TABLE V
In Vivo ACTIVITY[a]

Compd	ED_{50}(mice), mg/kg			
	S. aureus		*S. pyogenes*	
	PO	SC	PO	SC
2	>250	125	150	27
13	65	144	16.5	12.5
20	*b*	*b*	100	<60
22	65	110	1.6	1.6
23	>250	>250	6.25	10
25	*ca.* 250	350	7.5	4.8

[a] See ref 6. [b] Not tested.

ring or introduction of alkyl groups in the 5 position reduced antibacterial activity in all cases.

Some of the compounds were tested against *S. aureus* and *S. pyogenes* in mice by oral and subcutaneous administration (Table V). The most active of these were 1-[4-(5-nitro-2-furyl)-2-thiazolyl]hydantoin, **13**, and the 3-(dimethylcarbamoyl)methyl analog **22**. Again, expansion of the ring, or introduction of a simple alkyl group at the 3 or 5 positions reduced activity. Several of the compounds studied (**14**, **22**, **24**, and **26**) had high *in vitro* activity against *Mycobacterium tuberculosis;* all of these were inactive in the *in vivo* screen however.

Acknowledgments—The authors are indebted to Dr. R. E. Bowman for advice and encouragement, to Mr. F. H. Oliver for microanalyses, to Miss E. M. Tanner for the physical chemistry measurements, Mrs. M. R. Johnson for the preparation of some of the intermediates, and to Dr. M. W. Fisher and his associates of the Department of Microbiology, Parke, Davis and Co. Inc., Detroit, for the biological data.

Synthesis and Pharmacology of *N*-Cyano-(β-arylethyl)amines

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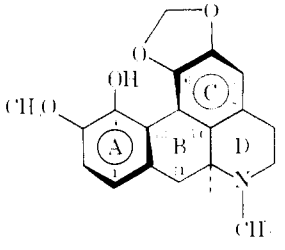
In an attempt to prepare compounds which would reverse or block catatonia produced by bulbocapnine, a series of *N*-cyano-*N*-methylarylethylamines were synthesized. Preliminary pharmacology is reported.

Bulbocapnine (**1**) is a drug which has frequently been used to produce syndromes similar to schizophrenia. It is obtained from the plant *Corydalis cava* and it belongs chemically to the aporphine group of alkaloids. De Jong and his collaborators studied the



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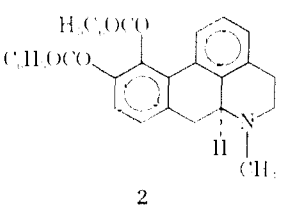
catatonic state associated with bulbocapnine administration[2,3] and in addition to this agent other aporphine alkaloids were found to be catatonia-producing substances.[4-9]

According to Chapman and Walaszek[10] catatonia produced by bulbocapnine may be the result of a combination of actions, among which are serotonin and adrenergic blockade as well as a histaminergic mechanism.

The purpose of this investigation was to prepare compounds which could act as antagonists to bulbocapnine-induced catatonia. As a working postulate, it was assumed that either ring A or ring C of the aporphine system could be the aromatic group of a β-phenethylamine. Initially, an attempt was made to break the N–C bond between the D and B rings or to remove the Me group from the N in bulbocapnine. The von Braun[11] reaction was thought to offer a possible route to the desired compounds.

The only report of this reaction being used on an aporphine compound involved *d*-apomorphine dibenzoate (**2**). The product obtained from this reaction contained no Br and, unlike the starting material, was optically inactive. Based on this evidence, structure **3** was assigned to the material obtained.[12]



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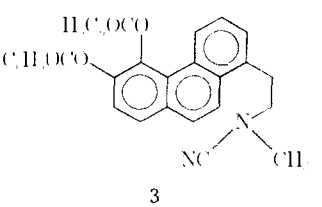

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While performing the von Braun reaction on *d*-bulbocapnine attempts were made to avoid ring cleavage while forcing the attack of Br^- to take place selectively on the *N*-Me group. For this purpose conditions favoring an S_N2 type substitution reaction over an S_N1 reaction or an elimination reaction were employed. Only one product, 1-[2-(*N*-cyano-*N*-methylaminoeth-

(1) Taken in part from the dissertation presented by A. C. Makriyannis, March 1967, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

(2) H. H. de Jong and H. Barouk, "La Catatonie Experimentale par la Bulbocapnine; Etude Physiologique et Clinique," Masson, Paris, France, 1930.

(3) H. H. de Jong, "Experimental Catatonia," Williams and Wilkins, Baltimore, Md., 1945.

(4) R. A. Waud, *J. Pharmacol.*, **50**, 100 (1934).

(5) T. Tobitani, *Okayama Igakkai Zasshi*, **51**, 1447 (1939).

