Solutions or suspensions were administered orally except where mentioned otherwise.

Acute Toxicity. The compounds were administered to three albino mice (CFW) weighing 19–21 g in doses up to 800 mg/kg orally. The mice were observed over 48 h for mortalities and other gross behavioral changes. LD_{50} values were approximated from the results.

Mouse Hypothermia. The rectal temperature of groups of three CFW mice was measured at 15 min, 2.5 h, and 5 h after administration of the compounds. In order to simplify the recording of hypothermia, the "temperature index" method of assessment[13] was used. Taking as a base the mean initial temperature of each group, the mean temperature changes from this figure at the three time intervals were summed and termed the "temperature index". The results are expressed as ED_{min} values, which are the minimum doses (mg/kg po) of the compounds giving a temperature index of at least 5 lower than that of a control group of animals.

Conditioned Avoidance Response (CAR) in Rats. The method was essentially that described by Jacobsen and Sonne.[14] Lilly Wistar rats (120–130 g) were trained to pass from one side of a shuttle box to the other on hearing a 5-s buzzer. Failure to respond within 1 s from the end of the buzzer resulted in the animals receiving a mild electric shock. The compound under tests was administered to only those animals which showed a high level of conditioned response. Groups of five animals were dosed orally 1 h 50 min prior to placing them individually in the shuttle boxes. After a 10-min habituation period, they were tested for 20 min. During this period the number of times the buzzer sounded, as well as the number of shocks received by the animal, was recorded. The degree of conditioned avoidance blockade was calculated by expressing the number of shocks received as a percentage of the number of stimuli presented.

Rat Catalepsy. The method used was essentially that described by Costall and Olley.[15] Groups of eight Lilly Wistar rats (180–190 g) were assessed for the presence of catalepsy at 0.5, 1, 1.5, 2, 3, 4, and 5 h after the oral administration of the compound. The front paws of each animal were placed on a wooden rod 1.5-cm in diameter suspended 7 cm above a table. The length of time the animal maintained this position was recorded up to a maximum of 20 min. Animals were considered to be noncataleptic if they removed their front paws from the bar within 10 s. Each cataleptic animal was assigned a score of from 0 to 5 depending on how long they maintained the imposed posture (0 = <10 s; 1 = 10 s–2.5 min; 2 = 2.5–5 min; 3 = 5–10 min; 4 = 10–20 min; 5 = >20 min). The maximum scores obtained for each animal, regardless of time after dosing, were summed, thus giving a maximum score of 40 for each group.

Acknowledgment. We thank David J. Steggles and Graham H. Timms for some experimental work, Dr. D. M. Rackham and his associates for spectral evidence, G. Maciak for microanalyses of the compounds, S. Bruty for excellent technical help and L. A. Saunders for precision typing of the manuscript.

10-Piperazinyl-4*H*-thieno[3,2-*b*][1,5]- and -[3,4-*b*][1,5]benzodiazepines as Potential Neuroleptics[1]

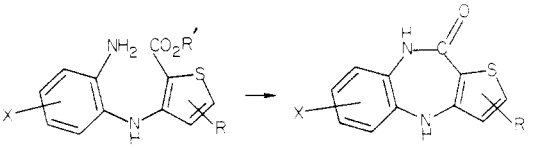
Jiban K. Chakrabarti,* John Fairhurst, Norman J. A. Gutteridge, Linda Horsman, Ian A. Pullar, Colin W. Smith, David J. Steggles, David E. Tupper, and Francesca C. Wright

Lilly Research Centre Limited, Windlesham, Surrey GU20 6PH, England. *Received January 22, 1980*

The synthesis of 10-piperazinyl-4*H*-thieno[3,2-*b*][1,5]- and -[3,4-*b*][1,5]benzodiazepines is described. The activity of these compounds has been assessed on the basis of their ability to produce hypothermia in mice and block a conditioned avoidance response (CAR) and produce catalepsy in rats, and the results are compared with various classical and nonclassical neuroleptic drugs. A number of compounds (**6**, **17**, **21**, and **22**) demonstrate potency greater than clozapine and also show low degree of catalepsy. It is believed that this profile of activity, unlike standard neuroleptics, is associated with the relative lack of extrapyramidal side effects in the clinic. The corresponding 9-piperazinyl-4*H*-thieno[1,4]benzodiazepines (**12** and **35**), limited analogues prepared in the respective series, were inactive.

In the previous paper in this issue,[2] we described the synthesis and evaluation of the neuroleptic activity of a series of 4-substituted 10*H*-thieno[2,3-*b*][1,5]benzodiazepines. This paper is concerned with the preparation of the other two isomeric 10-piperazinyl-4*H*-thieno[3,2-*b*][1,5]- and -[3,4-*b*][1,5]benzodiazepines.[3] The gross CNS activity of these compounds has been established by studying their effects on the behavior of mice. Neuroleptic activity has been examined in terms of their ability to produce hypothermia in mice and inhibit a conditioned avoidance response and produce catalepsy in rats. The results have been compared with various typical and atypical neuroleptics. The respective 9-piperazinyl-4*H*-thieno[1,4]benzodiazepines (**12** and **35**) in each series have also been prepared for comparison of activity.

