3}H]γAbu Binding in Rat and Human Brains. The affinity of the compounds for the [^{3}H]γAbu binding site to membranes prepared from rat whole brains (Triton-X-100 treated) or human cerebellar cortex (no Triton treatment) was determined by the method of Enna and Snyder,[18] as modified by Lloyd et al.[19] Compounds (final concentration range 5×10^{-9} to 10^{-4} M) were incubated in the presence of 4×10^{-9} M [^{3}H]γAbu (45 Ci/mmol, Amersham Nuclear), and the displacement of [^{3}H]Abu binding was determined by scintillation spectrometry (Nuclear Chicago Mark III).

γAbu Mimetic Activity on Rat Dorsal-Root Ganglion Neurons. Compounds were administered by transient superfusion of rat dorsal-root ganglia in vitro. Single-barrel intracellular electrodes were used to record the membrane potential and also to pass constant-current transmembrane pulses, by means of which the membrane conductance could be estimated.[20] With this method of application, threshold responses (1 mV) are obtained with concentrations of 5×10^{-6} to 5×10^{-5} M γAbu. The maximum response (up to 25 mV) is obtained at concentrations greater than 10^{-4} M.

Acknowledgment. The authors thank J. P. Merda and F. Laurent for the technical assistance in the chemistry work and Dr. J. P. Renou for the ^{13}C NMR data.

(17) Miller, L. C.; Tainter, M. L. *Proc. Soc. Exp. Biol. Med.* **1944**, *57*, 261–264.

(18) Enna, S. J.; Snyder, S. H. *Brain Res.* **1975**, *100*, 81–97.

(19) Lloyd, K. G.; Shemen, L.; Hornykiewicz, O. *Brain Res.* **1977**, *127*, 269–278.

(20) Desarmenien, M.; Feltz, P.; Headley, P. M. *J. Physiol. (Paris)*, in press.

Neuroleptic 4-Aryltetrahydropyrrolo[3,4-*b*]indoles

Willard M. Welch,* Charles A. Harbert,

Department of Medicinal Chemistry

and Albert Weissman

Department of Pharmacology, Pfizer Central Research Laboratories, Groton, Connecticut 06340. *Received November 8, 1979*

7-Fluoro-4-(4-fluorophenyl)-2-[4-(4-fluorophenyl)-4-hydroxybutyl]-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole displayed neuroleptic-like activity in an animal model approximately equipotent with that of chlorpromazine but was of substantially greater duration of action. Structure–activity relationships of the series are discussed.

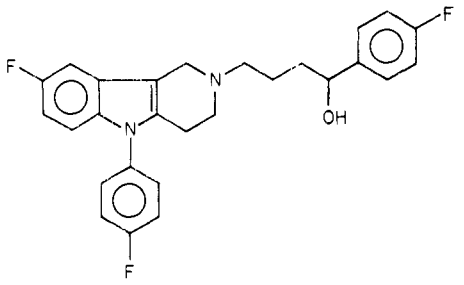
Previous papers from our laboratories have described the discovery of potent neuroleptic activity in a series of 5-aryl-1,2,3,4-tetrahydro-γ-carbolines[1,2] and the development of structure–activity relationships within this series[3] leading to the potent and long-acting derivative CP-36 584 (I). This paper extends the previously reported work to a series of 4-aryl-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indoles

(1) B. K. Koe, A. Weissman, J. J. Plattner, C. A. Harbert, and W. M. Welch, *Pharmacologist*, **21**, 180 (1979).

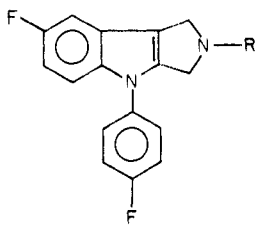
(2) C. A. Harbert, J. J. Plattner, W. M. Welch, A. Weissman, and B. K. Koe, *Mol. Pharmacol.*, **17**, 38 (1980).

(3) C. A. Harbert, J. J. Plattner, W. M. Welch, A. Weissman, and B. K. Koe, *J. Med. Chem.*, **23**, under articles in this issue (1980).

