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Studies on Psychotropic Agents. V.¹⁾ Synthesis of 1-Substituted
Spiro[dibenz[*b,f*]oxepin-11,4'-piperidine]-10(11*H*)-one
and Related Compounds²⁾

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Tricyclic compounds (12, 17 and 20) combined with a spiro-system at the 4 position of 1-substituted piperidine were synthesized for pharmacological testing. They could be prepared by a sequence of reactions involving the Pinacol rearrangement of 9-(1-ethoxycarbonyl-4-piperidinyl)fluorene-9,4'-diol (9) or the cyclization of 1-benzyl-4-(*o*-substituted phenyl)-4-carboxy (or cyano)piperidine (15a and 16). 9-(1-Methyl-1,2,3,6-tetrahydro-4-pyridinyl)xanthene (or -anthracene) (21 and 26) and 3-methyl-2,3,4,5-tetrahydro-1*H*-phenanthro[9,10-*d*]azepine (27) were also prepared by the Wagner-Meerwein rearrangement of α hydroxy spiro compounds (19b, 19d, and 11, respectively).

Among the compounds synthesized, 1-methyl-1,2,3,5,6,7-hexahydrospiro[[4*H*]azepine-4,9'-fluorene]-5-ol (8) showed marked anti-convulsant activity.

Keywords—spiro[phenanthrene-10,4'-piperidine]; spiro[dibenz[*b,f*]oxepin-11,4'-piperidine]; spiro[10*H*-dibenzo[*a,d*]cycloheptene-11,4'-piperidine]; spiro[[4*H*]azepine-4,9'-fluorene]; dispiro[fluorene-9,2'-oxirane-3',4''-piperidine]; 1*H*-phenanthro[9,10-*d*]azepine; Wagner-Meerwein rearrangement; Pinacol rearrangement; anti-convulsant activity

It has been reported that dibenzepine (I)⁴⁾ and 11-(2-dimethylaminoethyl)dibenzo[*b,f*]thiepin-10(11*H*)-one (II),⁵⁾ which consist of a 6,7,6-tricyclic system and dimethylaminoethyl group, exhibited thymoleptic properties in animal tests, and I has been used clinically as a thymoleptic. On the other hand, 1-substituted 4-benzoylpiperidine derivatives (III)⁶⁾ have been reported to possess central nervous system (CNS) depressing activities. These reports prompted us to synthesize tricyclic compounds (IV) combined with a spiro-system at the 4 position of 1-substituted piperidine, which contain both II or an analogous tricyclic structure and III, for pharmacological evaluation.

The Grignard reaction of the tricyclic ketones (1) with 1-benzyl-4-piperidinylmagnesium chloride gave the carbinols (3), which were treated with dil. hydrochloric acid and then with ethyl chloroformate in benzene to give the carbamates (5). Epoxidation of 5a with *m*-chloroperbenzoic acid afforded the epoxide (6) in 78% yield, but the same treatment of 5b resulted in recovery of the starting material. Treatment of 6 with borontrifluoride etherate in benzene or with aluminum chloride in nitrobenzene afforded the azepine (7) by migration of the alkyl group instead of the desired phenanthrenone (10). Reduction of 7 with lithium aluminum hydride (LAH) gave the carbinol (8); its nuclear magnetic resonance (NMR) spectrum showed a proton (C₅-H) α to the hydroxyl group at δ 3.96 as a doublet of doublets ($J=8$ and 3 Hz).

- 1) Part IV: Y. Nagai, A. Irie, H. Uno, and S. Minami, *Chem. Pharm. Bull.* (Tokyo), 27, 1922 (1979).
- 2) This work was presented at the 97th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1977.
- 3) Location: 33-94, Enokicho, Suita, Osaka.
- 4) 10-[2-Dimethylaminoethyl]-5,10-dihydro-5-methyl-1*H*-dibenzo[*b,e*][1,4]dibenzepin-11-one, G. Stille, *Arzneimittel-Forsch.*, 14, 534 (1964).
- 5) R. Smrž, J.O. Jílek, B. Kabác, J. Holubek, E. Svátek, M. Bartosová, and M. Protiva, *Collect. Czech. Chem. Commun.*, 41, 3420 (1976).
- 6) R.L. Duncan, Jr., G.C. Helsley, W.J. Westead, Jr., J.P. DaVanzo, W.H. Funderburk, and C.D. Lunsford, *J. Med. Chem.*, 13, 1 (1970).

This supported the structure **8**. The ultraviolet (UV) spectrum of **8** showed absorption maxima at 270, 292 and 303 nm, like that of fluorene. Conversion of **6** into the diol (**9**) with 6% perchloric acid followed by Pinacol rearrangement with zinc chloride in acetic anhydride gave the desired phenanthrenone (**10**) in 49% yield. Reduction of **10** with LAH gave the carbinol (**11**), which showed a benzylic proton (C_9-H) at δ 4.75 as a singlet. Oxidation of **11** with chromic anhydride in pyridine gave the desired ketone (**12**).

