

had ir and uv spectra in agreement with its assigned structure; purity was confirmed by tlc using Brinkmann silica gel GF. Melting points are uncorrected and were taken in capillary tubes on a Mel-Temp block.

α -(2-Chloro-4-nitrophenoxy)-*m*-toluic acid, a precursor for the synthesis of inhibitors 34–40, has already been described.⁶ The base-catalyzed ester hydrolysis was modified by using aqueous DMSO in place of aqueous MeOH. In this medium the reaction was essentially complete in 1 hr at 80–85°, with yields of up to 79% being obtained.

***N*-Arylamides (Method A).** Conversion of the nitro-substituted acid to the acid chloride and condensation with the arylamine in toluene at reflux was performed as previously described.⁶ Compounds prepared in this manner are listed in Table IV.

***N,N*-Dialkylamides (Method B).** *N,N*-Diethyl-*p*-nitrophenoxyacetamide (54). A mixture of 983 mg (5.0 mmol) of *p*-nitrophenoxyacetic acid, 4 ml of SOCl₂, and 8 ml of C₆H₆ was stirred under reflux for 4.5 hr, then cooled, and spin evaporated *in vacuo*. The residual oil was dissolved in 8 ml of CH₂Cl₂ and cooled in an ice bath. The cold solution of acid chloride was added slowly with stirring to a chilled solution of 802 mg (11 mmol) of Et₂NH in 10 ml of CH₂Cl₂. Stirring was continued under protection from moisture for 10 min, while maintaining the temperature below 10°. Next, the mixture was diluted with 35 ml of CH₂Cl₂ and shaken with 50 ml of H₂O. The organic layer was washed with 1% HCl (1 × 50 ml) and 5% Na₂CO₃ (3 × 50 ml), then dried (MgSO₄), and evaporated to dryness. Upon trituration with petroleum ether (bp 30–60°) and scratching, the residual oil solidified. Recrystallization from EtOAc-petroleum ether (bp 65–110°) afforded 1.01 g (80%) of very pale yellow crystals, mp 64–65° (tlc in 1:1 EtOAc-petroleum ether). *Anal.* (C₁₂H₁₆N₂O₄) C, H, N. For additional compounds prepared by this method, see Table IV.

2-Chloro-4-nitrophenyl Benzyl Ethers (80–82) (Method C). The α -bromination of substituted toluenes and subsequent reaction with 2-chloro-4-nitrophenol were carried out in the usual manner.⁸ Physical properties of the ethers are given in Table IV.

The reaction of *N,N*-dimethyl-*p*-toluenesulfonamide with NBS was complicated by side reactions, resulting in a low overall yield of 81. A possible alternative route to compound 76, involving α -bromination of *N,N*-diethyl-*m*-toluamide followed by reaction with 2-chloro-4-nitrophenol, was unsuccessful on account of the mixture of products formed when the diethyltoluamide was treated with NBS.

4,6-Diamino-1,2-dihydro-2,2-dimethyl-*s*-triazine Ethanesulfonates (5–43) (Methods D–F). The nitro intermediates 45–82 were hydro-

genated over PtO₂ (Method D), Raney Ni (Method E), or 5% Pd/C (Method F); the resulting crude amines were condensed with cyano-guanidine and Me₂CO¹⁶ in the presence of EtSO₃H as previously described.⁸ Compounds obtained by this procedure are shown in Table V.

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Studies on Psychotropic Drugs. 18.¹ Synthesis and Structure-Activity Relationships of 5-Phenyl-1,3-dihydro-2*H*-thieno[2,3-*e*][1,4]diazepin-2-ones

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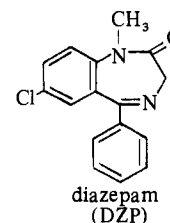
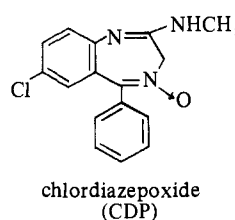
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A series of 5-phenyl-1,3-dihydro-2*H*-thieno[2,3-*e*][1,4]diazepin-2-ones was synthesized and evaluated for CNS depressant activity. Structure-activity relationships were discussed.

It is well known that a number of 1,4-benzodiazepine derivatives show potent antianxiety activity.² From the standpoint of bioisosterism, we synthesized a series of thienodiazepine derivatives, which have a thieno moiety in place of the benzo moiety of the benzodiazepine ring system, starting from readily obtainable 2-amino-3-benzoylthiophenes according to Gewald, *et al.*³ 5-Phenyl-1,3-dihydro-2*H*-thieno[2,3-*e*][1,4]diazepin-2-ones thus synthesized were pharmacologically screened and, as was expected, several compounds in this series (84, 109, and 110) were found to show higher CNS depressant activity than CDP and not less than DZP. These compounds were observed to have similar low toxicity to CDP and DZP.

Chemistry. The synthetic route to thienodiazepine derivatives is shown in Scheme I.

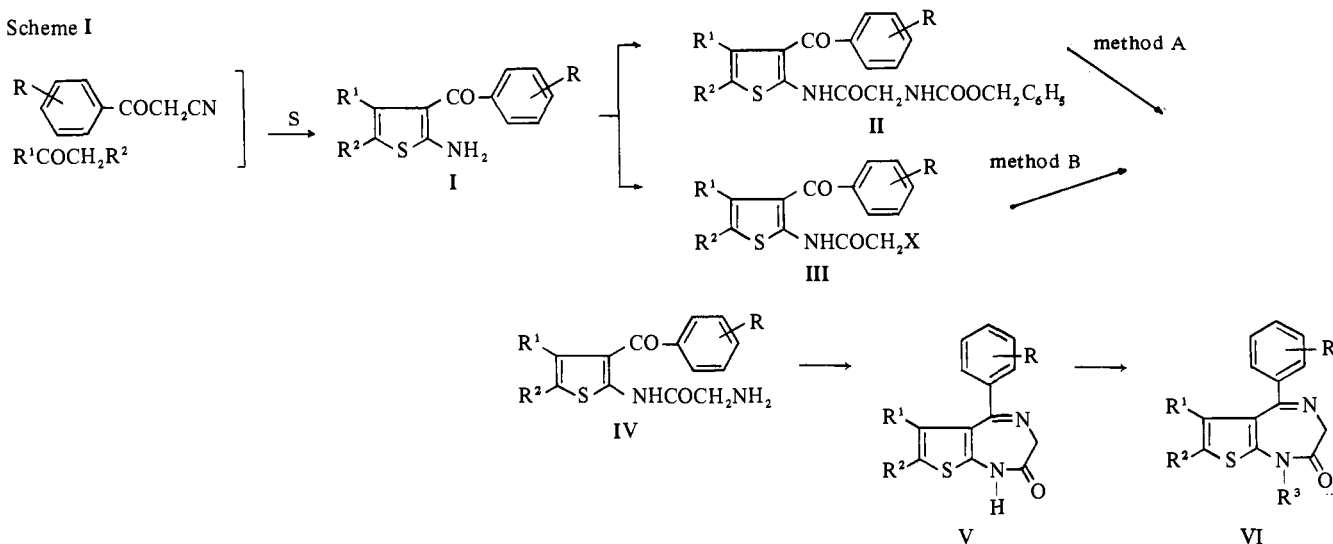
Starting materials, 2-amino-3-benzoylthiophenes (I), were