(6) T. A. Henry, "The Plant Alkaloids," P. Blakinston Co., Philadelphia, Pa, 1949, p 312.

(7) L. Butturini, *Boll. Soc. Ital. Biol. Sper.*, **15**, 614 (1940).

(8) H. Kreitmar, *Pharmazie*, **7**, 507 (1952).

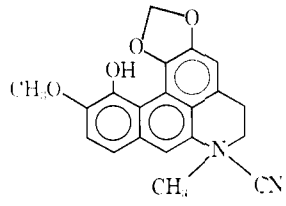
(9) R. A. Waud, *J. Pharmacol.*, **55**, 40 (1935).

(10) J. E. Chapman and E. J. Walaszek, *J. Pharmacol. Exp. Ther.*, **137**, 285 (1962).

(11) H. A. Hageman, *Org. React.*, **7**, 198 (1953).

(12) J. von Braun and E. Aust, *Chem. Ber.*, **50**, 43 (1917).

yl)]-3,4-methylenedioxy-5-hydroxy-6-methoxyphenanthrene (4) was obtained from *d*-bulbocapnine.



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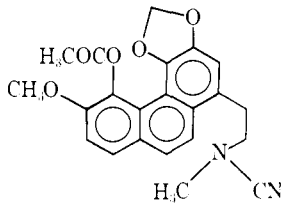
In an investigation of its pharmacological actions, this compound, 4, was found to possess unique properties, and thus other analogs were prepared.

1-[2-(*N*-Cyano-*N*-methylaminoethyl)]-3,4-methylenedioxy-5-acetoxy-6-methoxyphenanthrene (5), was prepared by acetylating the free phenolic OH of 4 using Ac_2O and pyridine. 1-[2-(*N*-Carbamyl-*N*-methylaminoethyl)]-3,4-methylenedioxy-5-hydroxy-6-methoxyphenanthrene (6) was achieved by partial hydrolysis of the N-CN analog, 4. It was found that selective hydrolysis of the CN group could be effected by refluxing with EtOH in the presence of a small



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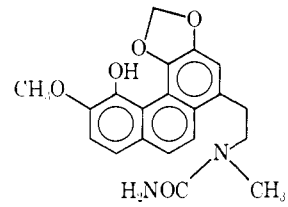

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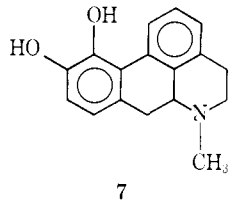
amount of dilute H_2SO_4 without affecting the methylenedioxy and methoxy groups. The product was identified by the absence of ir absorption in the region characteristic of the C≡N stretching and the presence of an NHCO peak at 1640 cm^{-1} as well as the presence of the intact methylenedioxy and CH_3O protons as two singlets at δ 6.18 and 4.02, respectively, in the nmr spectrum.

Upon treatment of the aporphine alkaloids, *l*-apomorphine (7) and *d*-boldine (8) with BrCN, ring cleavage with aromatization produced 1-[2-(*N*-cyano-



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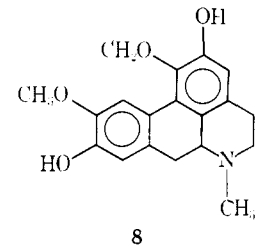

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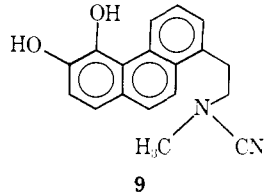
N-methylaminoethyl)]-5,6-dihydroxyphenanthrene (9) and 1-[2-(*N*-cyano-*N*-methylaminoethyl)]-3,7-dihy-



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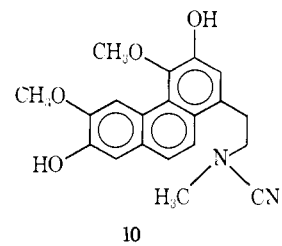

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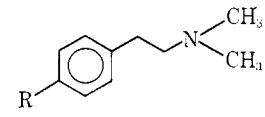
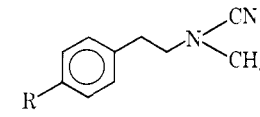
droxy-4,6-dimethoxyphenanthrene (10). "Infracor" glass and the absence of O_2 were required in these experiments. Attempts to purify the products failed. The ir spectra of the products showed the presence of CN and the nmr spectra indicated no N–Me cleavage had occurred.