An alternative synthetic route was attempted. It has been reported⁷⁾ that the reaction of dibenzo[*b,f*]thiepin-10(11*H*)-one (Vc) with dialkylaminoalkyl halide and sodium amide in

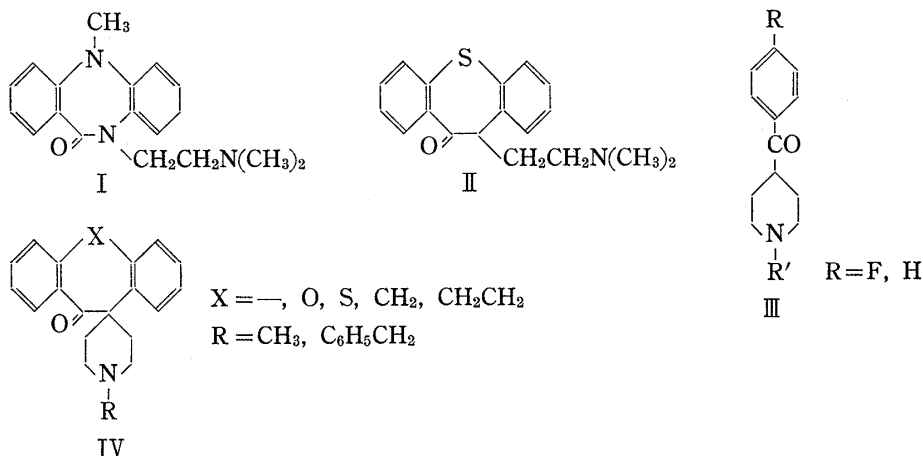


Chart 1

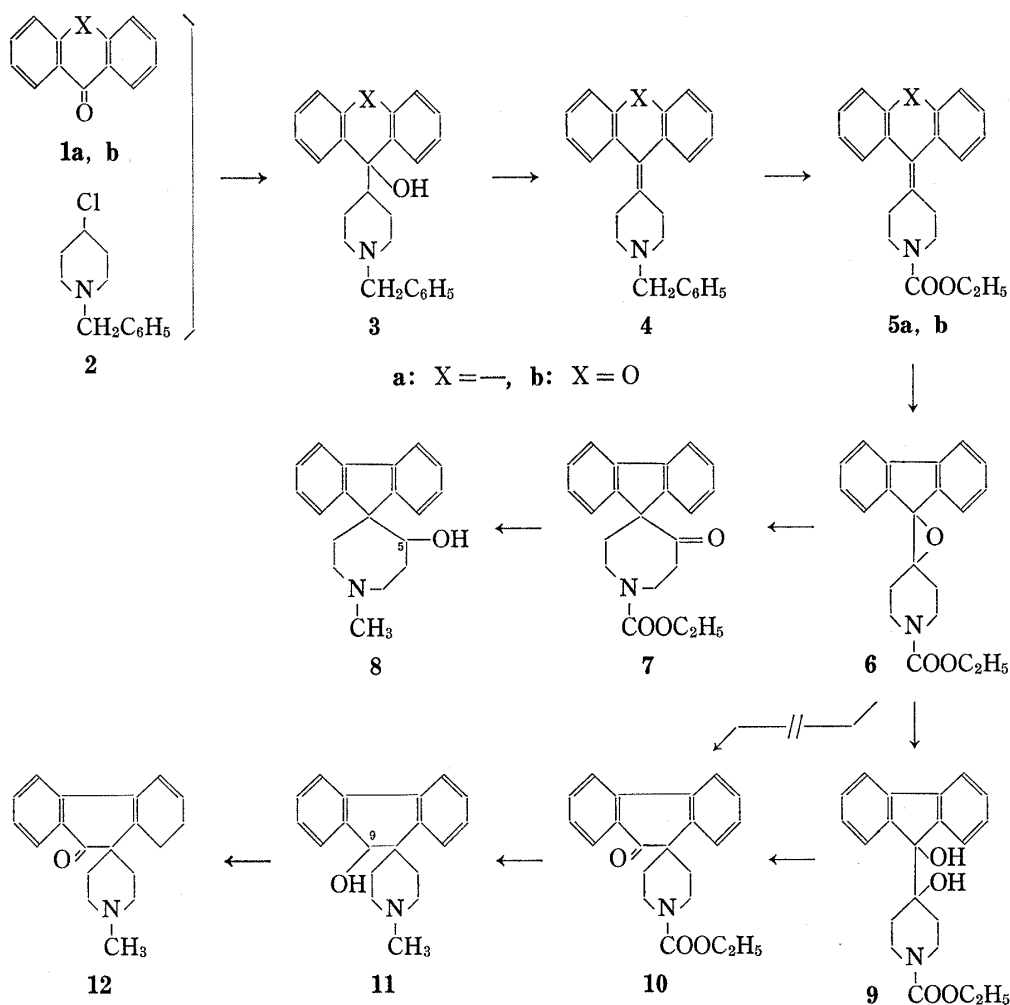
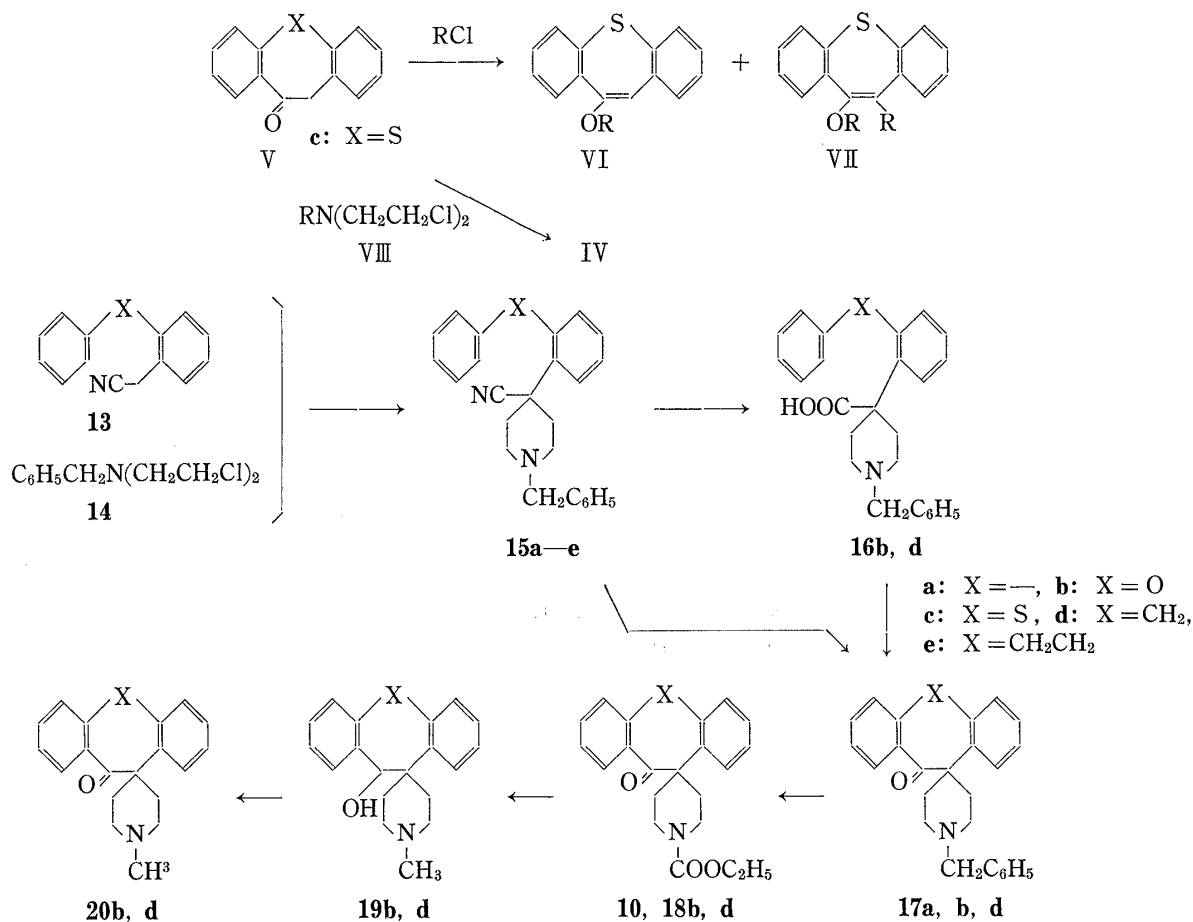


