Synthesis and Biological Properties of 1-Dimethylamino-3-methyl-3-(3-hydroxyphenyl)butane, a Potential Analgetic

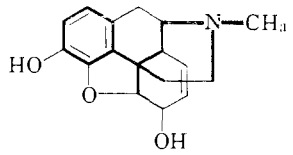
B. PECHERER, R. SUNBURY, L. RANDALL, AND A. BROSSI

Research Departments of Hoffmann-La Roche Inc., Nutley, New Jersey 07110

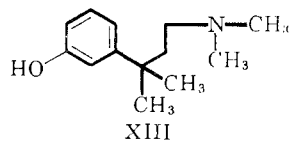
Received August 28, 1967

The phenolic amine XIII, which represents a simple open-chain modification of the morphine molecule, has been synthesized. It has been found to have relatively little analgetic activity.

The conviction that some fragments of the morphine molecule (I) would retain the "desirable" biological effects of morphine has been greatly stimulated by the finding of analgetic activity among 4-phenyl-substituted piperidines, morphinans, and benzomorphans.[1,2] All of these structures contain a quaternary carbon atom and a tertiary N-methylamino group separated from the quaternary carbon atom by a two-carbon side chain. The searches for new, centrally active analgetics based on the morphine model have usually considered these concepts. In this paper, we would



I



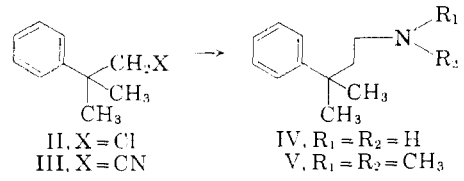
XIII

like to report the synthesis and biological properties of 1-dimethylamino-3-methyl-3-(3-hydroxyphenyl)butane (XIII). This phenolic amine can, theoretically, be regarded as the simplest structure containing these essential requirements.

The route selected for the synthesis of XIII involves, in the earlier stages, the conversion of a substituted neophyl chloride into its corresponding nitrile. Although bimolecular displacements of this type have been reported to be impractical,[3] neophyl chloride (II), because it was readily accessible, was selected for model experiments (Chart I). When treated with sodium cyanide in DMSO at 145°, the chloride II was converted into the nitrile III in 81% yield. The nmr spectrum of the oily nitrile showed that no skeletal rearrangement had occurred. Reduction of III with lithium aluminum hydride yielded the primary amine IV, which was characterized as its crystalline hydrochloride. The conversion of IV into the corresponding tertiary amine was achieved by refluxing it with a mixture of formic acid and formalin.

The synthesis of XIII accordingly proceeded as outlined in Chart II. Repeated alkylation of the sodium salt of 3-methoxyphenylacetonitrile (VI)[4] with dimethyl sulfate in liquid ammonia[5] yielded an inseparable mixture of starting material, 2-(3-methoxyphenyl)propionitrile and 2-methyl-2-(3-methoxyphenyl)propionitrile VII. The main fraction, after two alkylations, however, contained at least 90% of VII (based on glpc analysis) and was used further. Alkaline hydrolysis of this material afforded crystalline 2-methyl-2-(3-methoxyphenyl)propionic acid (VIII) along with a small amount of the corresponding amide. Acid hydrolysis yielded a much higher proportion of the amide. Reduction of the crystalline VIII with lithium aluminum hydride gave the liquid alcohol IX. Attempts to convert IX into a 3-methoxyneophyl halide with hydrogen chloride, phosphorus tribromide, or thionyl chloride failed. Reaction with methanesulfonyl chloride in pyridine, however, afforded a crude mesylate which, upon reaction with sodium cyanide in DMSO at elevated temperature, could be converted into practically pure nitrile X. Reduction of X with lithium aluminum hydride and N-methylation of the primary amine XI with formic acid and formalin yielded the tertiary aminomethyl ether XII. The nmr spectrum of the crystalline hydrochloride shows four aromatic protons between δ 6.6 and 7.5 and proves that no cyclization has taken place *para* to the aromatic methoxy group. Ether cleavage of XII with 48% HBr gave the phenolic base XIII which could be isolated as a crystalline hydrochloride. The structures of XII and XIII were fully ascertained by physical data (see Experimental Section).