Scheme I



Chemistry. 4*H*-Thieno[3,2-*b*][1,5]benzodiazepinones. The synthetic route to the diazepinones (**36–39**, Table II) using cyclization of the corresponding amino ester (Scheme I) was previously reported.[4]

4*H*-Thieno[3,4-*b*][1,5]benzodiazepinones. The route to the synthesis of the diazepinones (**40**, **43**, **45**, and **47**) using cyclization of the corresponding amino esters (Scheme I) was described in our earlier paper.[4] The amino

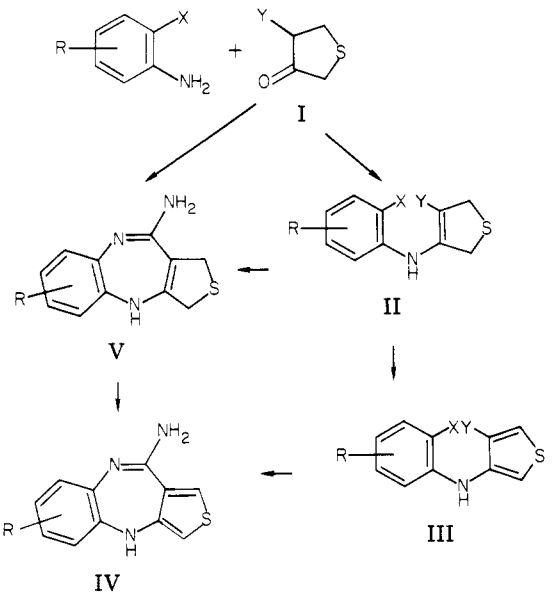
(1) Part 4 of the series: Heteroarenobenzodiazepines; J. K. Chakrabarti and D. E. Tupper, British Patent Application 51 240, 1974; Belgium Patent 835 932, 1976. For part 3, see ref 2.

(2) J. K. Chakrabarti, L. Horsman, T. M. Hotten, I. A. Pullar, D. E. Tupper, and F. C. Wright, *J. Med. Chem.*, preceding paper in this issue.

(3) During the final stage of preparation of our manuscript, a paper reporting 10-(alkylamino)-4*H*-thieno[3,4-*b*][1,5]benzodiazepines as potential neuroleptic agents [J. B. Press, C. M. Hofmann, N. H. Eudy, W. J. Fanshawe, I. P. Day, E. N. Greenblatt, and S. R. Safir, *J. Med. Chem.*, **22**, 725 (1979)] came to our attention. We describe here the different routes to the synthesis of this series of compounds and their pharmacological profile, which is at variance with their observation.

0022-2623/80/1823-0884$01.00/0

Scheme II



esters (III) **68** and **69** were also derived from the condensation of 4-(carboxymethyl)-2,3,4,5-tetrahydrothiophen-3-one[5] with an appropriate 1,2-diaminobenzene and aromatization of the resulting dihydrothiophene (**59**, **60**) by chloranil in boiling toluene/xylene. Similar reaction of the above keto ester with 4-methoxy-2-nitroaniline produced **61**, which on subsequent aromatization gave the nitro ester **70**. Catalytic reduction to the amino ester and cyclization produced the diazepinone **47**. The amino ester **59**, prior to aromatization, was also cyclized to 4*H*-1,3-dihydrothieno[3,4-*b*][1,5]benzodiazepin-10(9*H*)-one, which was also obtained directly by reacting the keto ester with 1,2-diaminobenzene in boiling benzene.[6] 3-Methyl-4*H*-1,3-dihydrothieno[3,4-*b*][1,5]benzodiazepin-10(9*H*)-one (**76**) was similarly prepared and aromatized to **42**.

Alternatively, the diazepinones **40**, **41**, **44**, **46**, **48**, and **49** were prepared by base hydrolysis of the corresponding amidines (IV) which, in turn, were synthesized using two routes (Scheme II), both starting from the readily available 4-cyano-2,3,4,5-tetrahydrothiophen-3-one.[7]

(1) The reaction of a suitably substituted or unsubstituted 2-nitroaniline with the ketone function of I (Y = CN) in the presence of a catalytic amount of BF_3–Et_2O or $TiCl_4$ afforded the nitro enamines **62**–**66**. These readily underwent aromatization with chloranil to give the desired thiophenes **71**–**75** in excellent yields. Catalytic reduction of the nitro group produced the corresponding aminonitriles, which, without further purification, were subjected to acid-catalyzed ring closure to give the required amidines (IV) **50**–**58**.

(2) The other route involved the condensation of 5-(trifluoromethyl)-1,2-diaminobenzene with I (Y = CN) to give dihydrothiophene **67**, which on acid cyclization produced the amidine salt (V) **56**. Conversion to the free base and aromatization gave the required amidine (IV) **58**. It was, however, found that the amidine (V) **55** can be obtained in good yields directly from I (Y = CN) and the corresponding 1,2-diaminobenzene by the same route but without isolating the intermediate aminonitrile (II).