prepared by the reaction of ω -cyanoacetophenone with aldehyde or ketone and sulfur in the presence of catalytic amine (Table I). Compounds of type I were converted into corresponding aminoacetamide derivatives IV *via* methods A and B, respectively.

Method A. Benzyloxycarbonylaminoacetamide intermediates II were synthesized by condensation of I with benzyloxycarbonylaminoacetyl chloride in CHCl₃ at low

Scheme I



temperature (Table II). Then II was deprotected with HBr-AcOH to give IV.

Method B. Haloacetamide intermediates III (Table III) were ammonolyzed by passing NH_3 gas in CHCl_3 -MeOH solution to give IV (Table IV). Chloro- or bromoacetamides were obtained by the corresponding halogenoacetylation of I in boiling CHCl_3 , and iodoacetamides were prepared by the reaction of chloroacetamides, which could only be ammonolyzed with difficulty, with NaI in boiling Me_2CO .

The ring-closure reaction of IV to 5-phenyl-1,3-dihydro-2H-thieno[2,3-e][1,4]diazepin-2-ones (V) was carried out by refluxing a mixture of IV and equimolar AcOH in pyridine- C_6H_6 solution with azeotropic removal of water. Finally, compounds V were alkylated to give the corresponding 1-substituted derivatives VI.

Results and Discussion

In Table V, the results of two preliminary screening tests for thienodiazepine derivatives are summarized in comparison with those of CDP and DZP.

Generally, it is said that in the benzodiazepine series, the C-7 substitution with an electron-releasing group results in a withdrawal of the potency and the introduction of a halogen atom in the ortho position of a C-5 phenyl or methylation at the 1 position potentiates the activity.⁴

In order to study the structure-activity relationships in thienodiazepine series, first of all, we varied the substituents at C-6 from H to *i*-Pr, at C-7 from H to *n*-Bu (81, 83, 90, 91, 95, and 96), and the combined alkylene linkage at C-6 and C-7 from 3 to 5 methylenes (97, 98, 103, and 104). Several compounds (81, 83, and 91) showed potent activity by this modification. Among them, compound 83 which possesses an ethyl group at C-7 and a H atom at C-6 was found to impart optimum activity. Increasing the bulkiness of the substituents at C-6 and/or C-7 seemed to decrease the activity. However, introduction of an alkylene linkage between C-6 and C-7 (97 and 98) still afforded slightly lower activity than 83.

Attention was then turned to the substituent effect on the C-5 phenyl moiety. The introduction of a halogen atom,

Table I. 2-Amino-3-benzoylthiophenes (I)

| No. | R ¹ | R ² | R | Mp, °C | Yield, % | Crystn solvent ^a | Formula ^b |
|-----|--|---|----------------------------|----------|----------|-----------------------------|--|
| 1 | H | CH ₃ | <i>o</i> -Cl | 160-162 | 75 | E | C ₁₂ H ₁₀ CINOS |
| 2 | H | C ₂ H ₅ | H | 87-88 | 70 | H/E | C ₁₃ H ₁₃ NOS |
| 3 | H | C ₂ H ₅ | <i>o</i> -F | 114-116 | 68 | H | C ₁₃ H ₁₂ FNOS |
| 4 | H | C ₂ H ₅ | <i>o</i> -Cl | 132-133 | 61 | H/E | C ₁₃ H ₁₂ CINOS |
| 5 | H | C ₂ H ₅ | <i>o</i> -Br | 123-125 | 60 | H/C | C ₁₃ H ₁₂ BrNOS |
| 6 | H | C ₂ H ₅ | <i>o</i> -CH ₃ | 110-112 | 58 | H/E | C ₁₄ H ₁₅ NOS |
| 7 | H | C ₂ H ₅ | <i>o</i> -OCH ₃ | 145-147 | 73 | E | C ₁₄ H ₁₅ NO ₂ S |
| 8 | H | <i>i</i> -C ₃ H ₇ | <i>o</i> -Cl | <i>c</i> | | | |
| 9 | H | <i>n</i> -C ₄ H ₉ | H | <i>c</i> | | | |
| 10 | CH ₃ | CH ₃ | H | 140-141 | 72 | E | C ₁₃ H ₁₃ NOS |
| 11 | CH ₃ | CH ₃ | <i>o</i> -Cl | 151-152 | 59 | E | C ₁₃ H ₁₂ CINOS |
| 12 | CH ₃ | CH ₃ | <i>p</i> -Cl | 127-129 | 52 | E | C ₁₃ H ₁₂ CINOS |
| 13 | CH | CH ₃ | <i>m</i> -CF ₃ | <i>c</i> | | | |
| 14 | CH ₃ | <i>n</i> -C ₃ H ₇ | H | <i>c</i> | | | |
| 15 | <i>i</i> -C ₃ H ₇ | H | H | <i>c</i> | | | |
| 16 | -(CH ₂) ₃ - | | H | 176-177 | 51 | E | C ₁₄ H ₁₃ NOS |
| 17 | -(CH ₂) ₄ - | | <i>p</i> -Cl | 138-139 | 68 | E | C ₁₅ H ₁₄ CINOS |
| 18 | -(CH ₂) ₄ - | | <i>o</i> -OCH ₃ | 181-182 | 71 | E | C ₁₆ H ₁₇ NO ₂ S |
| 19 | -(CH ₂) ₄ - | | <i>m</i> -CF ₃ | 123-124 | 60 | E | C ₁₆ H ₁₄ F ₃ NOS |
| 20 | -CH ₂ CH ₂ CH(CH ₃)CH ₂ - | | H | 118-119 | 67 | E | C ₁₆ H ₁₇ NOS |
| 21 | -(CH ₂) ₅ - | | H | 115-116 | 58 | E | C ₁₆ H ₁₇ NOS |

^aE, EtOH; H, hexane; C, EtOAc. ^bAnalyzed for C, H, and N. ^cNot isolated and used crude in next step.