0022-2623/80/1823-0704$01.00/0



I

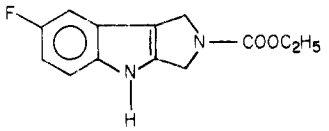


II

II which serve as highly rigid, conformationally restrained probes of structural features necessary for interaction with dopamine receptor(s) in mammalian brain. Since we had previously found in the γ-carboline series that fluorine in position 8 and 4-fluorophenyl at position 5 conferred optimal neuroleptic potency in that series, the synthetic effort in the pyrroloindole series was directed primarily to side-chain derivatives of II bearing fluorine substituents at these positions.

Tetrahydropyrrolo[3,4-*b*]indoles have not been extensively investigated, although a limited number of these compounds have been prepared.[4,5] 4-Aryl derivatives of this interesting heterocycle were not previously known in the chemical literature until a recent publication[6] from this laboratory.

Synthesis. 2-Carbethoxy-7-fluoro-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole (III) was prepared in 35% overall yield



III

by Fischer cyclization of the hydrazone prepared from 4-fluorophenylhydrazine and *N*-carbethoxy-3-pyrrolidinone.[7] This cyclization was sensitive to reaction conditions and was best accomplished in 85% phosphoric acid at or slightly above room temperature. The previously described[3] modified Ullmann arylation procedure applied to this compound gave the 4-(4-fluorophenyl) derivative **1** in 60% yield. Subsequent hydrolysis and alkylation procedures applicable to the synthesis of the various alkyl derivatives listed in Table I have been previously described.[3]

Pharmacology. Potential antipsychotic activity of the compounds appearing in Table I was assessed by their ability to antagonize the stereotypy induced in rats by *d*-amphetamine (5 mg/kg, ip) as described by Weissman.[8] Amphetamine was given 1, 5, and 24 h after the administration of drug to assess the duration of action of the listed compounds. Although ip values are presented in Table I, active compounds were orally effective at approximately three times the ip dose.

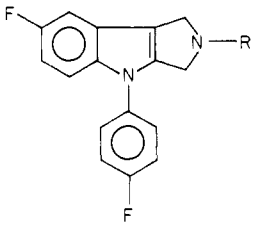
Structure–Activity Relationships. Since structure–activity relationships (SAR) in this series were expected to parallel those previously developed in the 8-fluoro-5-(4-fluorophenyl)-1,2,3,4-tetrahydro-γ-carboline series,[3] this nuclear substitution pattern was selected as a basis for investigation. The results presented in Table I show that this series does not possess the potency or duration of action advantages previously seen with the corresponding tetrahydro-γ-carboline derivatives; in general, however, the SAR paralleled that seen with the carbolines. Thus, the 2-methyl analogue **3** shows evidence of amphetamine antagonism in the rat; however, this compound is only about one-third as active as the corresponding γ-carboline derivative (ED_{50} = 1.0–3.2 mg/kg)[3] and its duration of action is much shorter. The secondary amine **1** and compounds **4–6**, bearing larger simple alkyl groups in position 2, were inactive at the highest doses tested (32 mg/kg).

Enhanced potency and duration of action were achieved through butyrophenone substitution at position 2. It is clear that the 4′-fluorobutyrophenone derivative **9** and its reduced congener **10** are superior to both the unsubstituted analogues **7** and **8** and the homologues **11** and **12**. Although **10** is as potent as chlorpromazine (ED_{50} = 3.2 mg/kg) and longer acting, its activity is remarkably diminished by comparison with I, suggesting that the pyrroloindole nucleus of **10** lacks the more precise spatial conformation of the carboline nucleus that is required to fit dopamine binding site(s), other elements of these two molecules being very nearly the same. As was the case in the carboline series, the secondary alcohols **8**, **10**, and **12** were, in all cases, more potent than the corresponding ketones, again suggesting that the role of the 4-hydroxy-4-phenylbutyl side chain is to assist in transport to the receptor site rather than receptor interaction.