10-Piperazinyl-4*H*-thieno[3,4-*b*][1,5]- and -[3,2-*b*][1,5]benzodiazepines. The amidines (Table I) in the respective series were prepared by reacting the corresponding diazepinones (Table II) with N-substituted piperazines in the presence of $TiCl_4$ and anisole as described in the previous paper.[2] It was, found, however, that the direct reaction of the amidine **57** with *N*-methylpiperazine at higher temperatures gave the desired product in low yield. Similar treatment of the dihydrothiophene **55** produced the same product. TLC monitoring indicated that aromatization to **57** occurred prior to transamination in this case. The 4′-*N*-(carboxyethyl)piperazine compounds were hydrolyzed to give the N-unsubstituted derivatives, which were alkylated to produce the corresponding *N*-alkyl-substituted piperazine compounds.[2] Compound **13** was formylated to give the diamide **34**. Compound **17** on similar formylation and subsequent $NaBH_4$ reduction afforded the 4-methyl derivative **33**. 9-Piperazinyl-4*H*-thieno[1,4]benzodiazepines (**12** and **35** in Table I) were similarly prepared from the corresponding 4*H*-thieno[3,2-*b*][1,4]- and -[3,4-*b*][1,4]benzodiazepin-9-ones.[8]

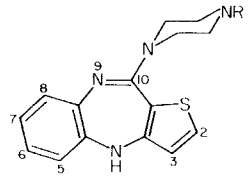
Results and Discussion

A number of compounds in both series show potent neuroleptic activity. Consistent with our observation on 4-piperazinyl-10*H*-thieno[2,3-*b*][1,5]benzodiazepines,[2] it seems that 4′-*N*-methylpiperazinyl compounds are the most active. The compounds with a piperazine unsubstituted at the distal nitrogen or substituted with either a benzyl, hydroxyalkyl, or carbethoxy group show reduced activity. The substitution of the phenyl ring with a halogen (Cl, F) atom at position 7 produces a marked increase in activity in compounds (**6**, **4**) in the [3,2-*b*][1,5] series. Contrary to this, however, such a substitution in the [3,4-*b*][1,5] series appears to attenuate the activity.[3] The 7-chloro compound **21** retains similar activity to the unsubstituted analogue **17**, but other 7 or 6,7 substituted compounds show reduction in activity. In contrast to the [2,3-*b*][1,5] series, a methyl substitution on the thiophene ring causes a drastic reduction in activity. A methyl substitution (**33**) on the bridging nitrogen at position 4 also reduces activity. The corresponding two compounds (**12** and **35**) 9-piperazinyl-4*H*-thieno[3,2-*b*][1,4]- and -[3,4-*b*][1,4]benzodiazepines prepared in the respective series have been found inactive.

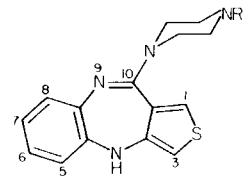
Neuroleptics are believed to act by blocking dopamine receptors in the brain and the tests, reported here, relate to this activity. It is now thought that a neuroleptic's beneficial antipsychotic effect is derived from its action in the mesolimbic area, while the undesirable extrapyramidal side effects are attributed to blockade of dopamine receptors in the nigrostriatal system and that the latter activity is related to the ability of compounds to produce a characteristic catalepsy in animals. Unlike the classical neuroleptics, clozapine blocks a conditioned avoidance response in rats at doses much lower than that needed to produce catalepsy. It is believed that this profile of activity is associated with the relative lack of extrapyramidal symptoms produced by this compound in the clinic. It will be seen from the present investigation that a number of compounds (**6**, **17**, **21**, **22**) demonstrate potency greater than clozapine and yet show a low degree of cataleptogenic

(4) J. K. Chakrabarti, T. A. Hicks, T. M. Hotten, and D. E. Tupper, *J. Chem. Soc., Perkin Trans. 1*, 937 (1978).
(5) R. B. Woodward and R. H. Eastman, *J. Am. Chem. Soc.*, 68, 2232 (1946).
(6) O. Hromatka, D. Binder, and K. Eichinger, *Monatsh. Chem.*, 106(2), 375 (1975); S. R. Safir, U.S. Patent 3953430, 1976.
(7) A. H. Georg, M. Willi, and R. Heinrich, Netherlands Patent Application 6604742, 1966; *Chem. Abstr.*, 67, 21811 (1967).
(8) J. K. Chakrabarti, T. M. Hotten, D. J. Steggles, and D. E. Tupper, *J. Chem. Res., Synop.*, 428 (1978); *J. Chem. Res., Miniprint*, 5101 (1978).

Table I[a]