Table II. 2-Benzyloxycarbonylaminoacetamido-3-benzoylthiophenes (II)

| No. | R ¹ | R ² | R | Mp, °C | Yield, % | Crystn solvent ^a | Formula ^b |
|-----|--|---|----------------------------|----------|----------|-----------------------------|--|
| 22 | H | CH ₃ | <i>o</i> -Cl | 153-154 | 70 | E | C ₂₂ H ₁₉ ClN ₂ O ₄ S |
| 23 | H | C ₂ H ₅ | H | 100 | 73 | E | C ₂₃ H ₂₂ N ₂ O ₄ S |
| 24 | H | C ₂ H ₅ | <i>o</i> -Cl | 118-119 | 61 | E | C ₂₃ H ₂₁ ClN ₂ O ₄ S |
| 25 | H | C ₂ H ₅ | <i>o</i> -CH ₃ | 128-129 | 70 | E | C ₂₄ H ₂₄ N ₂ O ₄ S |
| 26 | H | C ₂ H ₅ | <i>o</i> -OCH ₃ | 77-78 | 62 | E | C ₂₄ H ₂₄ N ₂ O ₅ S |
| 27 | H | <i>i</i> -C ₃ H ₇ | <i>o</i> -Cl | 112-114 | | E | C ₂₄ H ₂₃ ClN ₂ O ₄ S |
| 28 | H | <i>n</i> -C ₃ H ₇ | H | 91-92 | | E | C ₂₅ H ₂₆ N ₂ O ₄ S |
| 29 | CH ₃ | CH ₃ | H | 145-146 | 67 | E | C ₂₃ H ₂₂ N ₂ O ₄ S |
| 30 | CH ₃ | CH ₃ | <i>p</i> -Cl | 157-159 | 74 | E | C ₂₃ H ₂₁ ClN ₂ O ₄ S |
| 31 | CH ₃ | CH ₃ | <i>m</i> -CF ₃ | 125-126 | | E | C ₂₃ H ₂₁ F ₃ N ₂ O ₄ S |
| 32 | CH ₃ | <i>n</i> -C ₃ H ₇ | H | 97-98 | | E | C ₂₅ H ₂₆ N ₂ O ₄ S |
| 33 | <i>i</i> -C ₃ H ₇ | H | H | <i>c</i> | | | |
| 34 | -(CH ₂) ₃ - | | H | 114-115 | 72 | E | C ₂₄ H ₂₂ N ₂ O ₄ S |
| 35 | -(CH ₂) ₄ - | | <i>p</i> -Cl | 124-125 | 73 | E | C ₂₅ H ₂₃ ClN ₂ O ₄ S |
| 36 | -(CH ₂) ₄ - | | <i>o</i> -OCH ₃ | <i>c</i> | | | |
| 37 | -(CH ₂) ₄ - | | <i>m</i> -CF ₃ | 135 | 68 | E | C ₂₆ H ₂₃ F ₃ N ₂ O ₄ S |
| 38 | -CH ₂ CH ₂ CH(CH ₃)CH ₂ - | | H | 139-140 | 71 | E | C ₂₄ H ₂₄ N ₂ O ₄ S |
| 39 | -(CH ₂) ₅ - | | H | 140-141 | 67 | E | C ₂₆ H ₂₆ N ₂ O ₄ S |

^aE, EtOH. ^bAnalyzed for C, H, and N. ^cNot isolated and used crude in next step.

Table III. 2-Haloacetamido-3-benzoylthiophenes (III)

| No. | R ¹ | R ² | R | X | Mp, °C | Yield, % | Crystn solvent ^a | Formula ^b |
|-----|-----------------|------------------------------------|----------------------------|----|---------|----------|-----------------------------|---|
| 40 | H | CH ₃ | <i>o</i> -Cl | Cl | 127-128 | 85 | M | C ₁₄ H ₁₁ Cl ₂ NO ₂ S |
| 41 | H | C ₂ H ₅ | H | Cl | 114-115 | 89 | M | C ₁₅ H ₁₄ ClNO ₂ S |
| 42 | H | C ₂ H ₅ | <i>o</i> -F | Cl | 87-88 | 82 | E | C ₁₅ H ₁₃ ClFNO ₂ S |
| 43 | H | C ₂ H ₅ | <i>o</i> -Cl | Cl | 99-100 | 81 | E | C ₁₅ H ₁₃ Cl ₂ NO ₂ S |
| 44 | H | C ₂ H ₅ | <i>o</i> -Br | Cl | 90-91 | 78 | E | C ₁₅ H ₁₃ BrClNO ₂ S |
| 45 | H | C ₂ H ₅ | <i>o</i> -CH ₃ | Cl | 78-79 | 80 | M | C ₁₆ H ₁₆ ClNO ₂ S |
| 46 | H | C ₂ H ₅ | <i>o</i> -OCH ₃ | Cl | 141-142 | 82 | M | C ₁₆ H ₁₆ ClNO ₃ S |
| 47 | CH ₃ | CH ₃ | <i>o</i> -Cl | Cl | 182-183 | 87 | M | C ₁₅ H ₁₃ Cl ₂ NO ₂ S |
| 48 | | -(CH ₂) ₃ - | H | Cl | 121-122 | 82 | E | C ₁₄ H ₁₄ ClNO ₂ S |
| 49 | | -(CH ₂) ₅ - | H | Cl | 119-120 | 86 | E | C ₁₆ H ₁₆ ClNO ₂ S |
| 50 | H | C ₂ H ₅ | <i>o</i> -Cl | Br | 105-106 | 78 | E | C ₁₅ H ₁₃ BrClNO ₂ S |
| 51 | CH ₃ | CH ₃ | H | Br | 106-107 | 81 | M | C ₁₅ H ₁₄ BrNO ₂ S |
| 52 | H | CH ₃ | <i>o</i> -Cl | I | 140-142 | 87 | E | C ₁₄ H ₁₁ ClINO ₂ S |
| 53 | H | C ₂ H ₅ | H | I | 87-88 | 88 | M | C ₁₅ H ₁₄ INO ₂ S |
| 54 | H | C ₂ H ₅ | <i>o</i> -F | I | 96-97 | 89 | H | C ₁₅ H ₁₃ FINO ₂ S |
| 55 | H | C ₂ H ₅ | <i>o</i> -Cl | I | 100-101 | 86 | E | C ₁₅ H ₁₃ ClINO ₂ S |
| 56 | H | C ₂ H ₅ | <i>o</i> -Br | I | 94-96 | 87 | H/E | C ₁₅ H ₁₃ BrINO ₂ S |
| 57 | H | C ₂ H ₅ | <i>o</i> -CH ₃ | I | 78-79 | 81 | E | C ₁₆ H ₁₆ INO ₂ S |
| 58 | H | C ₂ H ₅ | <i>o</i> -OCH ₃ | I | 115-117 | 83 | E | C ₁₆ H ₁₆ INO ₃ S |
| 59 | CH ₃ | CH ₃ | <i>o</i> -Cl | I | 140-141 | 87 | E | C ₁₅ H ₁₃ ClINO ₂ S |