Chart 2



toluene gives VI and VII. This experimental result suggested that the direct synthesis of IV from the tricyclic ketone (V) and the dihalide (VIII) would be difficult. Therefore, *o*-substituted phenylacetonitrile (13) was treated with N-benzyl 2,2'-dichlorodiethylamine (14) in the presence of 2.2 moles of sodium amide in toluene to give N-benzyl piperidine derivatives (15); however, the yield of 15c was very low (8%). Treatment of 15a with conc. sulfuric acid followed by hydrolysis gave the tricyclic compound (17a), but similar treatment of 15b, 15d and 15e was unsuccessful. As the nitrile group is sterically hindered, various conditions for hydrolysis were examined. Heating of 15b and 15d in a mixture of conc. hydrochloric acid and acetic acid for 70 hours gave the carboxylic acids (16b and 16d), but hydrolysis of 15e under these conditions did not proceed, presumably because its steric hindrance would be most severe among compounds 15. On heating with polyphosphoric acid (PPA) 16b and 16d cyclized to the tricyclic ketones (17b and 16d) in good yields. Treatment of 17a, 17b and 17d with ethyl chloroformate in benzene gave the carbamates (10, 18b and 18d). Reduction of 18 with LAH followed by oxidation with chromic anhydride afforded the desired ketones (20b and 20d).

The 1-methyl-4-piperidinylidene derivatives (IX)⁸⁾ and tetracyclic dihydropyrrole derivatives (X)⁹⁾ have been reported to possess CNS depressing activities in animal tests. On the

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- 9) H. Blattner and W. Schindler (Ciba-Geigy A.-G.), Ger. Offen., 2125892 (1971) [*C.A.*, **76**, 72494 (1972)]; H. Blattner (Ciba-Geigy A.-G.), Ger. Offen., 2505155 (1975) [*C.A.*, **84**, 17313 (1976)]; J. Gosteli and W. Schindler (Ciba-Geigy A.-G.), Ger. Offen., 2125634 (1972) [*C.A.*, **76**, 113066 (1972)].

other hand, the tetracyclic tetrahydropyridines (XI)¹⁰⁾ are known to possess thymoleptic activities. We therefore attempted to prepare the 4-piperidinylidene derivatives (XII) or the tetracyclic tetrahydroazepines (XIII) from the α hydroxy spiro compounds (19b, 19d and 11) by Wagner-Meerwein rearrangement. Treatment of 19b with PPA at 170 °C for 8