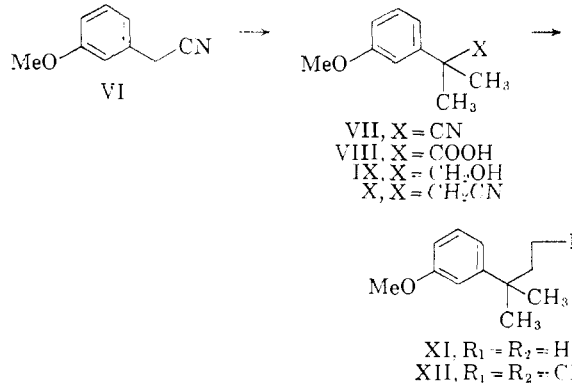
CHART I



II, X = Cl
III, X = CN

IV, $R_1 = R_2 = H$
V, $R_1 = R_2 = CH_3$

CHART II



VI

VII, X = CN
VIII, X = COOH
IX, X = CH_2OH
X, X = CH_2CN

XI, $R_1 = R_2 = H$
XII, $R_1 = R_2 = CH_3$

Biological Evaluation.—The water-soluble hydrochlorides of V, XII, and XIII were evaluated as anal-

(1) E. L. May and L. J. Sargent in "Analgetics," G. DeStevens, Ed., Academic Press Inc., New York, N. Y., 1966.

(2) J. Helterbach, O. Schnider, H. Besendorf, B. Pellmont, N. B. Eddy, and E. L. May in "Synthetic Analgesics," Part II, International Series of Monographs in Organic Chemistry, Vol. 8, D. H. R. Barton and W. von Doering, Ed., Pergamon Press, New York, N. Y., 1966.

(3) F. C. Whitmore, C. A. Weisgerber, and A. C. Shabica, Jr., *J. Am. Chem. Soc.*, **65**, 1469 (1943).

(4) J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 684 (1942).

(5) E. M. Hancock and A. C. Cope, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 219.

TABLE I
RESULTS OF BIOLOGICAL SCREENING

Compound	ED_{50}, mg/kg: Hot plate test	Writhing test	Yeast inflammatory, rat, analgetic	Toxicity LD_{50} (mice), mg/kg ip
Codeine	50 *po* 26 sc	22.8 *po* 3.9 sc	40 *po*	212
Phenylbutazone	150 *po* 120 sc	64 *po*	200 *po*	75
V	<200 *po* 50 sc	76 *po*	>200 *po*	152
XII	>200 *po* 80 sc	46 *po*	>200 *po*	152
XIII	>200 *po* 33 sc	58.5 *po*	>200 *po*	210

getics in the hot plate test,[6,7] the phenylquinone writhing test,[8] and the yeast-inflamed foot test[9] (see Table I). For the determination of the acute toxicity, CF-1 mice of both sexes weighing 17–22 g were used, and the compounds were administered intraperitoneally.[10] Codeine and phenylbutazone were used as reference substances. The data reported in Table I show that XIII is active in the hot plate test when administered subcutaneously, weakly active in the writhing test, but inactive in the yeast inflammatory test. Compounds V and XII are much less active in all three tests. Although many important elements of the morphine structure are present in XIII, the extreme simplification of the structure has resulted in the elimination of certain apparently necessary steric and conformational requirements present in the polycyclic structure of morphine, morphinans, and benzomorphans.[11]

Experimental Section

Melting points were determined on a Thomas–Hoover apparatus and are corrected. Boiling points are uncorrected. Infrared spectra were determined on a Beckman IR-5 recording spectrophotometer. Nmr spectra were determined on a Varian A-60 spectrometer (TMS) and are reported in ppm (δ). Vapor phase chromatography was performed with 4% polyethylene glycol (molecular weight 4000) monostearate on Chromosorb W columns, unless otherwise stated. The instruments used were either the Beckman GC2A with Thermotrac or the F & M-810, R 13N. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Ir spectra were as expected.

Neophyl Cyanide (3-Methyl-3-phenylbutyronitrile, III).—A mixture of 84.3 g (0.5 mole) of II,[12] 30.6 g (0.625 mole) of NaCN, and 168 ml of DMSO was heated and stirred in a dry atmosphere for 18 days at 100°. The cooled mixture was poured into H_2O and extracted with C_6H_6. The extract was washed several times with H_2O, then dried ($MgSO_4$). Evaporation of the solvent at reduced pressure left 77 g of an amber residue which, on distillation, gave 40 g (50%)[13] of a colorless oil, bp 141–145° (15 mm), $n^{23}D$ 1.5123–1.5133. Glpc showed the material to have a purity in excess of 99%; nmr ($CDCl_3$), δ 1.48 [6 H, $C(CH_3)_2$], 2.58 (2 H, CH_2), and 7.33 (5 H, aromatic). *Anal.* ($C_{11}H_{13}N$) C, H, N.