^aM, MeOH; E, EtOH; H, hexane. ^bAnalyzed for C, H, and N.

especially a fluorine atom (84), in the ortho position very strongly enhanced the activity (84-86 and 99), while the methoxy group at the ortho position (88 and 101) or any substituent at the meta or para positions (93, 94, 100, and 102) was unfavorable.

It is of interest to consider whether the substitution at N-1 affords any influence on the activity. The regular tendency on the effect of N-1 methylation was not recognized. Thus, the activity was increased by N-1 methylation of 7-ethyl-5-*o*-chloro- or -bromophenyl derivatives (109 and 110), but no remarkable effect was observed in the 7-ethyl-5-*o*-fluorophenyl compound 108. N-1 methylation of the alkylene linked compounds (114-116 and 118) caused potentiation only in anti Met activity. As for the other compounds (105-107 and 111), reduction of both activities was observed. Introduction of more bulky substituents than the methyl group at N-1 seemed to lower the activity (119-121 and 122).

From these results, some compounds (83-85, 108, and 109) were selected and their general pharmacological properties were studied in some detail. As shown in Table VI, the prototype 83 had comparable activity with CDP, but it was found to be slightly toxic. However, potentiation of activity was found to occur by halogen substitution at the ortho position in the C-5 phenyl moiety of 83, not only in the two main activities discussed previously but also in other properties shown in Table VI. Furthermore, toxicity was lowered to some extent. Compounds 84, 108, and 109 had comparable activities with DZP in anticonvulsant, muscle-relaxant activities and taming effect but lower activity in narcosis potentiation. Compound 85, on the other hand, displayed comparable activities with DZP except taming effect.

Turning attention again to N-1 substitution, it was observed that the taming effect was increased by N-1 methylation (compare 84 with 108 and 85 with 109). However,

Table IV. 2-Aminoacetamido-3-benzoylthiophenes (IV)

| No. | R ¹ | R ² | R | Method ^a | Mp, °C | Yield, % | Crystn solvent ^b | Formula ^c |
|-----|--|---|----------------------------|---------------------|----------------------|-----------------|-----------------------------|--|
| 60 | H | CH ₃ | <i>o</i> -Cl | A, B | 183-186 | 83 ^d | E | C ₁₄ H ₁₃ ClN ₂ O ₂ S |
| 61 | H | C ₂ H ₅ | H | A, B | 169-171 | 72 ^e | E | C ₁₅ H ₁₆ N ₂ O ₂ S·HBr |
| 62 | H | C ₂ H ₅ | <i>o</i> -F | B | 145-147 | 75 | H/E | C ₁₅ H ₁₅ FN ₂ O ₂ S |
| 63 | H | C ₂ H ₅ | <i>o</i> -Cl | A, B | 148-149 | 85 ^d | E | C ₁₅ H ₁₅ ClN ₂ O ₂ S |
| 64 | H | C ₂ H ₅ | <i>o</i> -Br | B | 160-161 | 76 | E | C ₁₅ H ₁₅ BrN ₂ O ₂ S |
| 65 | H | C ₂ H ₅ | <i>o</i> -CH ₃ | A, B | 175-177 | 67 ^e | E | C ₁₆ H ₁₈ N ₂ O ₂ S·HBr |
| 66 | H | C ₂ H ₅ | <i>o</i> -OCH ₃ | A, B | 185-186 | 70 ^d | E | C ₁₆ H ₁₈ N ₂ O ₃ S |
| 67 | H | <i>i</i> -C ₃ H ₇ | <i>o</i> -Cl | A | 127-128 | 42 | E | C ₁₆ H ₁₇ ClN ₂ O ₂ S |
| 68 | H | <i>n</i> -C ₄ H ₉ | H | A | <i>f</i> | | | |
| 69 | CH ₃ | CH ₃ | H | A | 213-215 | 69 | E | C ₁₅ H ₁₆ N ₂ O ₂ S·HBr |
| 70 | CH ₃ | CH ₃ | <i>o</i> -Cl | B | 147-148 | 73 | H/E | C ₁₅ H ₁₅ ClN ₂ O ₂ S |
| 71 | CH ₃ | CH ₃ | <i>p</i> -Cl | A | 225-227 | 75 | E | C ₁₅ H ₁₅ ClN ₂ O ₂ S·HBr |
| 72 | CH ₃ | CH ₃ | <i>m</i> -CF ₃ | A | 234-235 ^g | 53 | E | C ₁₆ H ₁₅ F ₃ N ₂ O ₂ S·HBr |
| 73 | CH ₃ | <i>n</i> -C ₃ H ₇ | H | A | 170-173 | 64 | E | C ₁₇ H ₂₀ N ₂ O ₂ S |
| 74 | <i>i</i> -C ₃ H ₇ | H | H | A | <i>f</i> | | | |
| 75 | -(CH ₂) ₃ - | H | H | A, B | 130-131 | 73 ^d | E | C ₁₆ H ₁₆ N ₂ O ₂ S |
| 76 | -(CH ₂) ₄ - | <i>p</i> -Cl | A | A | 158-159 | 62 | E/T | C ₁₇ H ₁₇ ClN ₂ O ₂ S |
| 77 | -(CH ₂) ₄ - | <i>o</i> -OCH ₃ | A | A | 134-135 | | E | C ₁₈ H ₂₀ N ₂ O ₃ S |
| 78 | -(CH ₂) ₄ - | <i>m</i> -CF ₃ | A | A | 163 | 73 | E | C ₁₈ H ₁₇ F ₃ N ₂ O ₂ S |
| 79 | -CH ₂ CH ₂ CH(CH ₃)CH ₂ - | H | H | A | 156-157 | 69 | E | C ₁₈ H ₂₀ N ₂ O ₂ S |
| 80 | -(CH ₂) ₅ - | H | H | A, B | 185-186 | 72 ^e | E | C ₁₈ H ₂₀ N ₂ O ₂ S·HBr |