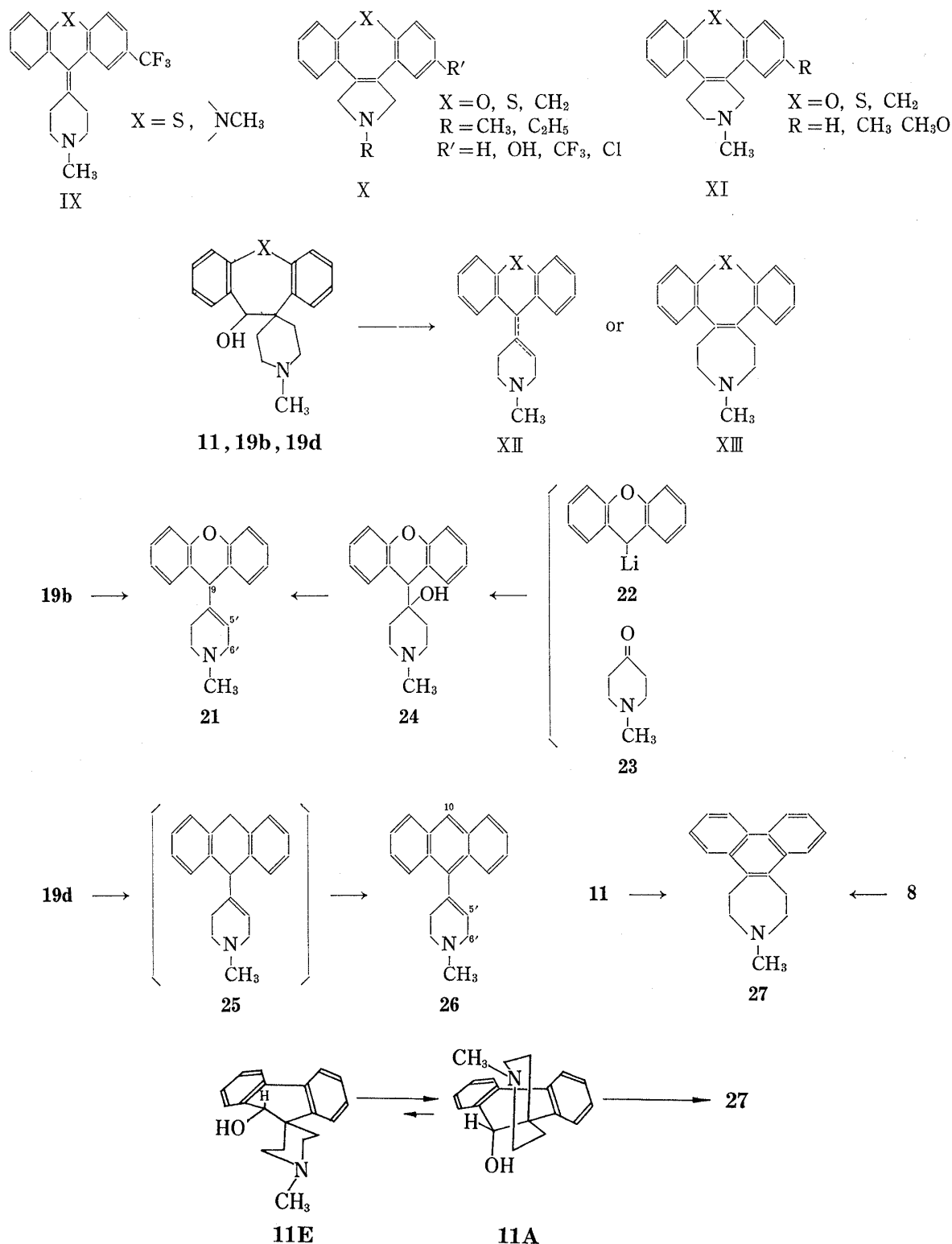


Chart 4

10) W.J. Van der Burg (Akzo N.V.), Ger. Offen., 2503407 (1975) [C.A., 83, 193278 (1975)].

minutes gave the 1,2,3,6-tetrahydropyridine derivative (**21**) in 59% yield by migration of the aryl group, but heating of **19b** with 48% hydrobromic acid resulted in decomposition. The NMR spectrum of **21** showed a proton (C_9-H) in the xanthene ring at δ 4.70 as a singlet and a vinyl proton ($C_5'-H$) in the tetrahydropyridine at δ 5.82 as a multiplet. The structure of **21** was confirmed by synthesis from the 4-hydroxypiperidine derivative (**24**), which was obtained from 9-lithioxanthene (**22**)¹¹⁾ and 1-methyl-4-piperidone (**23**). Similar treatment of **19d** with PPA or 48% hydrobromic acid gave the anthracene derivative (**26**) in 10 and 22% yields, respectively. The NMR spectrum of **26** showed a proton ($C_{10}-H$) in the anthracene ring at δ 8.34 as a singlet and a vinyl proton ($C_5'-H$) in the tetrahydropyridine ring at δ 5.82 as a multiplet. Compound (**26**) is presumably obtained *via* the dihydroanthracene derivative (**25**) followed by oxidation in the air.

On the other hand, similar treatment of **11** with PPA or 48% hydrobromic acid gave the phenanthrene derivative (**27**) in 57 and 52% yields, respectively, by migration of the alkyl group. The NMR spectrum of **27** showed the signal of the aromatic protons as an ABMX system identical with that ¹²⁾ of 9,10-dimethylphenanthrene, as shown in Figs. 1 and 2. The reaction of **8** with PPA or 48% hydrobromic acid also gave **27** in 57 and 51% yields, respectively.