N-Cyanophenethylamino Analogs.—*N*-Cyano-*N*-methylphenethylamine (12) was prepared by subjecting *N*,*N*-dimethylphenethylamine (11) to the von Braun reaction. The corresponding *p*-methoxy compound (14) was obtained in a similar manner from **13.**

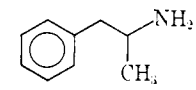


11, R = H
13, R = OCH_3



12, R = H
14, R = OCH_3

N-Cyano-α-methylphenethylamine (16) was prepared by refluxing amphetamine (15) with BrCN in



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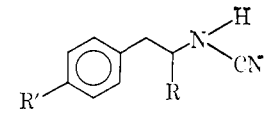


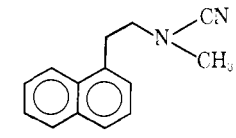
16, R′ = H; R = CH_3
17, R′ = H; R = H
18, R′ = OCH_3; R = H

C_6H_6. Amphetamine·HBr was obtained as a by-product. Due to its low stability this N-CN compound had to be analyzed and tested immediately.

N-Cyanophenethylamine (17) as well as *N*-cyano-2-(4-methoxyphenyl)ethylamine (18) were prepared by reaction of the corresponding primary amines with BrCN. These compounds were also found to be highly unstable.

The α- and β-unsubstituted *N*-cyano-*N*-methylnaphthylethyl amines (19, 20) were prepared from the corresponding *N*,*N*-dimethylamines *via* a von Braun reaction.

It has been reported[13] that hydrohydrastinine, an *N*-methyl tetrahydroisoquinoline alkaloid, when treated with BrCN underwent ring opening with no detectable N-dimethylation. 1,2,3,4-Tetrahydro-2-methylisoquinoline (21) was subjected to the action of the same reagent. The main product of this reaction (>54%) was shown to be devoid of the N-Me group



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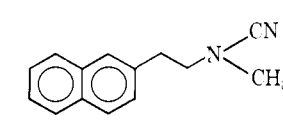

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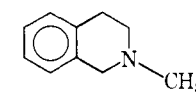

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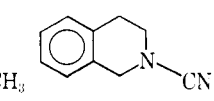

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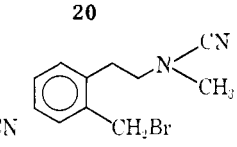

23

and to possess a CN group, thus providing evidence that this compound was 2-cyano-1,2,3,4-tetrahydroisoquinoline (22). The other N-CN product, 23, obtained from this reaction (<5%) gave a positive test for Br with ethanolic $AgNO_3$. Further evidence that the minor compound, 23, was the one resulting from

(13) J. von Braun, *Chem. Ber.*, **49**, 2624 (1916).

ring opening of the starting material, was provided from its nmr spectrum which indicated 4 aromatic protons at δ 6.77–7.15, 2 $C_6H_5CH_2$ as a singlet at δ 3.47, 4 CH_2 as a complex multiplet at δ 2.40–3.51 and 3 NCH_3 as a singlet at δ 2.33. The results obtained from this reaction contradict the reported results[14] and constitute a unique case of N-dimethylation of a benzylamine compound through a von Braun reaction. The product distribution indicates a probable kinetic control through an SN2 type reaction, the geometry of the reaction site probably playing the major role in the determination of the final product. It appears that in the case of bulbocapnine, of the two factors determining the reaction path, namely, the benzylic character of the bond cleaved, and the formation of a fully aromatized phenanthrene ring, it is the second factor which is the most critical in the determination of the product.

Biological Results.—Preliminary biological testing of the compounds prepared afforded the following results.

1-[2-(*N*-Cyano-*N*-methylaminoethyl)]-3,4-methylenedioxy-5-hydroxy-6-methoxyphenanthrene (**4**), given in doses of 20–250 mg/kg, ip, was a relatively nontoxic drug in rats which produced sedation, ptosis, and depressed respiration, but did not cause catalepsy nor substantially antagonize bulbocapnine-induced catatonia. The sedation was manifested by a decrease in spontaneous locomotor activity and disinclination to move about unless aroused by handling or noxious stimuli. The duration of these effects was greater than 4 hr.

1-[2-(*N*-Cyano-*N*-methylaminoethyl)]-5,6-dihydroxyphenanthrene (**9**), given in doses of 100–400 mg/kg, ip, was even more active. Injections of 100 mg/kg of this compound in rats caused sedation, ptosis, ataxia, increased defecation, and depressed respiration. The duration of action of these effects was greater than 4 hr. Catalepsy was neither produced by the compound nor were the effects of bulbocapnine administration prevented. Doses above 200 mg/kg produced extreme prostration leading to death.

1-[2-(*N*-Carbamyl-*N*-methylaminoethyl)]-3,4-methylenedioxy-5-hydroxy-6-methoxyphenanthrene (**6**), given in doses of 50 mg/kg, ip, and 150 mg/kg, and 1-[2-(*N*-cyano-*N*-methylaminoethyl)]-3,7-dihydroxy-4,6-dimethoxyphenanthrene (**10**), given in doses of 50–200 mg/kg, ip, produced a general state of sedation similar to that elicited by **4** and they also failed either to produce catatonia or substantially antagonize the effects of an intraperitoneal injection of 60 mg/kg of bulbocapnine. Bulbocapnine *N*-oxide administered in a dose of 50 mg/kg, ip, produced only a general sedative effect similar to that elicited by the previous compounds.