^aSee Experimental Section. ^bE, EtOH; H, hexane; T, toluene. ^cAnalyzed for C, H, and N. ^dYield per cent by method B. ^eYield per cent by method A. ^fNot isolated and used crude in next step. ^gDecomposed.

while N-1 methylation of 5-*o*-fluorophenyl derivative caused an increase in narcosis potentiation and a decrease in anti-convulsant and muscle-relaxant activities, N-1 methylation of the 5-*o*-chlorophenyl derivative resulted in a reverse change in all these properties.

In conclusion, the present results suggest the following matter: in this thienodiazepine series an ethyl group at C-7 is the most favorable substituent for the activity. It is possible to increase the potency by the introduction of a halogen atom in the ortho position of a C-5 phenyl, as the case of the benzodiazepine series. The effect of N-1 methylation depends on the property of the individual compound.

Experimental Section

Pharmacology Methods. The animals used were dd-strain mice weighing 20-25 g and Wistar rats weighing 140-170 g.

1. **Inhibition of Fighting Behavior (FE).** Fighting episodes were induced by the method of Tedeschi, *et al.*⁵ Groups of 12 female mice (six pairs) each were given the test compounds orally 60 min prior to receiving foot shock (530 V, 1.3 mA, 10 cps). The ED₅₀, the dose which inhibited the fighting in 50% pairs according to the same criterion of the Tedeschi, *et al.*,⁵ was determined graphically.

2. **Antipentetrazole Activity (Met).**⁶ Groups of five or seven male mice each were given the test compounds intraperitoneally 15 min prior to the treatment with pentetrazole, 150 mg/kg (sc). The ED₅₀, the dose which prevented the lethality within 3 hr in 50% of the animals, was calculated by the probit method.

3. **Anti-MES Activity.** Maximal electroshock (MES) was induced by the method of Nakanishi, *et al.*⁷ Groups of five or seven male mice each were challenged with a maximal electroshock (ac 2000 V, 12.5 mA, 0.2 sec) applied by the corneal electrodes 1 hr after the administration of the test compounds. The ED₅₀ values which prevented the tonic extensor of the hind limb in 50% of the animals were determined by the graphical interpolation or by the probit method.

4. **Antibemegride-Induced Convulsions.** Groups of five or seven male mice each were challenged with bemegride, 50 mg/kg (ip), 60 min after the treatment of the test compounds. The 50% effective dose (ED₅₀) in the prevention of the tonic extensor convulsion was determined by the graphical interpolation or by the probit method.

5. **Effects on Motor Coordination.** Groups of five female mice each were placed on a horizontal rotating cage⁸ and a horizontal rotating rod.⁹ The test compounds were given intraperitoneally 1

hr before the tests. The ED₅₀, the dose which dropped 50% of the animals from the apparatus within 1 min, was calculated by the probit method.

6. **Narcosis Potentiation.** Groups of seven male mice each were given the test compounds, intraperitoneally 30 min prior to the treatment with subnarcotic dose of hexobarbital (40 mg/kg, ip) or orally 30 min after the treatment of chlorprothixene hydrochloride (25 mg/kg, po). The animals were kept in a chamber at 26° and the righting reflex was checked 15 and 30 min after the treatment of hexobarbital or 60 and 90 min after the treatment of chlorprothixene. The PD₅₀, the dose which resulted in loss of the righting reflex for more than 30 sec in 50% of the animals, was determined graphically.

7. **Taming Effects in Olfactory Bulb-Removed Rats.** Groups of three female olfactory bulb-removed rats (O.B. rats)¹⁰ each were orally given the test compounds. The hyperemotionality of the animals was hourly scored for 6 hr by the rating scale method previously reported by the authors.⁵ The ED₅₀, the dose for 50% inhibition of the hyperemotionality, was determined graphically from the inhibitory rate at the most effective time.

8. **Acute Toxicity.** Groups of ten male mice each were given the test compounds intraperitoneally or orally. The 50% lethal dose (LD₅₀) was calculated by the probit method.

Synthetic Methods. Melting points were taken in a capillary tube and are uncorrected. The structures of all compounds were supported by ir, nmr, and mass spectra. The spectra were obtained from a Jasco Model IR-G spectrophotometer for the ir, by a Jeol Model PS-100 for the nmr, and by a Jeol Model JMS-01SG for the mass spectra. Analytical results obtained were within ±0.4% of the theoretical values. Representative procedures for the preparation of the compounds are illustrated below.