In the spiro dihydrophenanthrenol (**11**), the quasi-axial alcohol (**11A**), which has less interaction between the hydroxyl group and piperidine ring than the quasi-equatorial alcohol

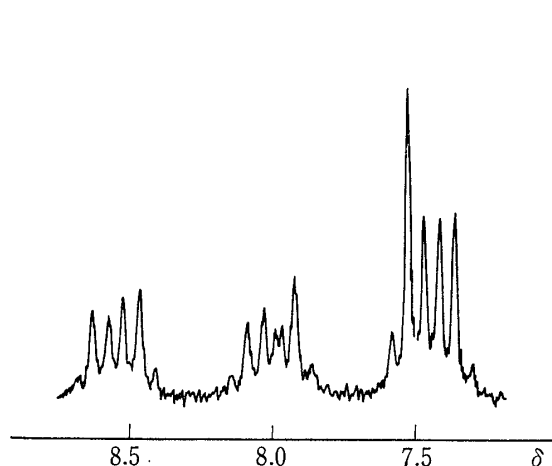


Fig. 1. NMR Spectrum of **27** in CS_2

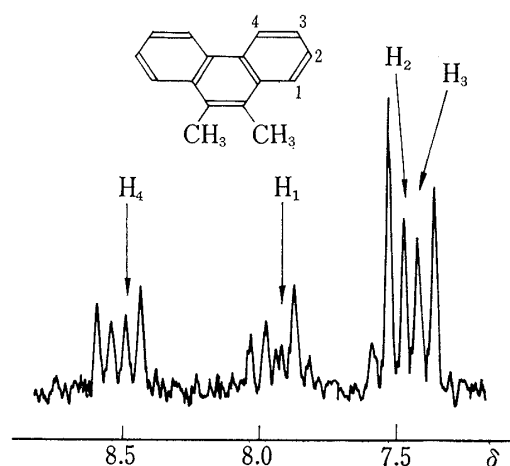


Fig. 2. NMR Spectrum of 9,10-Dimethylphenanthrene in CS_2 (from ref. 12)

TABLE I. Anti-convulsant Activities of **8**, **27** and Reference Compounds

	ED ₅₀ , mg/kg <i>p.o.</i> , mice	
	anti-MES ^{a)}	anti-PTZ ^{b)}
8	16.3	17.0
27	50.0	26.0
Phenacemide	61.2	65.0
Carbamazepine	13.3	10.3

^{a)} Y. Masuda, T. Karasawa, Y. Shiraishi, M. Hori, K. Yoshida and M. Shimizu, *Arzneim.-Forsch.*, in press.

^{b)} E.A. Swinyard, *J. Am. Pharm. Assoc.*, **38**, 201 (1963).

11) R. Nakai, M. Sugii, and H. Tomono, *Yakugaku Zasshi*, **75**, 1004 (1955).

12) P.M.G. Bavin, K.D. Bartle, and J.A.S. Smith, *Tetrahedron*, **21**, 1087 (1965).

(11E), should be predominant, and the ring expansion of 11A to the stable phenanthrene derivative (27) might easily occur by migration of the alkyl group antiparallel to the hydroxyl group. In addition, the thermodynamic stability of the phenanthrene ring may play an important role in forming 27. In the rearrangement of 19b and 19d the stable 6,6,6-system compounds (21 and 26) might be formed predominantly from the less stable 6,7,6-system ones by some thermodynamic driving force.

Pharmacology

All compounds prepared in this study were examined pharmacologically by the usual methods for neuroleptic and thymoleptic activities. Among them, 27 showed moderate CNS depressant activities and 20b exhibited mild anti-reserpine activity. On the other hand, 8 and 27 showed anti-convulsant activities more potent than that of phenacemide in the anti-maximum electroshock seizure test (anti-MES) and anti-pentylenetetrazole seizure test (anti-PTZ), as shown in Table I.

Experimental¹³⁾

1-Benzyl-4-piperidinylidene Tricyclic Compounds (4a and 4b)—A drop of methyl iodide was added to a mixture of magnesium (0.03 mol) and 1-benzyl-4-piperidyl chloride (0.03 mol) in dry THF (20 ml), and the mixture was heated under reflux for 1 hr. The mixture was diluted with THF (50 ml) and a solution of 1a (or 1b) (0.025 mol) in dry THF (15 ml) was added. The mixture was refluxed for 2 hr and the solvent was removed *in vacuo*. Aqueous ammonium chloride was added to the residue and the mixture was extracted with ether. The ether layer was extracted with 20% HCl and the extract was heated on a water-bath for 2 hr. The solution was made alkaline with 28% NH₄OH and extracted with ether. The extract was dried over Na₂SO₄ and concentrated. The residue was recrystallized from ether. 4a: mp 114–116°. Yield, 42%. *Anal.* Calcd. for C₂₅H₂₃N: C, 88.98; H, 6.89; N, 4.15. Found: C, 88.81; H, 7.11; N, 4.04. 4b: mp 115–117°. Yield, 38%. *Anal.* Calcd. for C₂₅H₂₃NO: C, 84.95; H, 6.56; N, 3.96. Found: C, 84.64; H, 6.81; N, 4.25.

1-Ethoxycarbonyl-4-piperidinylidene Tricyclic Compounds (5a and 5b)—Ethyl chloroformate (0.04 mol) was added to a solution of 4a (or 4b) (0.02 mol) in benzene (40 ml) at 60–70° with stirring, then the mixture was heated under reflux for 3 hr. The benzene solution was washed with dil. HCl and H₂O, dried over Na₂SO₄ and concentrated. The residue was recrystallized from ether. 5a: mp 115–117°. Yield, 78%. *Anal.* Calcd. for C₂₁H₂₁NO₂: C, 78.97; H, 6.63; N, 4.39. Found: C, 79.06; H, 6.46; N, 4.34. 5b: mp 98–101°. Yield, 71%. *Anal.* Calcd. for C₂₁H₂₁NO₃: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.35; H, 6.43; N, 3.88.

