colorless oil: bp 92–94° (0.01 mm); $n^{20}D$ 1.549. *Anal.* ($C_{12}H_{14}O_2$) C, H.

Amino Alcohols I and II.—The appropriate epoxide[17] (0.075 mole) and amine (0.1 mole) were dissolved in 70 ml of *i*-PrOH and heated in a sealed vessel at 80° for 4 hr. The solvent was removed under reduced pressure and the oily residue was distilled. Results are summarized in Tables I and II.

Acknowledgment.—The authors are indebted to Dr. P. Vaudescal for chemical cooperation, to Miss A. M. Conrard for biochemical analyses, and to Mr. P. Vassort for spectroscopic and analytical services.

(17) 1-(*p*-Cyclopropylphenoxy)-2,3-epoxypropane was prepared in a similar manner as for the *ortho* derivative and was used without distillation.

2,3,6-Trimethoxynitrostyrene and Its β-Phenethylamine

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Received May 6, 1970

In a report of a general synthesis of a number of β-phenethylamines, Merchant and Mountwala[1] condensed 2,3,6-trimethoxybenzaldehyde (2,4-DNP, mp 223°)[2] with $MeNO_2$ and obtained an oil. This was not further purified, and was reduced to yield an amine whose picrate melted at 166–167°. Clark, *et al.*,[3] following the above procedure, obtained a β-phenethylamine as a hydrochloride, mp 122–123°. In contrast to the other trimethoxy derivatives evaluated, these authors reported that this compound had no activity in the presence of soluble amine oxidase from rabbit liver.

We now doubt that the 2,3,6-trimethoxyphenethylamine reported in the previous two communications was the correct compound. Using a method different from that in ref 2, 2,3,6-trimethoxybenzaldehyde was prepared; its 2,4-dinitrophenylhydrazone melted at 207° which compares with that reported by Shulgin.[4]

Condensing the substituted aldehyde with $MeNO_2$ resulted in a *crystalline* substituted nitrostyrene which melted at 99–100°. The nmr signals at δ 8.60 and 8.96 were due to the ethylenic protons and a coupling constant of $J = 21$ Hz indicated[5] a *trans* configuration for this compound. The melting points of the picrate and hydrochloride of the corresponding β-phenethylamine are now given as 176 and 135°, respectively.

Biological Activity.—The compound produced hypomotility in 20-g Swiss-albino mice when administered ip as a saline solution at 16 mg/kg. At 31 mg/kg the compound induced fatal convulsions.

Following a modified monomine oxidase procedure of Wurtman and Axelrod[6] using homogenized mouse brain, the amine at a concentration of 2.5×10^{-4} *M* inhibited by 43% the production of indole-^{14}C acetic acid from tryptamine-2-^{14}C. This compound is either a competitive substrate for the monoamine oxidase or an inhibitor of that enzyme.

Experimental Section[7]

2,3,6-Trimethoxy-β-nitrostyrene.—A mixture of 4.5 g (0.025 mole) of 2,3,6-trimethoxybenzaldehyde, 1.3 g of NH_4OAc, 1.7 ml of $MeNO_2$, and 15 ml of AcOH was refluxed for 1.5 hr. On cooling, yellow crystals were separated. Recrystallization from EtOH gave 3.2 g (54%) of mp 99–100°; nmr ($CHCl_3$) δ 4.12, 4.16, 4.20 (s, 9, OCH_3), 7.08, 7.48 (AB pattern, 2, aromatic), 8.60, 8.96 (AB pattern, 2, J = 21 Hz, HC=CH); ir spectra as expected. *Anal.* ($C_{11}H_{13}NO_5$) C, H, N.

2,3,6-Trimethoxy-β-phenethylamine.—To a stirred suspension of 2.0 g of LAH in 120 ml of anhyd Et_2O was added slowly a soln of 2.9 (0.012 mole) of the nitrostyrene in 100 ml of Et_2O–C_6H_6. The mixture was refluxed 2 hr, excess of LAH was decomposed (wet Et_2O), and 6 *N* HCl was added until pH 6. Then it was treated with 29 g of potassium sodium tartrate followed by 25% NaOH soln until pH 9. The mixture was extracted with CH_2Cl_2 upon evaporation the free amine was obtained as a faintly yellow syrup.