(I) **2-Amino-3-benzoylthiophenes.** (a) From Aldehydes (Table I, 1-9). **2-Amino-3-*o*-chlorobenzoyl-5-ethylthiophene (4).** A solution of butyraldehyde (7.2 g, 0.1 mol) in EtOH (5 ml) was added dropwise to a stirred mixture of *o*-chloro- ω -cyanoacetophenone (18.0 g, 0.1 mol), powdered sulfur (3.5 g, 0.11 g-atom), DMF (30 ml), and triethylamine (8 ml) at 45-50° during 30 min. After stirring below 60° for an additional 1 hr, a suspension of the mixture in water was extracted with EtOAc. The extract was washed with 10% HCl, Na₂CO₃ solution, and water, successively, dried (Na₂SO₄), and then concentrated under reduced pressure. Recrystallization of the residue from hexane-EtOH gave 16.2 g of 4, mp 132-133°.

(b) From Ketones (Table I, 10-21). **2-Amino-3-*o*-chlorobenzoyl-4,5-dimethylthiophene (11).** A mixture of methyl ethyl ketone (7.2 g, 0.1 mol), *o*-chloro- ω -cyanoacetophenone (18.0 g, 0.1 mol), powdered sulfur (3.5 g, 0.11 g-atom), and morpholine (10 ml) in EtOH (50 ml) was stirred under reflux for 3 hr, cooled, and then concentrated under reduced pressure. The extract of the residue with

Table V. 5-Phenyl-1,3-dihydro-2H-thieno[2,3-e][1,4]diazepin-2-ones (V and VI)

| No. | R ¹ | R ² | R ³ | R | Mp, °C | Yield, % | Crystn solvent ^a | Formula ^b | Pharmacological data (1) ^c | |
|------------------|--|---|--|----------------------------|----------------------|----------|-----------------------------|--|---------------------------------------|-------------|
| | | | | | | | | | FE | Met |
| 81 ^d | H | CH ₃ | H | H | 207-210 | | | | 8 | 17 |
| 82 | H | CH ₃ | H | <i>o</i> -Cl | 212-213 | 74 | H/E | C ₁₄ H ₁₁ ClN ₂ OS | 15 | 0.9 |
| 83 | H | C ₂ H ₅ | H | H | 194-195 | 70 | T | C ₁₅ H ₁₄ N ₂ OS | 7 | 3.1 |
| 84 | H | C ₂ H ₅ | H | <i>o</i> -F | 178-180 | 82 | H/E | C ₁₅ H ₁₃ FN ₂ OS | 0.4 | 0.3 |
| 85 | H | C ₂ H ₅ | H | <i>o</i> -Cl | 204-206 | 81 | T | C ₁₅ H ₁₃ ClN ₂ OS | 5 | 3.3 |
| 86 | H | C ₂ H ₅ | H | <i>o</i> -Br | 208-209 | 79 | H/E | C ₁₅ H ₁₃ BrN ₂ OS | 4.5 | 3.6 |
| 87 | H | C ₂ H ₅ | H | <i>o</i> -CH ₃ | 182-183 | 76 | T | C ₁₆ H ₁₆ N ₂ OS | | 8 |
| 88 | H | C ₂ H ₅ | H | <i>o</i> -OCH ₃ | 168-169 | 64 | T | C ₁₆ H ₁₆ N ₂ O ₂ S | 19 | 17 |
| 89 | H | <i>i</i> -C ₃ H ₇ | H | <i>o</i> -Cl | 243-246 ^e | 84 | E | C ₁₆ H ₁₅ ClN ₂ OS | 20 | 10 |
| 90 | H | <i>n</i> -C ₄ H ₉ | H | H | 163-164 | | I | C ₁₇ H ₁₈ N ₂ OS | >80 (0) | >160 (16.7) |
| 91 | CH ₃ | CH ₃ | H | H | 236-237 | 75 | D/W | C ₁₅ H ₁₄ N ₂ OS | 20 | 15 |
| 92 | CH ₃ | CH ₃ | H | <i>o</i> -Cl | 251 | 72 | T/E | C ₁₅ H ₁₃ ClN ₂ OS | 10.5 | 47.0 |
| 93 | CH ₃ | CH ₃ | H | <i>p</i> -Cl | 243-245 ^e | 80 | H/E | C ₁₅ H ₁₃ ClN ₂ OS | >160 (0) | |
| 94 | CH ₃ | CH ₃ | H | <i>m</i> -CF ₃ | 220-222 | 75 | H/E | C ₁₆ H ₁₃ F ₃ N ₂ OS | >160 (0) | >160 (0) |
| 95 | CH ₃ | <i>n</i> -C ₃ H ₇ | H | H | 207-208 | 70 | E | C ₁₇ H ₁₈ N ₂ OS | 120 | >160 (16.7) |
| 96 | <i>i</i> -C ₃ H ₇ | H | H | H | 230-232 | | H/E | C ₁₆ H ₁₆ N ₂ OS | >160 (25) | 130 |
| 97 | | -(CH ₂) ₃ - | H | H | 243 ^e | 76 | E | C ₁₆ H ₁₄ N ₂ OS | 30 | 30 |
| 98 ^f | | -(CH ₂) ₄ - | H | H | 247-249 ^e | | | | 20 | 35 |
| 99 ^f | | -(CH ₂) ₄ - | H | <i>o</i> -Cl | 260-263 ^e | | | | 10 | 20 |
| 100 | | -(CH ₂) ₄ - | H | <i>p</i> -Cl | 253-254 ^e | 77 | D/W | C ₁₇ H ₁₅ ClN ₂ OS | >160 (0) | >160 (0) |
| 101 | | -(CH ₂) ₄ - | H | <i>o</i> -OCH ₃ | 241-242 ^e | 58 | H/E | C ₁₈ H ₁₈ N ₂ O ₂ S | >80 (25) | 80 |
| 102 | | -(CH ₂) ₄ - | H | <i>m</i> -CF ₃ | 217 | 69 | E | C ₁₈ H ₁₅ F ₃ N ₂ OS | 160 | >160 (0) |
| 103 | -CH ₂ CH ₂ CH(CH ₃)CH ₂ - | H | H | H | 224-225 ^e | 83 | H/C | C ₁₈ H ₁₈ N ₂ OS | 60 | 80 |
| 104 | | -(CH ₂) ₅ - | H | H | 228-229 ^e | 75 | M | C ₁₈ H ₁₈ N ₂ OS | 70 | >160 (0) |
| 105 | H | CH ₃ | CH ₃ | H | 234-235 ^e | 70 | C/E | C ₁₅ H ₁₄ N ₂ OS · HCl | 40 | >160 (0) |
| 106 | H | CH ₃ | CH ₃ | <i>o</i> -Cl | 232-234 ^e | 68 | C/E | C ₁₅ H ₁₃ ClN ₂ OS · HCl | 25 | 2.1 |
| 107 | H | C ₂ H ₅ | CH ₃ | H | 103-104 | 64 | E | C ₁₆ H ₁₆ N ₂ OS · HCl | 30 | 10 |
| 108 | H | C ₂ H ₅ | CH ₃ | <i>o</i> -F | 203-204 ^e | 68 | A/E | C ₁₆ H ₁₅ FN ₂ OS · HCl | 0.6 | 0.4 |
| 109 | H | C ₂ H ₅ | CH ₃ | <i>o</i> -Cl | 105-106 | 88 | H | C ₁₆ H ₁₅ ClN ₂ OS | 2.9 | 0.5 |
| 110 | H | C ₂ H ₅ | CH ₃ | <i>o</i> -Br | 100-102 | 80 | H/E | C ₁₆ H ₁₅ BrN ₂ OS | 1.2 | 0.3 |
| 111 | CH ₃ | CH ₃ | CH ₃ | H | 121 | 70 | H/E | C ₁₆ H ₁₆ N ₂ OS | 36 | 15 |
| 112 | CH ₃ | CH ₃ | CH ₃ | <i>o</i> -Cl | 235-236 | 83 | E | C ₁₆ H ₁₅ ClN ₂ OS · HCl | 12 | 12.5 |
| 113 | CH ₃ | CH ₃ | CH ₃ | <i>p</i> -Cl | 182-184 | 76 | H/E | C ₁₆ H ₁₅ ClN ₂ OS | >80 (0) | >160 (0) |
| 114 ^f | | -(CH ₂) ₄ - | CH ₃ | H | 128-129 ^e | | | | 35 | 15 |
| 115 | | -(CH ₂) ₄ - | CH ₃ | <i>o</i> -Cl | 137 | 87 | I | C ₁₈ H ₁₇ ClN ₂ OS | 30 | 3.7 |
| 116 | | -(CH ₂) ₄ - | CH ₃ | <i>o</i> -OCH ₃ | 148-149 | 88 | E | C ₁₉ H ₂₀ N ₂ O ₂ S | >80 (0) | 16 |
| 117 | | -(CH ₂) ₄ - | CH ₃ | <i>m</i> -CF ₃ | 141-141.5 | 77 | E | C ₁₉ H ₁₇ F ₃ N ₂ OS | | >160 (0) |
| 118 | | -(CH ₂) ₅ - | CH ₃ | H | 150-151 | 72 | E | C ₁₉ H ₂₀ N ₂ OS | 120 | >160 (16.7) |
| 119 | | -(CH ₂) ₄ - | -CH ₂ CH=CH ₂ | H | 139-140 | 71 | H/E | C ₂₀ H ₂₀ N ₂ OS | >160 (25) | >160 (16.7) |
| 120 | | -(CH ₂) ₄ - | -CH ₂ C≡CH | H | 137-138 | 70 | I | C ₂₀ H ₁₈ N ₂ OS | >160 (25) | >160 (0) |
| 121 | | -(CH ₂) ₄ - | <i>n</i> -C ₄ H ₉ | H | 101-102 | 82 | H/E | C ₂₁ H ₂₄ N ₂ OS | >160 (0) | >160 (0) |
| 122 | | -(CH ₂) ₄ - | -CH ₂ C ₆ H ₅ | H | 121-122 | 84 | I | C ₂₄ H ₂₂ N ₂ OS | >160 (25) | >160 (0) |
| Cf. CDP | | | | | | | | | 14.7 | 4.6 |
| Cf. DZP | | | | | | | | | 1.6 | 0.9 |