Epoxidation of 9-(1-Ethoxycarbonyl-4-piperidinylidene)fluorene (5a)—*m*-Chloroperbenzoic acid (85% pure, 2.3 g) was added to a solution of 5a (3.3 g) in CHCl₃ (60 ml) and the resulting mixture was stirred at room temperature overnight. Next, 20% Na₂SO₃ (60 ml) was added and the mixture was stirred vigorously for 1 hr. The CHCl₃ layer was washed with dil. NaOH and H₂O, dried over Na₂SO₄ and concentrated. The residue was recrystallized from acetone to give 2.7 g (78%) of 6, mp 147–148.5°. *Anal.* Calcd. for C₂₁H₂₁NO₃: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.04; H, 6.25; N, 4.07. MS *m/e*: 335 (M⁺).

Rearrangement of 1'-Ethoxycarbonyldispiro[fluorene-9,2'-oxirane-3',4''-piperidine] (6)—a) Boron-trifluoride etherate (47%, 2.2 ml) was added to a solution of 6 (1.9 g) in benzene (60 ml) at room temperature, and the mixture was allowed to stand at room temperature for 35 min. The solution was washed with H₂O, dried over Na₂SO₄ and concentrated. The residue was recrystallized from acetone to give 1.3 g (68%) of 7, mp 142–144°. *Anal.* Calcd. for C₂₁H₂₁NO₃: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.22; H, 6.45; N, 4.40.

b) Anhydrous aluminum chloride (0.4 g) was added to a solution of 6 (1 g) in nitrobenzene (20 ml), and the mixture was warmed at 75–80° for 40 hr. The solvent was removed *in vacuo* and H₂O was added to the residue. The mixture was extracted with ether and the extract was washed with H₂O, dried over Na₂SO₄ and concentrated. The residue was recrystallized from acetone to give 0.62 g (62%) of 7.

1-Methyl-1,2,3,5,6,7-hexahydrospiro[[4H]azepine-4,9'-fluorene]-5-ol (8)—A solution of 7 (1.4 g) in dry THF (10 ml) was added to a suspension of LAH (1 g) in dry ether (70 ml) at a rate sufficient to maintain gentle reflux. After addition, the mixture was refluxed with stirring for 3 hr, then treated with H₂O. The mixture was filtered, and the filtrate was dried over Na₂SO₄ and concentrated. The residue was converted into the hydrochloride with ethanolic HCl and recrystallized from EtOH-ether to give 0.9 g (69%) of 8·HCl,

13) All melting points are uncorrected. NMR spectra were taken with a Varian A-60 or Varian HA-100 spectrometer using TMS as an internal standard; s, singlet; d, doublet; q, quartet; m, multiplet. IR spectra were obtained with a Hitachi EPI-S2 spectrometer. Mass spectra were taken with Hitachi RMU-6L spectrometer using a heated direct inlet system.

mp 262—263°. *Anal.* Calcd. for $C_{19}H_{21}NO \cdot HCl$: C, 72.25; H, 7.02; Cl, 11.23; N, 4.44. Found: C, 72.25; H, 6.93; Cl, 11.43; N, 4.37. Free base, NMR (δ in $CDCl_3$): 3.96 (d-d, $J=8$ and 3 Hz, 1H, $-C-\overset{OH}{\underset{|}{CH}}-CH_2-$), UV λ_{max}^{EtOH} nm (log ϵ): 270 (4.08), 292 (3.57), 303 (3.71).

9-(1-Ethoxycarbonyl-4-piperidinyl)fluorene-9,4'-diol (9)—Perchloric acid (6%, 16 ml) was added to a solution of **6** (1 g) in THF (25 ml), and the solution was stirred at room temperature for 10 min. The solution was concentrated and the residue was extracted with ether. The extract was dried over Na_2SO_4 and concentrated. The residue was recrystallized from ether to give 0.79 g (75%) of **9**, mp 142—145°. *Anal.* Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.09; H, 6.65; N, 3.82. IR ν_{max}^{KBr} cm^{-1} : 3475, 3400 (OH).

1'-Ethoxycarbonylspiro[phenanthrene-10,4'-piperidine]-9(10H)-one (10)—A mixture of **9** (0.75 g) and zinc chloride (1.5 g) in acetic anhydride (40 ml) was heated at 90° for 4 min. The solvent was removed *in vacuo* and H_2O was added to the residue. The mixture was extracted with ether and the extract was dried over Na_2SO_4 then concentrated. The residue was chromatographed on neutral Al_2O_3 and eluted with *n*-hexane-ether (5:7). The product was recrystallized from *n*-hexane-acetone to give 0.35 g (49%) of **10**, mp 117—119°. *Anal.* Calcd. for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.02; H, 6.40; N, 4.18.

1'-Methyl-10,11-dihydrospiro[dibenz[*b,f*]oxepin-11,4'-piperidine]-10-ol (19b) and Related Compounds (11 and 19)—Compounds **10** and **18** were each reduced with LAH by the procedure described for the reduction of **7**. The product was recrystallized from a suitable solvent. The results are shown in Table III.

11, NMR (δ in $CDCl_3$): 4.75 (s, 1H, $=C-\overset{OH}{\underset{|}{CH}}-C-$).

1'-Methylspiro[dibenz[*b,f*]oxepin-11,4'-piperidine]-10(11H)-one (20b) and Related Compounds (12 and 20d)—Chromic anhydride (0.8 g) was added to pyridine (20 ml) at 0° and the solution was stirred at room temperature for 1 hr. A solution of **11** (or **19**) (0.8 g) in pyridine (5 ml) was added at 0° and the mixture was stirred with cooling on an ice-bath. Ice-water was added to the reaction mixture and the mixture was extracted with ether. The extract was washed with H_2O , dried over Na_2SO_4 and concentrated. The residue was converted into a salt and recrystallized from a suitable solvent. The results are shown in Table IV.