N-Cyano-*N*-methyl-*p*-methoxyphenethylamine (**14**), given in doses of 300 mg/kg, ip, produced no evidence of catatonia but made the rats shake and perhaps could be explored as a tremorine-like screening compound. At 50 mg/kg, ip, no effect was noted. Doses of 100 mg/kg caused sedation of approximately 3.5-hr duration, a hunching of the back and a "gnaw compulsion" syndrome similar to that seen with apomorphine. However, at 200 mg/kg, ip, when bulbocapnine was injected, catatonia still developed. Doses of 400 mg/kg, ip, caused extreme prostration and profuse salivation. In the rat 25 mg/kg of the test compound produced a fall in blood pressure which was blocked by 5 mg/kg of D.C.I., so this test compound appears to cause stimulation of β receptors.

dl-*N*-Cyano-α-methylphenethylamine (**16**), given in a dose of 10 mg/kg, ip, caused no locomotor stimulatory effect but did cause exopthalmos. After injection of 60 mg/kg of bulbocapnine ip, 20 mg/kg of this compound injected iv, caused a little antagonism but the bulbocapnine-treated animal would still assume bizarre positions and would hang. After an animal was made catatonic with 12.5 mg/kg of CPZ given ip, 20 mg/kg of **16** caused respiratory stimulation with deeper inspiration and frequency. The rats were slightly more reactive but the test drug did not bring the animal out of its catatonic stupor. With higher doses of 100 mg/kg of the test compound, after bulbocapnine, respiratory stimulation, salivation, mydriasis, and extreme prostration ensued but little antagonism to the catatonizing drug was noted. Death appeared to come from respiratory congestion.

Bulbocapnine methiodide injected ip, in doses above 50 mg/kg, was tremorigenic. Also a "gnaw-compulsion" syndrome and dyspnea were produced. This was followed by convulsions and death; at no time did a catatonic state follow. In lower doses below 10 mg/kg, injected iv, no antagonism to the effects of bulbocapnine could be observed.

N-Cyano-*N*-methylphenethylamine (**12**), *N*-cyano-*N*-methyl-2-(2-naphthyl)ethylamine (**20**), *N*-cyano-*N*-methyl-2-(1-naphthyl)ethylamine (**19**), and 2-cyano-1,2,3,4-tetrahydroisoquinoline (**22**), given in doses of 10 mg and 100 mg, ip, in rats showed no prominent effects. They also failed to either produce catatonia or antagonize the effects of an ip injection of 60 mg/kg of bulbocapnine.

Experimental Section[15]

Reaction of *d*-Bulbocapnine with BrCN.—"Infracor" glass apparatus was utilized in this reaction. To a solution of BrCN (6.00 g, 56.64 mmol) in 50 ml of $CHCl_3$, a solution of bulbocapnine (**1**) (13.00 g, 39.96 mmol) in 150 ml of $CHCl_3$ was added dropwise with continuous stirring over a period of 2 hr. The mixture was stirred for an additional 24 hr at 25° and the white precipitate of bulbocapnine·HBr (7.50 g, 18.50 mmol, 46.30%) was filtered and washed with 5 ml of $CHCl_3$. The solvent and the excess BrCN were distilled from the filtrate and the pale brown residue was recrystallized from abs EtOH to give colorless needles (6.50 g, 18.55 mmol, 46.42%) of **4**, mp 169°; ir (KBr): 2220 cm^{-1} (C≡N).

1-[2-(*N*-Cyano-*N*-methylaminoethyl)]-3,4-methylenedioxy-5-acetoxy-6-methoxyphenanthrene (5).—1-[2-(*N*-cyano-*N*-methylaminoethyl)]-3,4-methylenedioxy-5-hydroxy-6-methoxy-

(15) Melting points were determined on a calibrated Thomas-Hoover capillary melting point apparatus and were corrected. Ir spectra were recorded on Beckman IR-5 and IR-8 spectrophotometers. Nmr spectra were recorded on a Varian Associates Model A-60 spectrophotometer using Me4Si or 3-(trimethylsilyl)-1-propane sulfonic acid, Na salt as an internal standard. Gas chromatographic data were obtained on an F and M Model 810-19, using a flame detector and columns (1.34 m × 0.6 cm) packed with 12% w/w SE-30 (Wilkens Instrument & Research Inc.) (col I), and 12% w/w Carbowax 20M (Wilkens Instrument and Research Inc.) (col III) on Chromosorb W, 60–80 mesh, acid washed (Matheson Coleman and Bell). Microanalyses were performed on an F and M CHN analyzer Model 185 in this department and by Midwest Microlab, Inc., Indianapolis, Ill. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. The characterization of unstable compounds was based only on spectroscopic data.