4-Aryltetrahydropyrrolo[3,4-*b*]indoles thus represent a novel series of orally active neuroleptic agents exhibiting equal potency and superior duration of action to chlorpromazine but whose potency is lower (about one-third to one-tenth times) than that of the previously reported series of 5-aryltetrahydro-γ-carbolines.[3] Whereas certain of these compounds are sufficiently active to be of interest as potential antipsychotic agents, their overriding interest has been as conformationally restricted structures with the ability to block dopamine receptor(s). The rigidity of the tetrahydropyrrolo[3,4-*b*]indole tricyclic nucleus is marked and, by comparison with the less restricted γ-carbolines, permits certain conclusions to be drawn about the optimum stereospatial conformation of agents designed to fit dopamine receptor(s) in mammalian brain. In particular, Dreiding models of compound **10** indicate that, although the aromatic ring–basic nitrogen distance in tetrahydropyrrolo[3,4-*b*]indoles is very close (5.15 Å) to that observed in the tetrahydro-γ-carboline homologues (5.16 Å), the basic nitrogen atom at position 2 lies at most ±0.1 Å out of the plane of the indole ring. This distance is considerably less than the ±0.6 Å out-of-plane distance found for the more active γ-carboline homologues[9] and thus implies that the coplanarity of the aryl ring and basic nitrogen atom is deleterious to favorable interaction with such receptors.

(4) P. L. Southwick and R. J. Owellen, *J. Org. Chem.*, **25**, 1133 (1960).
(5) N. M. Sharkova, N. F. Kucherova, L. A. Aksanova, and V. A. Zagorevskii, *Khim. Geterotsikl. Soedin.*, 81 (1969); *Chem. Abstr.*, 71, 3204*w*.
(6) W. M. Welch, *J. Org. Chem.*, **41**, 2031 (1976).
(7) Prepared by modification of the procedure of Y.-H. Wu, W. G. Lobeck, Jr., and R. F. Feldkamp, *J. Med. Pharm. Chem.*, **5**, 762 (1962).
(8) A. Weissman, *Psychopharmacologia*, **12**, 142 (1968).
(9) J. Bordner, J. J. Plattner, and W. M. Welch, *Cryst. Struct. Commun.*, in press (1980).

Table I. 4-Aryl-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indoles



compd	R	yield, %	mp, °C	formula[a]	amphetamine blockade (rat): ED_{50},[b] mg/kg ip 1 h	5 h	24 h
1	$COOC_2H_5$	61	143-145	$C_{19}H_{16}O_2N_2F_2$	>32	>32	NT
2	H	63	143-150	$C_{16}H_{12}N_2F_2 \cdot HCl$	>32	>32	32
3	CH_3	65	161-164	$C_{17}H_{14}N_2F_2 \cdot HCl$	3.2-5.6	>10	NT
4	n-C_3H_7	80	193-195	$C_{19}H_{18}N_2F_2 \cdot HI$	>32	>32	NT
5	$CH_2C_6H_5$	49	224.5-226.0	$C_{23}H_{18}N_2F_2 \cdot HCl$	>32	>32	NT
6	$CH_2CH_2C_6H_5$	64	222-223	$C_{24}H_{20}N_2F_2 \cdot HCl$	>32	>32	NT
7	$(CH_2)_3COC_6H_5$	15	219.5-221.0	$C_{26}H_{22}ON_2F_2 \cdot HCl$	>32	>32	NT
8	$(CH_2)_3CHOHC_6H_5$	73	205.0-206.5	$C_{26}H_{24}ON_2F_2 \cdot HCl$	10-32	>10	>32
9	$(CH_3)_3CO(4\text{-}FC_6H_4)$	32	175-179 dec	$C_{26}H_{21}ON_2F_3 \cdot HCl$	3.2-10	3.2-10	>10
10	$(CH_2)_3CHOH(4\text{-}FC_6H_4)$	47	210.0-211.5	$C_{26}H_{23}ON_2F_3 \cdot HCl$	1.0-3.2	1.0-3.2	3.2-10
11	$(CH_2)_4CO(4\text{-}FC_6H_4)$	29	216-217	$C_{27}H_{23}ON_2F_3 \cdot HCl$	32	>32	NT
12	$(CH_3)_4CHOH(4\text{-}FC_6H_4)$	92	200.0-201.5	$C_{27}H_{25}ON_2F_3 \cdot HCl$	>32	10-32	NT
I					0.1-0.32	0.1-0.32	1.0-3.2
III		35	247-250	$C_{13}H_{13}O_2N_2F$	>32	>32	NT
chlorpromazine					3.2-10	17.8	56

[a] All compounds were analyzed for C, H, and N; values were within ±0.4% of calculated values. [b] Entries are ranges within which fall the ED_{50} values for blocking hyperactivity and stereotypy induced by amphetamine. Details are given under Experimental Section.