1-Benzyl-4-(*o*-substituted phenyl)-4-cyanopiperidine (15)—Sodium amide (0.066 mol) was added to a solution of **13** (0.03 mol) and **14** (0.033 mol) in toluene (45 ml), and the mixture was warmed gently, then heated under reflux for 1 hr. H_2O was added and the resulting mixture was stirred for a while. The organic layer was separated, dil. HCl was added and the mixture was again stirred. The crude hydrochloride of the product, if it separated as solid, was purified by recrystallization; if it was dissolved in the dil. HCl layer, the acidic layer was separated, made alkaline with NaOH (solid) and extracted with ether. The extract was dried over Na_2SO_4 and concentrated. The residue was converted into an appropriate salt and recrystallized from a suitable solvent. The results are summarized in Table II.

1'-Benzylspiro[phenanthrene-10,4'-piperidine]-9(10H)-one (17a)—Compound **15a** (6.3 g) was added gradually to cooled conc. H_2SO_4 (80 ml) at 0—5°, and the mixture was stirred at 0° for 2.5 hr. Ice-water was added and the resulting mixture was made alkaline with 28% NH_4OH then extracted with AcOEt. The AcOEt layer was extracted with dil. HCl. The extract was heated at 90° for 30 min, made alkaline with 28% NH_4OH and extracted with toluene. The extract was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was converted into the hydrochloride with ethanolic HCl and recrystallized from EtOH. IR ν_{max}^{KBr} cm^{-1} : 1680 (C=O).

TABLE II. 1-Benzyl-4-(*o*-substituted phenyl)-4-cyanopiperidines (**15**)

Compd. No.	X	mp (°C)	Yield (%)	Recrystst. solvent	Formula	Analysis (%)				
						Calcd. (Found)				
						C	H	Cl	N	S
15a	—	188—189	26	Acetone	$C_{25}H_{24}N_2$	74.34	6.02		5.98	
					$\cdot C_4H_4O_4^a$	74.26	5.75		6.04	
15b	O	>250	42	EtOH	$C_{25}H_{24}N_2O$	74.15	6.22	8.76	6.92	
					$\cdot HCl$	74.38	6.26	9.04	6.94	
15c	S	218—221	8	EtOH	$C_{25}H_{24}N_2S$	71.32	5.99	8.42	6.66	7.62
					$\cdot HCl$	71.27	6.07	8.48	6.42	7.85
15d	CH_2	>250	36	dil. EtOH	$C_{26}H_{26}N_2$	76.35	6.82	8.67	6.85	
					$\cdot HCl \cdot 1/3H_2O$	76.60	6.88	8.73	6.90	
15e	CH_2CH_2	238—240	19	EtOH	$C_{27}H_{28}N_2$	76.12	7.10	8.32	6.55	
					$\cdot HCl \cdot 1/2H_2O$	75.94	7.19	8.51	6.66	

^a) Maleate.

1'-Benzylspiro[dibenz[*b,f*]oxepin-11,4'-piperidine]-10(11*H*)-one (17b) and a Related Compound (17d)—A solution of **15b** (or **15d**) (0.01 mol) in a mixture of conc. HCl (40 ml) and AcOH (20 ml) was heated under reflux for 70 hr. The solution was concentrated *in vacuo*, then EtOH was added to the residue. The solution was again concentrated *in vacuo* to give an amorphous powder (crude **16b** or **16d**) which was used for the next reaction without further purification. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1710 (C=O). PPA (20 ml) was added to crude **16** and the mixture was heated at 120° with stirring for 3 hr. The mixture was made alkaline with 28% NH_4OH and extracted with AcOEt. The extract was dried over Na_2SO_4 and concentrated. The residue was converted into an appropriate salt and recrystallized from a suitable solvent. The results are summarized in Table IV.

TABLE III. 1'-Methyl-10,11-dihydrospiro[dibenz[*b,f*]oxepin-11,4'-piperidine]-10-ol and Related Compounds

Compd. No.	X	mp (°C)	Yield (%)	Recryst. solvent	Formula	Analysis (%)		
						Calcd. (Found)		
						C	H	N
11	—	168—171	72	EtOH- <i>n</i> -hexane	$\text{C}_{19}\text{H}_{21}\text{NO}$	81.68 81.68	7.58 7.89	5.01 4.87
19b	O	120—122	68	EtOH- <i>n</i> -hexane	$\text{C}_{19}\text{H}_{21}\text{NO}_2$	77.26 77.46	7.17 7.43	4.74 4.64
19d	CH_2	220—222	57	EtOH	$\text{C}_{20}\text{H}_{23}\text{NO}$	81.87 81.60	7.90 7.84	4.77 4.54

TABLE IV. 1'-Substituted spiro[dibenz[*b,f*]oxepin-11,4'-piperidine]-10(11*H*)-one and Related Compounds