1-11



13-34

compd	R	substituents	% yield	mp, °C	crystn solv	formula	anal.	LD_{50} (mice),[b] mg/kg po	hypothermia (mice) ED_{min},[c] mg/kg po	CAR block (rats)[d]	catalepsy (rats)[e]
					A. 10-Piperazinyl-4*H*-thieno[3,2-*b*][1,5]benzodiazepines						
1	H	H	87	202-206	CCl_4-$CHCl_3$	$C_{15}H_{16}N_4S$	C, H, N, S	400	50	1 (50.0)	0 (50.0)
2	H	7-F	90	167	CCl_4	$C_{15}H_{15}FN_4S$	C, H, N, F, S	400	50	2 (50.0)	1 (50.0)
3	CH_3	H	44	202-206	CCl_4	$C_{16}H_{18}N_4S$	C, H, N, S	100	25	3 (25.0)	2 (25.0)
4	CH_3	7-F	30	206-208	EtOAc	$C_{16}H_{17}FN_4S$	C, H, N	>25	12.5	3 (20.0)	2 (20.0)
5	CH_3	7-F, 2-CH_3	40	127-128	EtOAc	$C_{17}H_{19}FN_4S$	C, H, N, F, S	150	12.5	0 (10.0)	NT
6	CH_3	7-Cl	51	225-226	EtOAc-*n*-hexane	$C_{16}H_{17}ClN_4S$	C, H, N, Cl, S	50	6.25	3 (12.5)	2 (20.0)
7	$(CH_2)_2OH$	7-F	54	205-210	$CHCl_3$	$C_{17}H_{19}FN_4OS$	C, H, N, F, S	>400	25	2 (50.0)	0 (50.0)
8	$(CH_2)_3OH$	7-F	34	138-140	$CHCl_3$	$C_{18}H_{21}FN_4OS$	C, H, N, F, S	>400	200	0 (40.0)	0 (50.0)
9	$CO_2C_2H_5$	7-F	80	162-164	EtOAc	$C_{18}H_{19}FN_4O_2S$	C, H, N, F, S	>800	>800	1 (50.0)	NT
10	$CH_2C_6H_5$	H	85	198-200	EtOAc	$C_{22}H_{22}N_4S$	C, H, N, S	>400	200	0 (50.0)	NT
11	$CH_2C_6H_5$	7-F	52	181-182	$CHCl_3$	$C_{22}H_{21}FN_4S$	C, H, N, F, S	>400	100	0 (50.0)	NT
12	9-(4-methyl-1-piperazinyl)-[3,2-*b*][1,4]benzodiazepine		5	145-146	EtOAc-*n*-hexane	$C_{16}H_{18}N_4S$	*f*	>50	>50	NT	NT
					B. 10-Piperazinyl-4*H*-thieno[3,4-*b*][1,5]benzodiazepines						
13	H	H	81	233-235	CCl_4	$C_{15}H_{16}N_4S$	C, H, N, S	>400	50	0 (50.0)	1 (50.0)
14	H	7-F	94	192-193	CCl_4	$C_{15}H_{15}FN_4S$	C, H, N, F, S	600	100	0 (50.0)	0 (50.0)
15	H	7-Cl	74	178-179	CCl_4	$C_{15}H_{15}ClN_4S$	C, H, N, Cl, S	>400	25	0 (50.0)	0 (50.0)
16	H	6,7-Cl_2	56	213-214	CCl_4	$C_{15}H_{14}Cl_2N_4S$	C, H, N, Cl, S	>800	200	0 (50.0)	0 (50.0)
17	CH_3	H	80	198-199	CCl_4	$C_{16}H_{18}N_4S$	C, H, N, S	150	25	4 (25.0)	1 (25.0)
18	CH_3	1-CH_3	91	126-127	EtOAc-*n*-hexane	$C_{17}H_{20}N_4S$	C, H, N, S	>400	50	0 (25.0)	NT
19	CH_3	3-CH_3	51	158-159	EtOAc-*n*-hexane	$C_{17}H_{20}N_4S$	C, H, N, S	200	>100	0 (50.0)	0 (100.0)
20	CH_3	7-F	82	191-192	C_6H_6-pet. ether	$C_{16}H_{17}FN_4S$	C, H, N, F, S	100	6.25	1 (20.0)	1 (20.0)
21	CH_3	7-Cl	55	168-169	pet. ether (60-80 °C)	$C_{16}H_{17}ClN_4S$	C, H, N, Cl, S	75	3	3 (10.0)	1 (10.0)
22	CH_3	6,7-Cl_2	63	194-195	CCl_4	$C_{16}H_{16}Cl_2N_4S$	C, H, N, Cl, S	400	25	4 (50.0)	1 (50.0)
23	CH_3	6-CF_3	82	201-202	CCl_4	$C_{17}H_{17}F_3N_4S$	C, H, N, F, S	600	100	0 (50.0)	0 (50.0)
24	CH_3	7-CF_3	44	130-132	CCl_4	$C_{17}H_{17}F_3N_4S$	C, H, N, F, S	>200	50	3 (40.0)	NT
25	CH_3	7-SCH_3	61	195-196	EtOAc-*n*-hexane	$C_{17}H_{20}N_4S_2$	C, H, N, S	400	25	2 (25.0)	NT
26	CH_3	7-OCH_3	45	166-168	EtOAc-*n*-hexane	$C_{17}H_{20}N_4OS$	C, H, N, O, S	200	50	1 (50.0)	1 (50.0)
27	$CO_2C_2H_5$	H	56	186-187	EtOAc-*n*-hexane	$C_{18}H_{20}N_4O_2S$	C, H, N, O, S	>800	200	0 (50.0 ip)	NT
28	$CO_2C_2H_5$	7-F	57	198-199	EtOH	$C_{18}H_{19}FN_4O_2S$	C, H, N, F, S	>400	>400	0 (50.0)	NT
29	$CO_2C_2H_5$	6,7-Cl_2	64	185-186	EtOH	$C_{18}H_{18}Cl_2N_4O_2S$	C, H, N, Cl, O, S	>800	>800	0 (50.0 ip)	NT

30	$(CH_2)_3OH$	H	35	183–184	*n*-PrOH	$C_{18}H_{22}N_4OS$	C, H, N, S	>400	>400	1 (50.0)	NT
31	$CH_2C_6H_5$	H	55	221–222	EtOH	$C_{22}H_{22}N_4S$	C, H, N, S	800	800	0 (50.0)	NT
32	CH_3	H	80	198–199	CCl_4	$C_{16}H_{18}N_4S$	C, H, N, S	150	25	4 (25.0)	1 (25.0)
33	CH_3	4-CH_3	34	236	EtOH–Et_2O	$C_{17}H_{20}N_4S \cdot 2HCl$	C, H, N, Cl, S	150	25	2 (50.0)	0 (50.0)
34	CHO	4-CHO	77	123–124	CCl_4	$C_{17}H_{16}N_4O_2S$	C, H, N, O, S	400	200	0 (50.0)	NT
35	9-(4-methyl-1-piperazinyl)-[3,4-*b*][1,4]benzodiazepine		12	173–174	EtOAc–*n*-hexane	$C_{16}H_{18}N_4S$	C, H, N, S	50	50	0 (5.0)	NT
	clozapine							150	50	3 (30)	2 (80)
	haloperidol							>100	3.00	3 (1.25)	3 (1.25)
	chlorpromazine							400	6.25	3 (10)	1 (10)
	thioridazine							400	25	3 (50)	1 (25)
	cis-flupenthixol							300	3.00	2 (2.5)	4 (2.5)
	trans-flupenthixol							>400	>400	1 (50)	0 (50)