(14) J. von Braun, *Chem. Ber.*, **43**, 3209 (1910).

phenanthrene (**4**) (2.00 g, 5.71 mmol) was dissolved in 20 ml of anhydrous pyridine and 3 ml of Ac_2O was added. The mixture was heated on a steam bath for 30 min, allowed to stand for 5 hr, and poured slowly with continuous stirring into 200 ml of crushed ice. To the mixture was added 20 ml of a 20% NaOH solution and stirring was continued for 1 hr. The white precipitate was filtered, washed consecutively with 5 ml of a 5% NaOH solution, 10 ml of H_2O, and 10 ml of 5% HCl, dried, and purified by recrystallization from abs EtOH to give colorless needles (2.07 g, 5.27 mmol, 92.29%) mp 161°; ir (KBr): 2220 C≡N), 1760 (C=O) cm^{-1}. *Anal.* ($C_{22}H_{20}N_2O_5$) C, H, N.

1-[2-(*N*-Carbamyl-*N*-methylaminoethyl)]-3,4-methylenedioxy-5-hydroxy-6-methoxyphenanthrene (6).—1-[2-(*N*-cyano-*N*-methylaminoethyl)]-3,4-methylenedioxy-5-hydroxy-6-methoxyphenanthrene (**4**) (0.50 g, 1.43 mmol) was mixed with 150 ml of abs EtOH in a 300-ml Infracor flask equipped with N_2 tube. To the mixture, into which a steady stream of N_2 was bubbled, and refluxed for 30 min, was added 15 ml of 10% aq H_2SO_4 and refluxing was continued for 3 hr. After cooling, the mixture was transferred to an Infracor flask, 30 ml of H_2O was added and the mixture was concentrated to a total volume of 25 ml. The resulting white precipitate was filtered and washed twice with 1 ml of H_2O. When recrystallized from H_2O–EtOH (1:1) the product gave white platelets (0.32 g, 0.89 mmol, 60.84%); from Me_2CO it gave colorless needles, mp 150–152°; ir (KBr): 1640 (C=O), 1590 (aromatic C=C) cm^{-1}, no peaks in the C≡N region. *Anal.* ($C_{20}H_{20}N_2O_5$) C, H, N.

Reaction of *l*-Apomorphine (7) with BrCN.—The entire operation was conducted under N_2 using Infracor glass apparatus. To a suspension of *l*-apomorphine·HCl (10.00 g, 32.96 mmol) in 25 ml of H_2O, was added 50 ml of 10% aq $NaHCO_3$ in which a trace of Dry Ice had been dissolved. The free base was extracted 3 times with 50 ml of THF. After drying ($MgSO_4$) the organic extracts were mixed with a solution of BrCN (4.0 g, 37.8 mmol) in 25 ml THF. The mixture was allowed to stand for 5 hr with occasional shaking. The white precipitate of apomorphine·HBr (5.50 g, 15.81 mmol, 47.97%) was filtered and washed with 10 ml of THF. The filtrate was evaporated to dryness by passing through N_2 at room temperature. The residue was a pale yellow powder (4.20 g, 14.37 mmol, 43.59%). The substance **9** was stored in dark vials under N_2 at −5°; mp 128–130°; ir (KBr): 2220 cm^{-1} (C≡N).

Reaction of *d*-Boldine (8) with BrCN.—To a solution of *d*-boldine (2.00 g, 6.11 mmol) in 60 ml of $CHCl_3$, BrCN (0.70 g, 6.61 mmol) was added and the solution was allowed to stand for 5 hr with occasional shaking. The white precipitate of boldine·HBr (1.15 g, 2.82 mmol, 46.15%) was filtered and washed with 5 ml of $CHCl_3$. The filtrate was evaporated to dryness by passing a stream of N_2 at room temperature and the residue was placed in a desiccator over P_2O_5 and NaOH pellets under reduced pressure for 24 hr. The product **10** was a pale brown glassy mass (0.90 g, 0.255 mmol, 41.73%). It was stored in dark vials under N_2 at −5°; ir (KBr): 2220 cm^{-1} (C≡N).

***N*-Cyano-*N*-methylphenethylamine (12).**[14]—To a solution of BrCN (10.00 g, 94.40 mmol) in 50 ml of anhydrous C_6H_6 was added *N*,*N*-dimethylphenethylamine (**11**), (15.00 g, 100.51 mmol) in 100 ml of anhydrous C_6H_6, dropwise with continuous stirring. The product (9.40 g, 58.67 mmol, 58.37%) was a colorless slightly viscous liquid, bp 112° (0.3 mm); ir (neat): 2220 cm^{-1} (C≡N). *Anal.* ($C_{10}H_{12}N_2$) C, H, N.