Two drops of the free amine were added to a boiling solution of picric acid in EtOH, after 48 hr large, yellow crystals, mp 176° (sharp) were obtained. Merchant and Mountwala[1] reported mp 166–167°.

The rest of the syrup was dissolved in Et_2O and HCl gas was bubbled through the solution until saturation. On evaporation, a syrup was obtained which was crystallized from *i*-PrOH–EtOAc (1:3); 1.35 g (47%) of white needles, mp 130–133° were obtained.

Recrystallization from the same solvent gave mp 134–135°; tlc (on silica gel IB-F, developed with 1-BuOH–AcOH–H_2O, 4:1:1, and visualized by spraying with ninhydrin) R_f 0.65; nmr (D_2O) δ 3.05–3.22 (m, 4, aliphatic H), 3.82, 3.88 (s, 9, OCH_3), 9.90, 7.14 (AB pattern, 2, aromatic H); ir spectra as expected. *Anal.* ($C_{11}H_{18}ClNO_3$) C, H, N.

Acknowledgments.—We wish to thank Dr. R. S. deRopp for valuable discussion and Mrs. Lena Kastl for her help with the biological testing. This work was supported by National Institute of Mental Health Grant 5 RO1 MH13687-03.

(7) Melting points were taken on a Nalge-Axelrod micro hot stage and are corrected. Analytical results where indicated by symbols of the elements were within ±0.2 of theoretical values. The ir spectra were measured with a Perkin-Elmer Model 337 spectrophotometer, and nmr spectra with a Varian A-60 spectrometer.

Synthesis of B/C *trans*-Fused Morphine Structures. V.[1] Pharmacological Summary of *trans*-Morphine Derivatives and an Improved Synthesis of *trans*-Codeine

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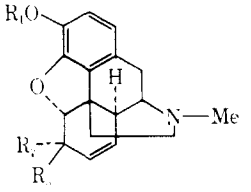
Received March 9, 1970

Preceding papers[1,4,5] from this laboratory presented the synthesis of B/C *trans*-morphine and related compounds. The present paper concerns the evaluation of the analgetic activities of these compounds and

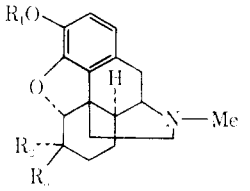
(1) J. R. Merchant and A. J. Mountwala, *J. Org. Chem.*, **23**, 1774 (1958).
(2) J. R. Merchant, R. M. Naik, and A. J. Mountwala, *J. Chem. Soc.*, 4142 (1957).
(3) L. C. Clark, F. Beningtom, and R. D. Morin, *J. Med. Chem.*, **8**, 353 (1965).
(4) A. Shulgin, *ibid.*, **9**, 445 (1960).
(5) D. W. Mathieson, *Nucl. Magn. Resonance Org. Chem.*, 187 (1967).
(6) R. J. Wurtman and J. Axelrod, *Biochem. Pharmacol.*, **12**, 1439 (1963).

(1) Part IV: H. Inoue, M. Takeda, and H. Kugita, *Chem. Pharm. Bull.*, in press.
(2) Present address: Research and Development Division, Tanabe Seiyaku Co., Ltd. (Osaka).
(3) To whom correspondence should be addressed.
(4) H. Kugita, M. Takeda, and H. Inoue, *Tetrahedron*, **25**, 1851 (1939).
(5) H. Kugita and M. Takeda, *Chem. Pharm. Bull.*, **13**, 1422 (1965).