[a] In the conditioned avoidance response and catalepsy experiments a limited dose–response curve was run. The maximum dose used was half the ED_{50} for disrupting the ability of rats to remain on a rotating rod. The doses quoted in the table were selected to allow, where possible, a comparison to be made between a compound's ability to produce catalepsy and to inhibit the conditioned avoidance response. [b] Figures represent approximate LD_{50} (mg/kg po) in mice. [c] See Pharmacological Methods. [d] Activity: 0 = no significant effect (0–25% block); 1 = 26–30% block; 2 = 31–50% block; 3 = 51–75% block; 4 = 76–99% block; 5 = complete block of conditioned and unconditioned response. Numbers in parentheses = dose, mg/kg po, unless otherwise stated. NT = not tested. [e] Activity: 0 = no significant effect (group score 0–3); 1 = group score 4–7; 2 = group score 8–15; 3 = group score 16–30; 4 = group score 31–40. Numbers in parentheses = dose, mg/kg po, unless otherwise stated. NT = not tested. [f] *m/e* 298 (M^+).

effect. Press and his associates[3] concluded on the basis of their tests on certain 10-(alkylamino)-4*H*-thieno[3,4-*b*][1,5]benzodiazepines that this class of compounds appears to behave as classical neuroleptic agents (e.g., chlorpromazine), since they exhibit a potential therapeutic effect in the same dose range which induces catalepsy. However, our results show that certain compounds in this series block conditioned avoidance response in rats at a dose level which produces virtually no catalepsy. This would indicate that these compounds are unlike standard neuroleptics.

Experimental Section

Melting points were determined with a Köfler hot stage apparatus and are not corrected. All the compounds were characterized on the basis of spectral (IR, NMR, UV) evidence. Microanalyses were within ±0.4% of the calculated values unless noted otherwise.

Method A. 7-Chloro-4*H*-thieno[3,4-*b*][1,5]benzodiazepin-10(9*H*)-one (44). 7-Chloro-10-amino-4*H*-thieno[3,4-*b*][1,5]benzodiazepine (**50**; 4 g, 0.15 mol) was dissolved in the minimum of water (100 mL), to which was added K_2CO_3 (13.0 g) in water (20 mL). Absolute EtOH (40 mL) was added to redissolve the amidine, and the mixture was refluxed for 17 h; during the last hour most of EtOH was distilled off. The solution was allowed to cool. Concentrated HCl (13 mL) was added dropwise in the presence of EtOAc until the solution was slightly acidic. The aqueous phase was extracted with EtOAc, and the organic phase was washed with water, dried, and evaporated to dryness under reduced pressure to leave a dark brown mass, which was triturated with ether and filtered to give a light brown solid. This was crystallized from EtOAc–*n*-hexane: yield 3.0 g (80%); mp 212–213 °C.

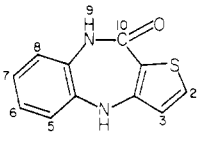
Method B. 3-(2-Aminoanilino)-4-(carbomethoxy)-2,5-dihydrothiophene (59). 4-(Carbomethoxy)-2,3,4,5-tetrahydrothiophen-3-one[5] (16.02 g, 0.1 mol) and 1,2-diaminobenzene (16.8 g, 0.1 mol) were dissolved in boiling ethanol (125 mL) and a few drops of acetic acid was added. The solution was heated at reflux under N_2 for 4 h and, when cold, filtered, and the solid was washed with ethanol and ether and dried under vacuum at 55 °C. The product was recrystallized from ethanol (charcoal) to give white needles: yield 21.5 g (86%); mp 100–101 °C.

Method C. 3-(4-Chloro-2-nitroanilino)-4-cyano-2,5-dihydrothiophene (62). A solution of 4-cyano-2,3,4,5-tetrahydrothiophen-3-one[7] (38.1 g, 0.25 mol) and 4-chloro-2-nitroaniline (51.8 g, 0.28 mol) in toluene (200 mL) with a few drops of BF_3–Et_2O was refluxed for 4 h (Dean and Stark). A brown solid precipitated from the solution; when cold, it was filtered, dried under vacuum at 60 °C, and crystallized from ethanol (charcoal) to give orange crystals: yield 56.24 g (80%); mp 154–155 °C.

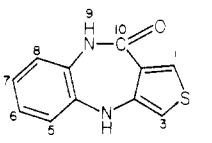
Method D. 3-(2-Aminoanilino)-4-(carbomethoxy)-thiophene (68). A mixture of 3-(2-aminoanilino)-2,5-dihydro-4-(carbomethoxy)thiophene (**59**; 25.0 g, 0.1 mol) and chloranil (24.6 g, 0.1 mol) was refluxed in xylene (900 mL) for 2 h and cooled, and the solvent was evaporated under reduced pressure. The dark brown solid obtained was triturated with EtOAc, filtered, and dried at 65 °C under vacuum. The product was crystallized from EtOAc to give pale brown crystals: yield 23.8 g (96%); mp 120–122 °C.