***N*-Cyano-*N*-methyl-*p*-methoxyphenethylamine (14).**—To a cooled solution of 90% HCOOH (16.90 g, 333 mmol) were added slowly, *p*-methoxyphenethylamine (**13**) (10.00 g, 66.13 mmol) and 15 ml of 37% aq HCHO. The mixture was refluxed at 95–100° for 10 hr and cooled; 33 ml of 4 *N* HCl was added and the solvent was distilled under reduced pressure. The yellow crystalline solid remaining was dissolved in 20 ml of H_2O and the free amine was liberated by the addition of 17 ml of 18 *N* NaOH. The upper (organic) phase was separated and the lower aq phase was extracted 3 times with 15 ml of C_6H_6. The combined organic phase and C_6H_6 extracts were dried (K_2CO_3) and filtered. The K_2CO_3 residues were washed 3 times with 5 ml of C_6H_6 and the washings were combined with the previous filtrate.

To a BrCN (7.50 g, 70.80 mmol) solution in 50 ml of anhydrous C_6H_6, the C_6H_6 solution of the amine was added dropwise with continuous stirring for a period of 2 hr. The mixture was stirred for a subsequent 12 hr and the pale yellow precipitate of the trimethylphenethylammonium bromide (2.50 g, 9.12 mmol) filtered and washed with 10 ml of C_6H_6. The solvent was removed from the filtrate and the dark brown residue was distilled under reduced pressure. The fraction between 125 and 130° (0.5 mm) was collected and further purified on a silicic acid (100 mesh, Mallinckrodt) column with $CHCl_3$ as the eluent. The product (8.20 g, 43.10 mmol, 65.17%) was a colorless slightly viscous liquid; ir (neat): 2220 cm^{-1} (C≡N). *Anal.* ($C_{11}H_{14}N_2O$) C, H, N.

***dl*-*N*-Cyano-α-methylphenethylamine (16).**—To a suspension of *dl*-α-methylphenethylamine sulfate (**15**) (5.00 g, 27.14 mmol) in 5 ml of H_2O, 25 ml of 10% aq Na_2CO_3 was added and the mixture was stirred for 30 min. The free base was extracted 3 times with 30 ml of C_6H_6 and the combined C_6H_6 extracts were washed with 10 ml of H_2O and dried ($CaSO_4$). To the C_6H_6 extract was added BrCN (3.00 g, 28.32 mmol) and the above procedure was followed. The product, (2.40 g, 14.98 mmol, 55.20%) was a colorless, slightly viscous liquid; ir (neat): 3240 (NH), 2220 (C≡N) cm^{-1}. *Anal.* ($C_{10}H_{12}N_2$) C, H, N.

***N*,*N*-Dimethyl-2-(2-naphthyl)ethylamine.**—To a stirred, ice-cooled mixture of LAH (1.50 g, 39.52 mmol) in 10 ml of anhydrous Et_2O, was added slowly a solution of *N*,*N*-dimethyl-2-naphthylacetamide (3.00 g, 14.06 mmol) in 30 ml of anhydrous Et_2O over a period of 90 min. The mixture was then refluxed for 12 hr and stirred at 25° for 18 hr after which the excess of LAH was decomposed by the slow addition of 6 ml of H_2O and the mixture was further stirred for 3 hr. The mixture was filtered, the white precipitate was washed several times with Et_2O, and the filtrate and ethereal extracts were combined and dried ($CaSO_4$). The residue obtained when the solvent was removed was a pale yellow oil (2.60 g, 13.04 mmol, 92.75%); ir (neat): 2820 and 2775 cm^{-1} [$N(CH_3)_2$].

The HCl salt was prepared in Et_2O solution. The white precipitate was washed with anhydrous Et_2O and recrystallized from EtOAc–abs EtOH (97:3) to give a white microcrystalline powder, mp 207° dec; ir (KBr): 2500–2780 (broad band), 2475 cm^{-1}.

***N*-Cyano-*N*-methyl-2-(2-naphthyl)ethylamine (20).**—To a BrCN (1.50 g, 14.16 mmol) solution in 15 ml of anhydrous C_6H_6 was added a solution of *N*,*N*-dimethyl-2-(2-naphthyl)ethylamine (2.50 g, 12.54 mmol) in 35 ml of anhydrous C_6H_6 dropwise with continuous stirring. The previous procedure for isolation and purification of the *N*-cyano compounds was utilized. The pale yellow crystalline solid obtained was recrystallized from C_6H_6 to give long colorless needles (1.44 g, 6.85 mmol, 54.62%) mp 51°; ir (neat): 2220 cm^{-1} (CN). *Anal.* ($C_{14}H_{14}N_2$) C, H, N.