Experimental Section

Melting points (uncorrected) were taken with a Thomas-Hoover capillary apparatus. NMR spectra were recorded on Varian A-60, T-60, and XL-100 spectrometers with Me_4Si as an internal standard. IR spectra were determined with a Perkin-Elmer Model 21 spectrophotometer. UV spectra were recorded on a Cary Model 14 spectrophotometer. Mass spectra were obtained with a Perkin-Elmer RMU-6E mass spectrometer. Microanalyses were performed by the Pfizer Analytical Department. Several of the compounds described in this paper retained a partial mole of water despite drying in vacuo.

Preparation of 2-Carbethoxy-7-fluoro-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole (III). To a rapidly stirred suspension of 5.67 g (35 mmol) of 4-fluorophenylhydrazine hydrochloride and 2.87 g (35 mmol) of sodium acetate in 200 mL of water was added a solution of 5.50 g (35 mmol) of *N*-carbethoxy-3-pyrrolidinone[7] in 15 mL of water. After 20 min, the resulting hydrazone was separated by filtration, washed with water, and partially dried by suction. An analytical sample was further dried and recrystallized from CH_2Cl_2–hexane. The damp solid above was stirred for 1 h at room temperature in 20 mL of 85% phosphoric acid (an initial slight exotherm occurred) and was then poured into 300 mL of ice–water. The solid which separated was filtered, air-dried, and recrystallized from ethanol to give 3.04 g (35%) of the desired product, mp 247–250 °C.

Preparation of 2-Carbethoxy-7-fluoro-4-(4-fluorophenyl)-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole (1). A mixture of 6.6 g (28 mmol) of 2-carbethoxy-7-fluoro-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole (III), 8.86 g (30.8 mmol) of Cu_2Br_2, 3.28 g (30.8 mmol) of Na_2CO_3, and 17.2 g (98 mmol) of 4-fluorobromobenzene in 75 mL of distilled anhydrous *N*-methylpyrrolidinone was heated at reflux under N_2 for 4 h. The cooled reaction mixture was poured over ice and water and 40 mL of ethylenediamine was added. The resulting suspension was extracted four times with benzene, and the combined organic extracts were then back-washed twice with water. The organic phase was dried over $MgSO_4$ and the solvent was evaporated. The residue was recrystallized from CH_2Cl_2/hexane or CH_3CN to yield the desired product: 5.8 g (60%); mp 143–148 °C.

Preparation of 7-Fluoro-4-(4-fluorophenyl)-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole Hydrochloride (2). A solution of 4.16 g (12 mmol) of the 2-carbethoxy derivative 1 and 13.5 g (0.24 mol) of KOH in 100 mL of ethanol and 10 mL of H_2O was heated at reflux for 18 h. The cooled reaction mixture was evaporated to a brown gum, which was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was further extracted three times with CH_2Cl_2, and then the extracts were combined, dried, and evaporated to a brown oil. This was dissolved in dry ether and treated with dry HCl gas to yield the product (2.6 g, 80%) as a tan crystalline powder. The analytical sample was recrystallized from CH_3CN/CH_3OH, mp 159–160 °C.

Preparation of 7-Fluoro-4-(4-fluorophenyl)-2-methyl-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole Hydrochloride (3). To a stirred solution of 244 mg (6.42 mmol) of lithium aluminum hydride in 20 mL of THF at −10 °C was added portionwise 284 mg (2.14 mmol) of anhydrous $AlCl_3$. This was kept at −10 °C for 30 min and then 1.0 g (2.92 mmol) of the 2-carbethoxy derivative 1 dissolved in 10 mL of THF was added dropwise. After 1 h at −10 °C, the reaction was quenched with 5 mL of H_2O added dropwise. Precipitated aluminum salts were filtered and washed with THF, and then the THF was removed from the filtrate by evaporation. The remaining suspension was extracted three times with ether, and then the combined organic extracts were dried and treated with dry HCl gas in ether to yield the desired product: 605 mg (65%); mp 161–164 °C (sealed tube).