Method E. 7-Chloro-10-amino-4*H*-thieno[3,4-*b*][1,5]-benzodiazepine (50). To a solution of 3-(4-chloro-2-nitroanilino)-4-cyanothiophene (**71**; 7.57 g, 0.03 mol) in EtOH (300 mL) and EtOAc (100 mL) was added a slurry of 10% Pd/C catalyst (2.3 g) in EtOH (50 mL). This was hydrogenated in a Parr hydrogenator for 2 h at room temperature and 60 psi. The solution was filtered under N_2, and the filtrate was evaporated to dryness under reduced pressure to give a pale brown solid, 3-(4-chloro-2-aminoanilino)-4-cyanothiophene: yield 7.49 g (100%). To a solution of the above (7.49 g, 0.3 mol) in *n*-PrOH (100 mL) was added carefully concentrated HCl (5 mL). The solution was heated gently at reflux for 24 h. Ten percent NaOH (10 mL) was added dropwise to the cooled solution to make it slightly basic. *n*-PrOH was then evaporated under reduced pressure, and the remaining solution was diluted with acetone, from which a pale brown solid deposited which was filtered and dried under vacuum

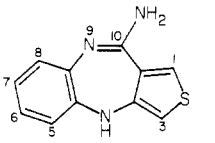
Table II. Physical Properties of Various Intermediates



36-39

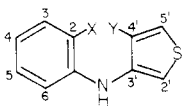


40-49



50-58

compd	substituents	% yield (method)	mp, °C	crystn solvent	formula	anal.
		A. 4*H*-Thieno[3,2-*b*][1,5]benzodiazepin-10(9*H*)-ones				
36	H	71	226	CCl_4	$C_{11}H_8N_2OS$	C, H, N, S
37	7-F	68	227-234	EtOAc	$C_{11}H_7FN_2OS$	C, H, N, F, S
38	7-Cl	57	255-256	EtOAc-*n*-hexane	$C_{11}H_7ClN_2OS$	C, H, N, Cl, S
39	7-F, 2-CH_3	79	261-263	EtOAc-*n*-hexane	$C_{12}H_9FN_2OS$	C, H, N, F, S
		B. 4*H*-Thieno[3,4-*b*][1,5]benzodiazepin-10(9*H*)-ones				
40	H	85 (ref 4, A)	233-234	EtOAc-*n*-hexane	$C_{11}H_8N_2OS$	C, H, N, O, S
41	1-CH_3	86 (A)	>250	EtOAc-*n*-hexane	$C_{12}H_{10}N_2OS$	C, H, N, O, S
42	3-CH_3	45 (ref 6)	184-185	EtOAc-*n*-hexane	$C_{12}H_{10}N_2OS$	C, H, N, O, S
43	7-F	43 (ref 4)	238	EtOAc-*n*-hexane	$C_{11}H_7FN_2OS$	C, H, N, F, S
44	7-Cl	80 (A)	212-213	EtOAc-*n*-hexane	$C_{11}H_7ClN_2OS$	C, H, N, Cl, S
45	6,7-Cl_2	37 (ref 4)	284-287	EtOAc-*n*-hexane	$C_{11}H_6Cl_2N_2OS$	C, H, N, Cl, S
46	7-SCH_3	42 (A)	86-88	EtOAc-*n*-hexane	$C_{12}H_{10}N_2OS_2$	C, H, N, O, S
47	7-OCH_3	24 (ref 4)	170-171	EtOAc-*n*-hexane	$C_{12}H_{10}N_2O_2S$	C, H, N, O, S
48	7-CF_3	40 (A)	107-108	CCl_4	$C_{12}H_7F_3N_2OS$	C, H, N, F, S
49	6-CF_3	58 (A)	213	CCl_4	$C_{12}H_7F_3N_2OS$	C, H, N, S
		C. 10-Amino-4*H*-thieno[3,4-*b*][1,5]benzodiazepines				
50	7-Cl	60 (E)	239-240	EtOH-acetone	$C_{11}H_8ClN_3S$	C, H, N, Cl, S
51	7-SCH_3	64 (E)	195-197	EtOAc-*n*-hexane	$C_{12}H_{11}N_3S_2$	C, H, N, S
52	7-OCH_3	27 (E)	172-174	EtOAc-*n*-hexane	$C_{12}H_{11}N_3OS$	C, H, N, S
53	7-CF_3	36 (E)	181-182	EtOAc-*n*-hexane	$C_{12}H_8F_3N_3S$	C, H, N, S
54	1-CH_3	60 (E)	146-148	EtOAc-*n*-hexane	$C_{12}H_{11}N_3S$	C, H, N, S
55	H (1,3-dihydro)	60 (E)	230-240	EtOH-acetone	$C_{11}H_{11}N_3S$	*a*
56	6-CF_3(1,3-dihydro)	87 (E)	200-210	EtOH-acetone	$C_{12}H_{10}F_3N_3S$	*a*
57	H	75 (D)	190 dec	water	$C_{11}H_9N_3S$	*a*
58	6-CF_3	21 (D)	178 dec	water	$C_{12}H_8F_3N_3S$	*a*