TABLE I
ANALGETIC ACTIVITY AND ACUTE TOXICITY OF *trans*-MORPHINE DERIVATIVES



1–4



5–7

No.	Compd	R_1	R_2	R_3	ED_{50}, mg/kg s.c.	Duration of effect (min.)	LD_{50}, mg/kg
1	*trans*-Morphine[a,b]	H	OH	H	11.7	153.2	199
2	*trans*-Isomorphine[a,c]	H	H	OH	5.9	160.4	*f*
3	*trans*-Codeine[b,d]	CH_3	OH	H	17.7	165.7	148
4	*trans*-Isocodeine[c,e]	CH_3	H	OH	3.9	149.3	50
5	*trans*-Dihydrocodeine[e,b]	CH_3	OH	H	15.5	156.4	132
6	*trans*-Dihydroisocodeine[e,c]	CH_3	H	OH	6.7	156.0	*g*
7	*trans*-Dihydrodesoxymorphine[d,e]	H	H	H	0.8	129.9	134
	Morphine				1.2[h]		407[i]
	Codeine				7.5		

[a] Hydrochloride. [b] See ref 4. [c] See ref 1. [d] Hydrobromide. [e] See ref 5. [f] At 25 mg/kg 3/5 died. [g] At 50 mg/kg 3/5 died. [h] Sulfate.

also an improved preparation of (+)-3-methoxy-6α-hydroxy-4,5α-epoxy-Δ⁷-*N*-methylisomorphinan (II, *trans*-codeine).

Chemistry.—Our earlier report[4] described a 5-step synthesis of *trans*-codeine (II) from isoneopine in 9.8% overall yield. It appeared later, however, that (−)-3-methoxy-6β,8α-ditosyloxy-4,5α-epoxy-*N*-methylisomorphinan (I),[6] when heated with KOAc in DMF, gave II in one step in 53.2% yield. Accordingly, by this method, II could be prepared in 3 steps from isoneopine in much increased overall yield (38%).

Oppenauer oxidation of (−)-3-methoxy-6α-hydroxy-4,5α-epoxy-*N*-methylisomorphinan (III, *trans*-dihydrocodeine)[4] gave the 6-oxo derivative which proved to be identical with an authentic sample of *trans*-dihydrocodeinone (IV).[7] This result provides an additional proof of the structure of *trans*-codeine.

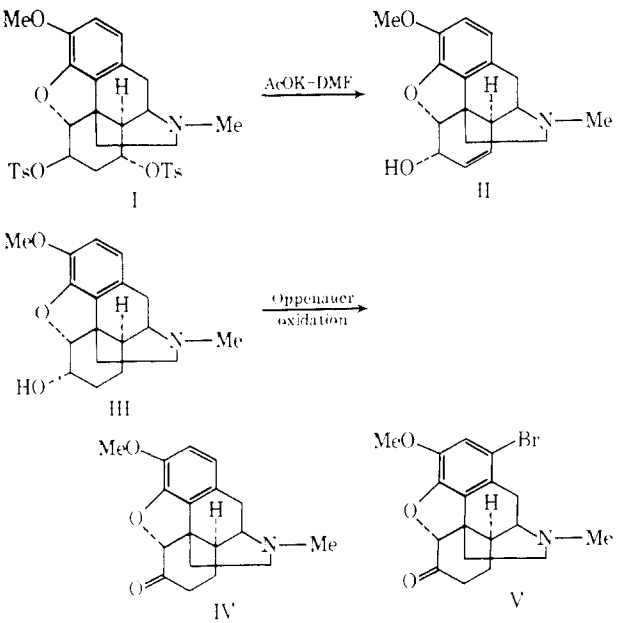
Pharmacology.—Recently, Bentley and coworkers synthesized 6,14-endoethenotetrahydrothebaine derivatives, the C_7–C_8 linkage of which might be considered as a part of the C-ring of the B/C *trans*-morphine structure.[8] In view of the very potent analgetic activity of those derivatives they suggested that B/C *trans*-morphine would have a higher potency than the natural *cis* derivative.[9]

Table I presents analgetic activities[10] and acute toxicities[11] of *trans*-morphine derivatives as well as the comparative data for morphine and codeine. *trans*-Morphine (**1**) was found to be only 0.1 as active as natural morphine. In general, *trans*-morphine derivatives were less effective than the corresponding B/C *cis* isomers except for **4**.[12]

Decrease of analgetic activity, usually seen in morphine-like analgetics by methylation of the phenolic OH, was not apparent in this series of compounds. Thus, *trans*-isocodeine (**4**) showed rather stronger activity than the OH derivative, *trans*-isomorphine (**2**).