^aH, hexane; E, EtOH; T, toluene; I, *i*-PrOH; D, DMF; W, H₂O; C, EtOAc; M, MeOH; A, Me₂CO. ^bAnalyzed for C, H, and N. ^cFE, the inhibition of fighting episodes. Met, the antagonism of pentylenetetrazole. Values are ED₅₀'s expressed in mg/kg. Values in parentheses express inhibitory rate (%) at induced dose. ^dInvag A.G., Netherlands Patent 6,918,485 (1970). ^eDecomposed. ^fPark, Davis and Co., Belgium Patent 745,560 (1970).

Table VI. Pharmacological Data (2)^a

| | Anticonvulsant activity | | Muscle-relaxant activity | | Narcosis potentiation | | Taming effect (O.B. rats), ED ₅₀ , po | Acute toxicity LD ₅₀ | |
|-----|---------------------------------------|------------------------------------|-----------------------------------|----------------------------------|---------------------------------------|--|--|------------------------------------|-----|
| | Electroshock ED ₅₀ , ip | Bemegride ED ₅₀ , ip | Rotacage ED ₅₀ , ip | Rotarod ED ₅₀ , ip | Hexobarbital PD ₅₀ , ip | Chlorprothixene PD ₅₀ , po | | ip | po |
| 83 | 12.0 | 5.3 | 32.4 | 31.0 | 2.9 | 17.6 | 34.0 | 300 | 480 |
| 84 | 3.9 | 0.4 | 4.2 | 3.5 | 2.1 | 3.5 | 12.4 | 330 | 580 |
| 85 | 7.0 | 1.3 | 17.2 | 6.4 | 0.6 | 0.2 | 64.0 | 410 | 670 |
| 108 | 4.6 | 0.5 | 9.7 | 6.3 | 1.3 | 0.8 | 9.3 | 390 | 640 |
| 109 | 8.0 | 0.6 | 8.1 | 3.3 | 1.5 | 0.5 | 16.1 | 440 | 636 |
| CDP | 16.0 | 3.3 | 19.2 | 14.2 | 1.6 | 9.2 | 80.0 | 380 | 950 |
| DZP | 7.0 | 0.7 | 7.2 | 5.3 | 0.5 | 0.5 | 14.6 | 410 | 740 |

^aValues are expressed in mg/kg.