compd	X	Y	substituents[b]	% yield (method)	mp, °C	crystn solv	formula	anal.
			D. 3-Amino-4-cyano- and 3-Amino-4-(carboxymethyl)thiophenes					
59	NH_2	CO_2CH_3	H	86 (B)	100-101	EtOH	$C_{12}H_{14}N_2O_2S$	C, H, N, O, S
60	NH_2	CO_2CH_3	4,5-Cl_2	75 (B)	161-162	EtOH	$C_{12}H_{12}Cl_2N_2O_2S$	C, H, N, Cl, S
61	NO_2	CO_2CH_3	4-OCH_3	84 (C)	196-197	MeOH	$C_{13}H_{14}N_2O_5S$	C, H, N, O, S
62	NO_2	CN	4-Cl	80 (C)	154-155	EtOH	$C_{11}H_5ClN_3O_2S$	C, H, N, Cl, S
63	NO_2	CN	4-SCH_3	57 (C)	141-142	EtOH	$C_{12}H_{11}N_3O_2S_2$	C, H, N, O, S
64	NO_2	CN	4-OCH_3	72 (C)	128-129	EtOH	$C_{12}H_{11}N_3O_3S$	C, H, N, O, S
65	NO_2	CN	4-CF_3	43 (C)	140-141	EtOH	$C_{12}H_8F_3N_3O_2S$	C, H, N, S
66	NO_2	CN	5'-CH_3	34 (C)	109-111	EtOH	$C_{12}H_{11}N_3O_2S$	C, H, N, O, S
67	NH_2	CN	5-CF_3	27 (B)	188-189	EtOH	$C_{12}H_{10}F_3N_3O_2S$	C, H, N, F, S
68	NH_2	CO_2CH_3	H	96 (D)	120-122	EtOAc	$C_{12}H_{12}N_2O_2S$	C, H, N, O, S
69	NH_2	CO_2CH_3	4,5-Cl_2	67 (D)	162-163	MeOH	$C_{12}H_{10}Cl_2N_2O_2S$	C, H, N, Cl, S
70	NO_2	CO_2CH_3	4-OCH_3	90 (D)	170-171	MeOH	$C_{13}H_{12}N_2O_5S$	C, H, N, O, S
71	NO_2	CN	4-Cl	99 (D)	213-214	MeOH	$C_{11}H_6ClN_3O_2S$	C, H, N, Cl, S
72	NO_2	CN	4-SCH_3	95 (D)	167-169	EtOH	$C_{12}H_9N_3O_2S_2$	C, H, N, S
73	NO_2	CN	4-OCH_3	88 (D)	149-150	EtOH	$C_{12}H_9N_3O_3S$	C, H, N, S
74	NO_2	CN	4-CF_3	85 (D)	156-157	EtOH	$C_{12}H_6F_3N_3O_2S$	C, H, N, S
75	NO_2	CN	5'-CH_3	62 (D)	127-128	EtOH	$C_{12}H_9N_3O_2S$	C, H, N

[a] Used for next stage without further purification. [b] Compounds 59-67 represent 2',5'-dihydrothiophenes.

at 60 °C: yield 3.28 g (60%); mp 239–240 °C dec (EtOH–acetone).

4-Formyl-10-(4-formyl-1-piperazinyl)-4*H*-thieno[3,4-*b*][1,5]benzodiazepine (34). To a solution of 10-piperazinyl-4*H*-thieno[3,4-*b*][1,5]benzodiazepine (**13**; 1.63 g, 0.0057 mol) in 98–100% formic acid (25 mL) was added acetic anhydride (2.0 mL). The solution was heated to boiling for 5 min, left to cool to room temperature, diluted with water (100 mL), and cooled in an ice bath. NaOH was added in portions, at <30 °C until the solution was neutral. The white solid obtained was filtered, dried under reduced pressure, and extracted in a soxhlet using petroleum ether (80–100 °C), followed by chromatography on a Florisil column using $CHCl_3$–MeOH (95:5). Recrystallization from CCl_4 gave a crystalline solid: yield 1.50 g (77%); mp 123–124 °C.

4-Methyl-10-(4-methyl-1-piperazinyl)-4*H*-thieno[3,4-*b*][1,5]benzodiazepine (33). Compound **17** was formylated as above to the 4-formyl derivative **32**, which was reduced[10] with $NaBH_4$ to give **33**.

3-Methyl-4*H*-1,3-dihydrothieno[3,4-*b*][1,5]benzodiazepin-10(9*H*)-one (76). A mixture of 2-methyl-4-(carbomethoxy)-2,3,4,5-tetrahydrothiophen-3-one[9] (6.44 g, 0.037 mol)

(9) R. M. Acheson, J. A. Barltrop, M. Hichens, and R. E. Hichens, *J. Chem. Soc.*, 650 (1961).

and 1,2-diaminobenzene (4.0 g, 0.037 mol) was refluxed in benzene (300 mL) (Dean and Stark) for 48 h. The solution was evaporated to dryness under reduced pressure to leave an oil, which was chromatographed on a Florisil column eluting with $CHCl_3$. On evaporation of the solvent, a yellow solid was obtained, which was crystallized from EtOAc–*n*-hexane to give yellow crystals: yield 4.2 g (49%); mp 230–240 °C dec. Anal. ($C_{12}H_{12}N_2OS$) C, H, N, S.

Pharmacological Methods. All compounds were dissolved in distilled water or suspended in 0.5% carboxymethylcellulose. Solutions or suspensions were administered orally except where noted otherwise.