Another feature characteristic of *trans*-morphine derivatives was that the isomers with 6β-OH (**2**,**4**,**6**) were more potent analgetics than the isomers with 6α-OH (**1**,**3**,**5**).

SCHEME I



Experimental Section

All melting points were determined in an open capillary tube and are uncorrected. Ir spectra were measured in Nujol. When

(6) M. Takeda, H. Inoue, and H. Kogita, *Tetrahedron*, **25**, 1839 (1969).

(7) IV was synthesized from *trans*-1-bromodihydrocodeinone (V) *via* ketalization, reductive debromination, and deketalization. Private communication from Professor M. Gates, University of Rochester. The authors thank Professor Gates for providing us with the sample of IV.

(8) K. W. Bentley, J. D. Bower, and J. W. Lewis, *J. Chem. Soc. C*, 2569 (1969), and ref therein to earlier papers.

(9) Personal communication from Dr. K. W. Bentley.

(10) These data were determined by hot-plate method at the National Institutes of Health, Bethesda, Md. N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, **107**, 385 (1953). See also A. E. Jacobson and E. L. May, *J. Med. Chem.*, **8**, 563 (1965) footnote 9.

(11) The test was conducted by Dr. G. Hayashi and associates, Clinical Pharmacology Department, Tanabe Seiyaku, Co., Ltd.

(12) Regarding the analgetic activity of B/C *cis*-morphine derivatives, see N. B. Eddy, H. Halbach, and O. J. Braenden, *Bull. W. H. O.*, **14**, 353 (1956).

analyses are indicated only by symbols of the elements, analytical results for those elements were within ±0.4% of the theoretical values.

(+)-3-Methoxy-6α-hydroxy-4,5α-epoxy-Δ⁷-N-methylisomorphinan (*trans*-**Codeine**) (**II**).—A mixture of **I** (2.8 g), AcOK (7 g), H_2O (2 ml), and DMF (40 ml) was refluxed for 23 hr and evaporated *in vacuo*. The residue was dissolved in H_2O, basified with NH_4OH, extracted with $CHCl_3$, dried, and evaporated. Conversion of the residue into the picrate in EtOH gave **II**·picrate (1.26 g, 53.2%), mp 244–245° dec (from Me_2CO–EtOH). This was identical with an authentic sample.

3-Methoxy-6-oxo-4,5α-epoxy-N-methylisomorphinan (*trans*-**Dihydrocodeinone**) (**IV**) **Picrate.**—A mixture of **III** (from 0.35 g of the hydrochloride), $Al(O\text{-}t\text{-}Bu)_3$ (0.35 g), benzophenone (1.7 g), and C_6H_6 (5 ml) was refluxed for 20 hr under N_2. The mixture was acidified with dil H_2SO_4, the H_2O layer was separated, basified with 10% NaOH, extracted with $CHCl_3$, dried, and evaporated. The residue was chromatographed on Al_2O_3 and eluted with C_6H_6–Et_2O (9:1). The eluate was converted into the picrate and recrystallized from EtOH–Me_2CO to give **IV**·picrate (0.06 g, 11%), mp 220–230° dec, ir, 1723 cm^{-1}. *Anal.* ($C_{24}H_{24}N_4O_{10}$) C, H, N. The free base was crystallized from Et_2O, mp 98–99°, identical with an authentic specimen. (mp, nmr, and tlc).

Acknowledgment.—The authors express their gratitude to Dr. Everette L. May, National Institutes of Health, for his aid in determination of the analgetic activity. Thanks are also due to Mr. M. Yamazaki, Dr. N. Sugimoto, and Dr. S. Sugasawa, Professor Emeritus of Tokyo University, for their interest and encouragement.