In a similar fashion, the 2-propionyl and 2-(2-phenyl)acetyl derivatives of 2 (prepared by standard acylation of 2 with the requisite acid chloride in CH_2Cl_2 in the presence of triethylamine) were reduced to give compounds 4 and 6 in the yields specified in Table I.

Preparation of 2-Benzyl-7-fluoro-4-(4-fluorophenyl)-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole (5). A solution of 500 mg (1.63 mmol) of compound 2, 418 mg (2.44 mmol) of α-bromotoluene, and 526 mg (4.08 mmol) of diisopropylethylamine in 5 mL of toluene was heated at slow reflux for 30 min. The reaction mixture was then cooled, diluted with 25 mL of ether, and filtered to remove insolubles. The filtrate was treated with dry HCl gas/ether, and the precipitate which formed was collected and recrystallized from acetone/ether to yield 316 mg (49%) of the desired product, mp 224.5–226.0 °C.

Preparation of Compound 9. A mixture of 2.50 g (9.2 mmol) of 7-fluoro-4-(4-fluorophenyl)-1,2,3,4-tetrahydropyrrolo[3,4-*b*]-indole, 2.76 g (13.9 mmol) of γ-chloro-*p*-fluorobutyrophenone, 2.9

g (27.8 mmol) of Na_2CO_3, and 1.5 g (9.7 mmol) of KI in 25 mL of dry DMF was heated at 150 °C for 2 h. Then the cooled reaction mixture was poured into 200 mL of H_2O and extracted with ether three times. The combined etheral extracts were dried, concentrated, and chromatographed on 150 g of silica gel using 1:1 benzene–ethyl acetate as eluent. Product-containing fractions were combined and evaporated, and the residues were dissolved in dry ether and treated with ethereal HCl to give 1.40 g (32%) of the desired product, mp 175–179 °C dec.

In a similar fashion, compound **2** was reacted with the appropriate ω-haloalkyl 4-fluorophenyl ketone to yield compounds **7** and **11** in the yields specified in Table I.

Preparation of Compound 10. A suspension of 700 mg (1.49 mmol) of compound **9** in 25 mL of THF and 5 mL of ethanol was treated with 282 mg (7.45 mmol) of $NaBH_4$ over a period of 30 min. After the solution was stirred an additional hour, the solvents were removed in vacuo, and the residues were taken up in water and repeatedly extracted with ether. The combined ether extracts were dried with $MgSO_4$ and then treated with a solution of dry HCl gas in ether to give 331 mg (47%) of compound **10**, mp 210.0–211.5 °C dec.

In a similar fashion, ketones **7** and **11** were reduced to give compounds **8** and **12** in the yields specified in Table I.

Biological Methods. Antagonism of (+)-Amphetamine-Induced Symptoms in Rats. Neuroleptic effects in vivo were estimated by the blockade of amphetamine stereotypy. Rats were placed individually in covered plastic compartments; after a brief period of acclimation in the cages, the rats in groups of five were treated intraperitoneally with compounds at doses separated by 0.5 log unit (i.e., ..., 1, 3.2, 10, 32, ... mg/kg). They were subsequently treated 1, 5, and 24 h later with *d*-amphetamine sulfate, 5 mg/kg ip. One hour after each amphetamine challenge each rat was assessed for its most characteristic behavior on a six-point scale.[10] These ratings represent increasing degrees of drug effect,[11] and the time of rating chosen coincides with the peak effect of amphetamine.[8] Scores were dichotomized (cf. ref 10), and approximate ED_{50} values were determined, based on the quantal data. Doses are expressed in terms of the respective salts.

Acknowledgment. The authors are grateful to Mrs. C. T. Lewis and to J. W. Homiski and R. L. Taylor for expert technical assistance.

(10) A. Weissman, B. K. Koe, and S. S. Tenen, *J. Pharmacol. Exp. Ther.*, 151, 339 (1966).
(11) R. M. Quinton and G. Halliwell, *Nature (London)*, 200, 178 (1963).