Compd. No.	X	R	mp (°C)	Yield (%)	Recryst. solvent	Formula	Analysis (%)			
							Calcd. (Found)			
							C	H	Cl	N
12	—	CH_3	190—191	65	Acetone	$\text{C}_{19}\text{H}_{19}\text{NO}$ $\cdot \text{C}_4\text{H}_4\text{O}_4^a$	70.21 69.97	5.90 5.66		3.56 3.64
17a	—	$\text{CH}_2\text{C}_6\text{H}_5$	254—256	72	EtOH	$\text{C}_{25}\text{H}_{23}\text{NO}$ $\cdot \text{HCl}$	77.01 76.95	6.21 5.91	9.09 9.30	3.59 3.50
17b	O	$\text{CH}_2\text{C}_6\text{H}_5$	258—260	73	EtOH-ether	$\text{C}_{25}\text{H}_{23}\text{NO}_2$ $\cdot \text{HCl}$	73.97 73.82	5.96 6.25	8.73 9.00	3.45 3.38
17d	CH_2	$\text{CH}_2\text{C}_6\text{H}_5$	189—191	68	Acetone	$\text{C}_{26}\text{H}_{25}\text{NO}$ $\cdot \text{C}_4\text{H}_4\text{O}_4^a$	74.51 74.50	6.05 6.24		2.90 2.99
20b	O	CH_3	282—284	62	EtOH-ether	$\text{C}_{19}\text{H}_{19}\text{NO}_2$ $\cdot \text{HCl}$	69.19 68.88	6.11 6.13	10.75 10.78	4.25 4.08
20d	CH_2	CH_3	275—280	24	EtOH	$\text{C}_{20}\text{H}_{21}\text{NO}$ $\cdot \text{HCl} \cdot 1/3\text{H}_2\text{O}$	71.95 71.70	6.84 6.54	10.62 10.91	4.27 4.21

^a) Maleate.

N-Ethoxycarbonylspiro[dibenz[*b,f*]oxepin-11,4'-piperidine]-10(11*H*)-one (18b) and Related Compounds (10 and 18d)—Compounds **17** were treated with ethyl chloroformate by the procedure described for the preparation of **5**. The oily products (**18b** and **18d**) did not contain **17** as determined by thin-layer chromatography (CHCl_3) and were used for the next reaction without purification.

Procedure for Wagner-Meerwein Rearrangement—Method A: A mixture of **11** (or **19**) (0.01 mol) in PPA (25 ml) was heated at 170° with stirring for 8 min. Ice-water was added, and the solution was made alkaline with 28% NH_4OH then extracted with CHCl_3 . The extract was dried over Na_2SO_4 and concentrated. The residue was recrystallized from a suitable solvent.

Method B: A mixture of **11** (or **19**) (0.01 mol) in 48% HBr (40 ml) was heated under reflux for 4 hr. The solution was made alkaline with 28% NH_4OH and extracted with CHCl_3 . The extract was dried over Na_2SO_4 and concentrated. The residue was recrystallized from a suitable solvent.

Wagner-Meerwein Rearrangement of 19b—Compound **19b** was treated by Method A and the crude product was recrystallized from acetone to give **21** in 59% yield. Treatment of **19b** by Method B, however did not give the expected product owing to decomposition. **21**: *Anal.* Calcd. for $\text{C}_{19}\text{H}_{19}\text{NO}$: C, 82.28; H, 6.91; N, 5.05. Found: C, 82.53; H, 6.80; N, 4.82. NMR (δ in CDCl_3): 4.70 (s, 1H, $\text{C}_9\text{-H}$), 5.82 (m, 1H, $\text{C}_5\text{'-H}$), 3.00 (q, 2H, $\text{C}_6\text{'-H}$).

9-(1-Methyl-4-hydroxy-4-piperidinyl)xanthene (24)—*n*-Butyllithium (20% in *n*-hexane, 10 g) was added dropwise to a solution of xanthene (5 g) in dry ether (40 ml), and the mixture was stirred at room temperature for 10 min. A solution of 1-methyl-4-piperidone (**23**) (3.1 g) in dry ether (30 ml) was added gradually and the resulting mixture was stirred at room temperature for 40 min. H_2O and dil. HCl were then added with cooling on an ice-bath. The aqueous layer was separated, made alkaline with 28% NH_4OH and extracted with ether. The extract was dried over Na_2SO_4 and concentrated. The residue was recrystallized from *n*-hexane-ether to give 3.5 g (43%) of **24**. *Anal.* Calcd. for $\text{C}_{19}\text{H}_{21}\text{NO}_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.12; H, 7.15; N, 5.03. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3250 (OH).

9-(1-Methyl-1,2,3,6-tetrahydro-4-pyridinyl)xanthene (21) from 24—Compound **24** was treated by Method A, and the crude product was recrystallized from acetone to give **21** in 78% yield.

Wagner-Meerwein Rearrangement of 19d—Compound **19d** was treated by Method A or B, and the crude product was recrystallized from *n*-hexane to give **26** in 10 and 22% yields, respectively. mp 166–170°. *Anal.* Calcd. for $\text{C}_{20}\text{H}_{19}\text{N}$: C, 87.87; H, 7.01; N, 5.12. Found: C, 87.51; H, 6.92; N, 4.87. NMR (δ in CDCl_3): 8.34 (s, 1H, $\text{C}_{10}\text{-H}$), 5.82 (m, 1H, $\text{C}_5\text{'-H}$), 3.32 (q, 1H, $\text{C}_6\text{'-H}$). MS m/e : 273 (M^+).

Wagner-Meerwein Rearrangement of 11—Compound **11** was treated by Method A or B, and the crude product was recrystallized from *n*-hexane to give **27** in 59 and 52% yields, respectively. mp 140–142°. *Anal.* Calcd. for $\text{C}_{19}\text{H}_{19}\text{N}$: C, 87.31; H, 7.33; N, 5.36. Found: C, 87.61; H, 7.07; N, 5.33. NMR (δ in CS_2): see Fig. 1. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 257 (4.37), 272 (3.94), 282 (3.71), 293 (3.66), 305 (3.70).

Wagner-Meerwein Rearrangement of 8—Compound **8** was treated by Method A or B to give **27** in 57 and 51% yields, respectively.

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