EtOAc was washed with water, 10% HCl, and Na₂CO₃ solution, successively, dried (Na₂SO₄), and then concentrated under reduced pressure. Recrystallization of the residue from EtOH gave 15.7 g of 11, mp 151–152°.

(II) 2-Benzoyloxy-carbonylaminoacetamido-3-benzoylthiophenes (Table II, 22–39). 2-Benzoyloxy-carbonylaminoacetamido-3-*o*-chlorobenzoyl-5-ethylthiophene (24). Benzoyloxy-carbonylaminoacetyl chloride (27.3 g, 0.12 mol) was added, with ice cooling, to a solution of 4 (26.6 g, 0.1 mol) in CHCl₃ (150 ml). After standing overnight in an ice box, the mixture was concentrated under reduced pressure. Recrystallization of the residue from EtOH gave 27.9 g of 24, mp 118–119°.

(III) 2-Haloacetamido-3-benzoylthiophenes. (a) Cl or Br Derivatives (Table III, 40–51). 2-Chloroacetamido-3-*o*-chlorobenzoyl-5-ethylthiophene (43). A solution of 4 (26.6 g, 0.1 mol) and chloroacetyl chloride (11.3 g, 0.11 mol) in CHCl₃ (130 ml) was refluxed for 1 hr. The solvent was concentrated under reduced pressure and the residue was recrystallized from EtOH to give 27.6 g of 43, mp 99–100°.

(b) Iodo Derivatives (Table III, 52–59). 2-Iodoacetamido-3-*o*-chlorobenzoyl-5-ethylthiophene (55). Sodium iodide (16.5 g, 0.11 mol) was added to a stirred solution of 43 (34.2 g, 0.1 mol) in Me₂CO (200 ml) and the mixture was refluxed for 30 min. After cooling, the inorganic salt was filtered off and the filtrate was concentrated under reduced pressure. Recrystallization of the residue from EtOH gave 37.3 g of 55, mp 100–101°.

(IV) 2-Aminoacetamido-3-benzoylthiophenes (Table IV, 60–80). Method A. 2-Aminoacetamido-3-*o*-chlorobenzoyl-5-ethylthiophene (63). A solution of 24 (45.7 g, 0.1 mol) in 20% HBr–AcOH (200 ml) was stirred at room temperature for 1 hr. Isopropyl ether (1 l.) was added to the mixture and the precipitated crystals were collected by filtration and washed with three 100-ml portions of isopropyl ether. A suspension of the crystals in water was made alkaline with NaHCO₃ and extracted with CHCl₃. The extract was dried (Na₂SO₄) and concentrated under reduced pressure. Recrystallization of the residue from EtOH gave 20.3 g of 63, mp 146–148°.

Method B. 2-Aminoacetamido-3-*o*-bromobenzoyl-5-ethylthiophene (64). Ammonia gas was introduced, with ice cooling, to a solution of 56 (20 g, 0.042 mol) in CHCl₃ (50 ml) and MeOH (5 ml) during 2 hr. After stirring at room temperature for additional 2 hr, the mixture was washed with ice-water and NaHCO₃ solution, successively, dried (Na₂SO₄), and then concentrated under reduced pressure. Recrystallization of the residue from EtOH gave 11.7 g of 64, mp 160–161°.

(V) 5-Phenylthieno[2,3-*e*][1,4]diazepines (Table V, 81–104). 5-*o*-Chlorophenyl-7-ethyl-1,3-dihydro-2*H*-thieno[2,3-*e*][1,4]diazepin-2-one (85). A solution of 63 (10.0 g, 0.031 mol) in a mixture of pyridine (50 ml), AcOH (1.9 g, 0.031 mol), and C₆H₆ (20 ml) was refluxed for 10 hr in a flask fitted with a water separator. The mixture was concentrated under reduced pressure. A suspension of the mixture in water was made alkaline with NaHCO₃ and extracted with CHCl₃. The extract was dried (Na₂SO₄) and concentrated under reduced pressure. Crystallization of the residue from toluene gave 5.9 g of 85, mp 204–206°.

(VI) 1-Substituted 5-Phenylthieno[2,3-*e*][1,4]diazepines (Table V, 105–122). 1-Methyl-5-*o*-chlorophenyl-7-ethyl-1,3-dihydro-2*H*-thieno[2,3-*e*][1,4]diazepin-2-one (109). A 50% suspension of NaH in mineral oil (2.9 g, 0.06 mol) was added portionwise to a solution of 85 (15.3 g, 0.05 mol) in DMF (100 ml). After stirring for 15 min at 50°, MeI (8.5 g, 0.06 mol) was added dropwise to the mixture with ice cooling and the solution was stirred for additional 30 min at room temperature. A suspension of the mixture in water was extracted with EtOAc. The extract was washed with water, dried (Na₂SO₄), and then concentrated under reduced pressure. Recrystallization of the residue from hexane gave 8.8 g of 109, mp 105–106°.

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Centrally Acting Emetics. 7. Hofmann and Emde Degradation Products of Apomorphine^{†,1}

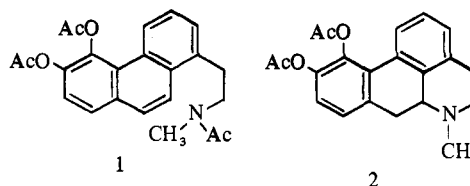
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Hofmann elimination of quaternary apomorphine derivatives has been studied with respect to direction of ring opening. Specificity of opening has been attained by choice of a suitable base, and some confusion and error existing in the older literature on the subject have been resolved. Emde degradations have been found to proceed smoothly and the structure of the product has been determined by nmr. Derivatives of the Hofmann and Emde products have been evaluated for emetic effects and these biological data have been rationalized on conformational grounds.

Tiffeneau and Porcher² first prepared "triacyl apomorphine" 1 by prolonged heating of apomorphine with excess acetic anhydride, and they reported it to be devoid of emetic activity; this observation was verified in this laboratory.³ Since the diacetate ester 2 of apomorphine has emetic activity nearly identical with that of apomorphine itself,³ it was



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speculated that the inactivity of triacyl apomorphine might be referable, at least in part, to the masking of the basicity of the nitrogen by the amide link. The great differences in emetic activity produced by relatively minor