2-(1-Naphthyl)ethylamine.—To a well-stirred mixture of finely powdered LAH (2.50 g, 65.87 mmol) in 100 ml of anhydrous THF, 1-naphthylacetamide (5.00 g, 26.99 mmol) was added in small portions. Essentially the same procedure for the isolation and purification of *N*,*N*-dimethyl-2-(2-naphthyl)ethylamine was utilized to yield a colorless viscous liquid (3.50 g, 20.44 mmol, 75.73%) bp 133° (0.3 mm) [lit.[16] bp 170–173° (16 mm)]; ir (neat): 3390, 2870 cm^{-1}. There were no peaks in the CO region.

The HCl salt was prepared in Et_2O solution. The white precipitate formed was washed with anhydrous Et_2O and recrystallized from EtOAc–abs EtOH (97:3), to give white platelets, mp 251–253° dec. *Anal.* ($C_{12}H_{14}ClN$) C, H, N.

***N*,*N*-Dimethyl-2-(1-naphthyl)ethylamine.**—To a cooled solution of 98% HCO_2H (6.0 ml), were added slowly 1-naphthylethylamine (2.00 g, 1168 mmol) and 6.0 ml of 40% aq HCHO. Essentially the same procedure utilized for **14** was employed to give a pale yellow oil (1.52 g, 7.63 mmol, 65.29%); ir (neat): 2890 and 2780 cm^{-1} [$N(CH_3)_2$].

The HCl salt was prepared in anhydrous C_6H_6. The white precipitate was washed with anhydrous C_6H_6 and recrystallized from EtOAc–abs EtOH (96:4) to give white needles, mp 210°; ir (KBr): ir (KBr): 2450–2675 (broad band) cm^{-1}. *Anal.* ($C_{14}H_{18}ClN$) C, H, N.

***N*-Cyano-*N*-methyl-2-(1-naphthyl)ethylamine (19).**—To a solution of *N*,*N*-dimethyl-2-(1-naphthyl)ethylamine (0.90 g, 4.16 mmol) in 30 ml of anhydrous C_6H_6, BrCN (1.50 g, 14.16 mmol) was added and the mixture was stirred for 15 hr at 25°. Essentially the same procedure used previously to obtain the N-CN compounds was employed to give a pale yellow viscous liquid (0.65 g, 3.09 mmol, 74.28%); ir (neat): 2220 cm^{-1} (C≡N). *Anal.* ($C_{14}H_{14}N_2$) C, H, N.

1,2,3,4-Tetrahydro-2-methylisoquinoline (21).—The procedure of Buck and Ide was employed to give a 92% yield of the desired product; hydrochloride, mp 227° (lit.[17] 227°).

(16) F. Mayer and A. Sieglitz, *Chem. Ber.*, **55**, 1847 (1922).

(17) J. S. Buck and W. S. Ide, *J. Amer. Chem. Soc.*, **60**, 2101 (1938).

Reaction of 1,2,3,4-Tetrahydro-2-methylisoquinoline with BrCN.—To a solution of BrCN (7.50 g, 70.80 mmol) in 50 ml of anhydrous C_6H_6, a solution of 1,2,3,4-tetrahydro-2-methylisoquinoline (**21**) (6.00 g, 40.75 mmol) in 100 ml of anhydrous C_6H_6 was added slowly over a period of 2 hr. Essentially the same procedure was previously employed to obtain N-CN compound was utilized to give a colorless viscous residue which crystallized into fine needles, **22** (3.52 g, 22.25 mmol, 54.60%), mp 43–44°; ir (neat): 2220 cm^{-1} (C≡N). *Anal.* ($C_{11}H_{10}N_2$) C, H, N.

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Studies of Piperidine Derivatives. I

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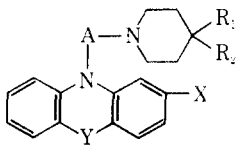
Some tricyclic compounds having a 4,4-disubstituted piperidine substituent were synthesized. The phenothiazines thus prepared showed potent CNS depressant action, while the iminodibenzyls, iminostilbenes, and 9,9-dimethylacridans exhibited coronary vasodilating effects. Phenothiazines as well as iminostilbenes possessed potent antiinflammatory activity.