Analeptics. 1-Formimidoylindolines

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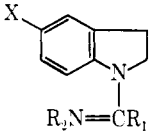
Received March 23, 1970

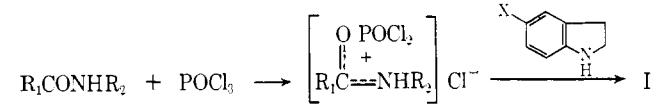
Although the value of analeptics in the treatment of CNS depression is uncertain,[2] bemegride has been generally recognized as useful in treating patients with severe barbiturate intoxication. In the course of investigation of amidines as medicinals, we discovered that certain 1-formimidoylindolines (I) have analeptic effects comparing favorably with bemegride. We wish to report the results of analeptic screening on these compounds. In I, X represents H, Ac, and NO_2 groups;



(I)

and R_1, R_2 represent H, alkyl, and alkylamino groups. R_1 and R_2 may join together to form a cyclic moiety.

These compounds were synthesized by the action of an amide–$POCl_3$ adduct[3] on an appropriate indoline. Their physical constants are tabulated in Table I.



Biological Data and Correlations. Analeptic Activity.—With few exceptions, the compounds listed in this report were screened for analeptic activity by both: (1) the antagonism of pentobarbital in cats and (2) the antagonism of chloral hydrate in mice.

Pentobarbital Antagonism.—Cats of either sex, previously equipped with chronically indwelling iv cannulas, were individually placed into an observation cubicle (60 × 60 × 60 cm) and allowed to move about freely at the end of a leash. A dose of 12 mg/kg of aq pentobarbital sodium was infused at the rate of approximately 2 mg/kg per min *via* tubing contained in the leash. One-half hour after the start of this infusion the animals were in a stage of light anesthesia characterized by unconsciousness, immobility, relaxed nictitating membranes, and irresponsiveness to handling, but active pinnal, palpebral, and paw-pinch withdrawal reflexes. At this time the test compound in aq solution was infused in a concentration of 10 mg/ml and at a rate of 0.2 ml/min until (a) consciousness was restored, (b) a total of 25 mg/kg of test compound was administered, or (c) mounting toxicity interfered. Recovery of consciousness was recognized by the presence of alertness to surroundings, including the ability of the eyes to follow the movement of a nearby object, and attempts to change to an upright position. Results are presented in Table I. All compounds were tested in two cats.

Chloral Hydrate Antagonism.—Groups of 20 fasted, male, albino mice were administered an oral dose of 20 mg/kg of the test compound followed immediately by an ip dose of 300 mg/kg of chloral hydrate. If the duration of the ensuing hypnosis was 50% or less of that produced in saline-treated controls additional doses were administered and the dose which would reduce sleeping time by 50% was determined graphically from a dose–response curve. Results appear in Table I. Three compounds (**8**, **13**, and **17**) approximated the analeptic potency of bemegride in this test.

Discrepancies between the results of these two tests may result from the chemical difference in the hypnotics themselves as well as the species in which they are employed. In addition, the infusion technique used in cats requires that the test compound be prompt in exerting its analeptic effect before its toxic actions intervene. Indeed, convulsant stimulation is a common toxic manifestation in this series and in some cases analepsis may actually have been a result of it.

Extended testing with the more active compounds demonstrated that motor stimulation is not a necessary concomitant of analeptic action. According to an activity cage technique using rats,[4] **2** and **8** were inactive, **6** and **13** were depressant, and **17** was mildly stimulant. Bemegride is mildly depressant to motor activity, although amphetamine is markedly stimulant.

Other Tests. Analgesia.—Thirteen compounds were screened for analgetic properties in mice by means of the phenylquinone writhing test.[5] Compounds **6**, **9**, **13**,

(1) To whom inquiries should be addressed.
(2) F. Hahn, *Pharmacol. Rev.*, **12**, 447 (1960).
(3) H. Brederick and K. Brederick, *Chem. Ber.*, **94**, 2278 (1961).
(4) J. W. Kissel, *Science*, **139**, 1224 (1963).
(5) L. C. Hendershot and J. Forsaith, *J. Pharmacol. Exp. Ther.*, **125**, 237 (1959).