Acute Toxicity. The compounds in doses up to 800 mg/kg were administered orally to groups of three albino mice (CFW) each weighing 19–21 g. The mice were observed over 48 h for gross behavioral changes and mortalities. LD_{50} values were approximated from the results.

Mouse Hypothermia. The rectal temperature of groups of three mice (CFW) was measured 15 min, 2.5 h, and 5 h after administration of the compound. The assessment of hypothermia using the "temperature index" method was carried out as described in the earlier paper.[2] The results are expressed as ED_{min} values, which are the minimum doses (mg/kg) of the compounds giving a temperature index of at least 5 lower than that of a control group of animals.

Conditioned Avoidance Response (CAR) in Rats. The method was essentially that described by Jacobsen and Sonne.[11] Lilly Wistar rats (120–130 g) were trained to pass from one side of a shuttle box to the other on hearing a 5-s buzzer. Failure to respond within 1 s from the end of the buzzer resulted in the animals receiving a mild electric shock. The compound under tests was administered to only those animals which showed a high level of conditioned response. Groups of five animals were dosed orally 1 h 50 min prior to placing them individually in the shuttle boxes. After a 10-min habituation period, they were tested for 20 min. During this period the number of times the buzzer sounded, as well as the number of shocks received by the animal, was recorded. The degree of conditioned avoidance blockade was calculated by expressing the number of shocks received as a percentage of the number of stimuli presented.

Rat Catalepsy. The method used was essentially that described by Costall and Olley.[12] Groups of eight Lilly Wistar rats (180–190 g) were assessed for the presence of catalepsy at 0.5, 1, 1.5, 2, 3, 4, and 5 h after the oral administration of the compound. The front paws of each animal were placed on a wooden rod 1.5 cm in diameter suspended 7 cm above a table. The length of time the animal maintained this position was recorded up to a maximum of 20 min. Animals were considered to be noncataleptic if they removed their front paws from the bar within 10 s. Each cataleptic animal was assigned a score of from 0 to 5 depending on how long they maintained the imposed posture (0 = <10 s; 1 = 10 s–2.5 min; 2 = 2.5–5 min; 3 = 5–10 min; 4 = 10–20 min; 5 = >20 min). The maximum scores obtained for each animal, regardless of time after dosing, were summed, thus giving a maximum score of 40 for each group.

Acknowledgment. We thank Dr. D. C. Horwell for his interest and help in some experimental work, Dr. D. M. Rackham and his associates for the spectral evidence, G. Maciak for microanalyses, and S. Bruty for her excellent technical assistance.

(10) V. Hach, *Synth. Commun.*, 342 (1974).
(11) E. Jacobsen and E. Sonne, *Acta Pharmacol. Toxicol.*, 11, 135 (1955).
(12) B. Costall and J. E. Olley, *Neuropharmacology*, 10, 297 (1971).

Ultraviolet Photoelectron Spectroscopy of Cyclic Amidines. 2. Electronic Structure of Clonidine and Some Related 2-(Phenylimino)imidazolidines with α-Adrenergic Activity[1]

A. P. de Jong*

Universiteit van Amsterdam, Vakgroep Farmaceutische Scheikunde, Plantage Muidergracht 24, 1018 TV Amsterdam, The Netherlands

and H. van Dam

Vakgroep Anorganische Chemie, J. H. van't Hoff Instituut, Nieuwe Achtergracht 166, Amsterdam, The Netherlands.
Received November 21, 1979

Ultraviolet photoelectron spectroscopy (UV PES) and CNDO/s molecular orbital calculations have been employed to investigate the electronic structure of clonidine and some other 2-(phenylimino)imidazolidines. The assignment of the bands in the spectra to particular molecular orbitals is based on the CNDO/s results in conjunction with Koopmans' theorem, substituent effects, and differences in intensity between the He(I) and He(II) spectra. The location of the energy levels of orbitals with mainly n_N and σ character is not correctly estimated by CNDO/s, while the π orbital energy levels are satisfactorally predicted. The UV PES and CNDO/s results indicate, in contrast to earlier CNDO/2 total energy calculations, that the phenyl and imidazolidine rings are perpendicular for all investigated 2-(phenylimino)imidazolidines, which may indicate that differences in hypotensive activity cannot be ascribed to variations in steric hindrance within the molecules. The first ionization energies of the pharmacologically active 2-(phenylimino)imidazolidines do not correlate with hypotensive activity based on dosage data after intravenous administration to rats.

Clonidine, 2-[(2,6-dichlorophenyl)imino]imidazolidine, is an antihypertensive drug widely used therapeutically. It has a dual effect on blood pressure. Intravenous application of clonidine results in an initial hypertension, followed by a long-lasting decrease in blood pressure, which is accompanied by bradycardia. The rise in blood pressure is caused by vasoconstriction, which is a result of the direct stimulation of peripheral α-adrenergic receptors. The hypotensive activity and bradycardia seem to be of a central origin. A central inhibition of peripheral sympathetic activity by stimulation of central α-adrenergic receptors has been proposed.[2] Slight alterations in the

(1) For part 1, see de Jong, A. P.; van Dam, H. *J. Med. Chem.* **1979**, *22*, 1290.
(2) For reviews, see (a) Van Zwieten, P. A. *Prog. Pharmacol.* **1975**, *1*, 1. (b) Schmitt, H. *Handb. Exp. Pharmacol.* **1977**, *39*, 299.

0022-2623/80/1823-0889$01.00/0