The spectrum of biological activities of tricyclic psychotropic drugs depends to a large extent upon the nature of the amino group. We have synthesized and examined the biological properties of some new 4,4-disubstituted piperidine derivatives represented by formula **1**. Tables I, II, III, and IV display the



1

A = CH_2CH_2, $CH_2CH_2CH_2$, $CH_2CHMeCH_2$
R_1 = H, OH, $CONH_2$, $CONC_4H_8$, NMe_2, CH_2NHAc, CN, Ac, OMe, CO_2Et
R_2 = C_6H_5, *p*-Cl or *m*-Cl or *p*-Me or *p*-MeO or *p*-F-C_6H_4, $CH_2C_6H_5$, NMe_2, NC_4H_8, NC_5H_{10}
Y = S, CH_2CH_2, CH=CH, CMe_2
X = H, Cl, Me, OMe, CF_3, SMe, SBu, Ac

resulting phenothiazines, iminodibenzyls, iminostilbenes, and 9,9-dimethylacridanes, respectively.

These compounds were evaluated pharmacologically with respect to inhibition of locomotor activity, suppression of fighting episodes, coronary vasodilation, and antiinflammatory action. Recent reports, moreover, claim that some of the same or similar tricyclic compounds have coronary vasodilating[1–6] and antiinflammatory actions.[7–11]

(1) Sandoz Ltd., Netherlands Patent 6,705,359 (1967).
(2) J. R. Geigy Chem. Corp., South African Patent 6,603,362 (1966).
(3) J. R. Geigy Chem. Corp., Netherlands Patent 6,608,101 (1965); *Chem. Abstr.*, **67**, 11503 (1967).
(4) Sterling Drug Co., Netherlands Patent 6,801,093 (1968).
(5) Boehringer and Soehne G. m. b. H., British Patent 1,134,589 (1967); *Chem. Abstr.*, **71**, 22041*g* (1969).
(6) K. P. F. Brocades Stehman and Pharmacia, Netherlands Patent Application 6,608,741 (1966); *Chem. Abstr.*, **67**, 11438*h* (1967).
(7) American Home Products Corp., U. S. Patent 3,320,245 (1967); *Chem. Abstr.*, **67**, 100146 (1967).
(8) G. D. Searle & Co., U. S. Patent 3,320,246 (1967); *Chem. Abstr.*, **67**, 90823 (1967).
(9) J. R. Geigy Chem. Corp., U. S. Patent 2,965,639 (1960); *Chem. Abstr.*, **55**, 12437*g* (1961).
(10) J. R. Geigy Chem. Corp., British Patent 1,111,733 (1968); *Chem. Abstr.*, **69**, 67224 (1968).
(11) G. D. Searle & Co., U. S. Patent 3,350,402 (1967); *Chem. Abstr.*, **68**, 105239 (1968).

The inhibitory effect of each of the test compounds on locomotor activity was examined with d,d-strain mice by the photocell method described by Dews.[12] The rate of inhibiting fighting episodes was determined by giving electric stimuli, according to the technique of Tedeschi,[13] to the test animals previously treated with the test compound. The effect on the coronary blood flow was assessed by the technique of Yago,[14] using dogs anesthetized with 30 mg/kg of secobarbital iv. The antiinflammatory effect was estimated by the method of Winter, *et al.*,[15] using Donryu male rats previously given 1% carrageneen or 1% dextran as a phlogistic agent. The LD_{50} value was calculated from the lethality rate in 2 days after the treatment by the Litchfield-Wilcoxon method.

The results obtained are shown in Table V. Each of compounds **11**, **12**, **14**, **21**, and **26** exhibited potent inhibition of locomotor activity and suppression of fighting episodes. Compound **26** showed high toxicity, however. Compound **21** was one-third as active as chlorpromazine in inhibition of fighting activity and 6 times as potent in suppressing locomotor activity. Compound **22** showed high toxicity. These phenothiazine derivatives were regarded as potent CNS depressants.

On the other hand, the compounds of iminodibenzyl and iminostilbene increased coronary blood flow. Compounds **34**, **40**, **41**, **45**, and **46**—most of them belonging to the iminostilbene series—exhibited 10–20 times greater potency than prenylamine.[16] The iminostilbene derivatives also inhibited locomotor activity. Compound **46** which possesses mild locomotor supression may serve as a candidate antianginal drug. Considerable antiinflammatory action was found in the phenothiazines and iminostilbenes such as **11**, **12**, **43**,

(12) P. B. Dews, *Brit. J. Pharmacol.*, **8**, 46 (1953).
(13) R. E. Tedeschi, D. H. Tedeschi, A. Mucha, L. Cook, P. A. Mattis, and E. J. Fellows, *J. Pharmacol. Exp. Ther.*, **125**, 28 (1959).
(14) N. Yago, *Nippon Yakurigaku Zasshi*, **57**, 380 (1961).
(15) C. A. Winter, E. A. Resley, and G. W. Nuss, *J. Pharmacol. Exp. Ther.*, **141**, 369 (1963).
(16) *N*-(3,3-Diphenylpropyl)-α-methylphenethylamine. Farbwerke Hoechst.