Book Reviews

The Chemistry of Heterocyclic Compounds. Volume 34. Thiazole and Its Derivatives. Part 2. Edited by Jacques V. Metzger. Wiley-Interscience, New York. 1979. xii + 590 pp. 16 × 23.5 cm. $80.00.

The thiazoles of greatest interest to the medicinal chemist are probably those based on the 2-amino derivative. The chemistry of these useful building blocks is discussed in a 361-page chapter in this second volume of a three-part set devoted to thiazoles edited by Professor Jacques V. Metzger. The authors contributing to this monograph hail from Metzger's institution, the University of Aix-Marseilles.

The first section, a nonchapter and running only 9 pages (by M. Chanon), gives a general introduction to protomeric thiazoles. Chapter 6 (by R. Barone, M. Chanon, and R. Gallo) discusses aminothiazoles and their derivatives from the synthetic, spectroscopic, and mechanistic viewpoints. In addition, at the end of the chapter there is a listing of mp/bp data and literature citations pertaining to some 6000 aminothiazoles. Chapter 7 (by C. Roussel, M. Chanon, and R. Barone) describes in a similar manner mercaptothiazoles, hydroxythiazoles and their derivatives. Both chapters have surveys of the medicinal applications of compounds possessing a thiazole ring.

As in Chapter 6, Chapter 7 has a large number (54) of tables listing mp/bp and literature references. The authors are to be complimented for undertaking such extensive compilations; however, locating specific compounds, other than the simplest, is not an easy task. An index to the tables (considering that Chapter 6 has 80 of them) would have been helpful. Furthermore, the tables in Chapter 6 also lack descriptive headings.

In the introduction to the tables of Chapter 7 one is referred to page 171 for "easier use of these tables". On page 171 one finds a few preliminary words regarding the tables of Chapter 6 and then one is referred to Part (Volume) 1, pages 2 and 3, for a guide to the abbreviations used. It is assumed that the reader has a copy available. Certainly, repetition of this list of 22 abbreviations in the second volume would have made life easier for the reader, especially one lacking a copy of Part 1. Furthermore, on page 171, the reader is warned to watch out for l's (ells) following reference numbers and not confuse them with 1's (ones). Indeed, an encounter with a reference number in the tables ending in an l or 1 does require the reader to take a particularly careful look.

The authors do not appear to have been overly concerned with the problem of nomenclature. Examples: one sees "1-morpholino" and "1-piperidino", wherein the 1's are superfluous; throughout Chapter 7 there is constant use of Δ's as in "Δ-4-thiazoline-2-thione". The deltas are also unnecessary and have not been used by Chemical Abstracts since the 1930's. Evidence of French authorship (e.g., ICH_3, pipéridine, NO_3H) is less apparent than in the preceding volume.

Yet, because of the extensive coverage of the subject matter, this volume can be recommended as an important new reference source for those involved in heterocyclic chemistry. The price of $80.00 will probably limit its sale to those individuals working with thiazoles, but scientific libraries will definitely want a copy.

Walter Reed Army Institute of Research **Daniel L. Klayman**

Immunochemistry in Clinical Laboratory Medicine. Edited by A. Milford Ward and J. T. Whicher. University Park Press, Baltimore, Md. 1979. 16.5 × 22.5 cm. x + 247 pp. $29.95.

This book contains the proceedings of a symposium held at the University of Lancaster, March, 1978, and is divided into three basic sections. The first deals with methods and problems in immunochemistry. The seven chapters in this section each give a general overview ranging from antisera production to their use for the quantitation of various body-fluid proteins. All chapters provide readers with a good introduction to both the potential and limitations of various methods utilized for clinical analysis. A major drawback is that the chapters lack sufficient detail to actually duplicate the procedures.

The second section includes chapters on specific proteins in laboratory diagnosis. Introductory chapters discuss the structure and function of the immunoglobulins. Other chapters review the role of albumin, the complement system, alphafetoprotein, α-antitrypsin, haptoglobin, and orosomuscoid in various benign and neoplastic diseases. The chapters are written for those that require a general review or introduction to these proteins as they relate to clinical medicine. As the authors clearly state, there is additional extensive detail published in other reference works.

The third section contains two chapters, one on urinary proteins and the other on the immunochemistry of CSF proteins. These