3-Methyl-3-phenylbutylamine (IV).—III (35 g, 0.22 mole) was added dropwise to a stirred suspension of 12.5 g (0.33 mole) of $LiAlH_4$ in 500 ml of Et_2O, and the mixture was stirred and refluxed for an additional 2 hr. Work-up in the usual manner after decomposition with H_2O afforded 37 g of crude base. Distillation gave 32 g (89%) of colorless oil, bp 113–114° (2 mm), $n^{24}D$ 1.5168. Glpc (15% DM-Corning Fluid 710 plus 10% NaOH on Chromosorb W) showed the material to be homogeneous. *Anal.* ($C_{11}H_{17}N$) C, H.

Hydrochloride of IV.—The base was dissolved in *i*-PrOH, and a slight excess of HCl was added. After two evaporations to dryness with *i*-PrOH, the solid residue was recrystallized from *i*-PrOH–EtOAc to give dense white plates, mp 191.5–193°. *Anal.* ($C_{11}H_{17}N \cdot HCl$) C, H.

3,N,N-Trimethyl-3-phenylbutylamine (V) Hydrochloride.—Ten grams (0.0614 mole) of IV, 14.1 g (0.31 mole) of HCO_2H, and 15.9 g (0.18 mole) of CH_2O (as a 37% solution) were refluxed for 17 hr. The mixture was acidified with 20 ml of 12 *N* HCl and all volatile material was removed in a rotary evaporator. The crystalline residue was taken to dryness twice, after suspending in *i*-PrOH, and then recrystallized from a mixture of *i*-PrOH and EtOAc; yield 8.3 g of hydrochloride in the form of white plates: mp 202–205°; ν_{max}^{KBr} 3000, 2630, 2570, 2540, 2440, 1950–1650 (broad and diffuse), and 1610 cm^{-1}; nmr ($DMSO\text{-}d_6$), δ 1.30 [6 H, $C(CH_3)_2$], 2.06 (2 H, CH_2), 2.5–2.8 [8 H, $CH_2N(CH_3)_2$], 7.0–7.4 (5 H, aromatic), and 11.23 (1 H, NH^+). *Anal.* ($C_{13}H_{21}N \cdot HCl$) C, H, Cl.

2-(3-Methoxyphenyl)-2-methylpropionitrile (VII).—A solution of 264 g of 3-methoxyphenylacetonitrile[4] in 264 ml of dry Et_2O was added to a suspension of $NaNH_2$ prepared in the described manner[5] from 51.7 g of Na and 1400 ml of liquid NH_3, Et_2O (1 l.) was added to the dark red mixture, and, after the bulk of the NH_3 had boiled off, 283.5 g (2.25 moles) of Me_2SO_4 in 200 ml of Et_2O was added dropwise with stirring to the refluxing suspension. After 2 hr of refluxing, the product was collected in the usual manner and distilled. The fraction boiling at 150–165° (20 mm), 251 g, contained some starting material and, in addition, mono- and dimethylated nitrile. It was alkylated once more in the same manner using 44.6 g (1.94 g-atoms) of Na in 1 l. of liquid NH_3 and 245 g (1.94 g-atoms) of Me_2SO_4. The product was worked up as before, and the material boiling at 136–142° (20 mm) was collected: 201 g, $n^{24}D$ 1.5087–1.5142. Redistillation gave four fractions with the characteristics shown in Table II.

TABLE II

Fraction	Bp, °C (mm)	Wt, g	$n^{24}D$	Content of VII, %[a]
1	147–157(23)	15.3	1.5085	75.1
2	157–161(23)	108.0	1.5117	92.5
3	161–165 (23)	48.0	1.5155	83.6
4	165–175(23)	20.5	1.5291	19.3
Residue		7.0		

[a] Based on glpc and nmr data.

2-(3-Methoxyphenyl)-2-methylpropionic Acid (VIII).—Fraction 2 of VII (79 g, 0.45 mole) was refluxed with 101 g (1.8 moles) of KOH in 403 ml of 95% EtOH for 48 hr. The EtOH was distilled at reduced pressure, and 1 l. of H_2O was added to the residue. HCl was added to pH 2, and the mixture was extracted with three 200-ml portions of 1:1 Et_2O–C_6H_6. The extracts were washed once with H_2O, dried with $MgSO_4$, and concentrated at reduced pressure to give 83.5 g of an oil. The oil was distilled, and the product boiling at 128° (0.7 mm) was collected; yield 73 g (90%) of colorless oil which eventually solidified to a mass of crystals, mp 58–60°. Glpc showed the product to consist of a single component; nmr ($CDCl_3$), δ 1.58 [6 H, $(CH_3)_2C$], 3.80 (3 H, CH_3O), 6.75–7.42 (4 H, aromatic). *Anal.* ($C_{11}H_{14}O_3$) C, H.

In some runs, the diluted hydrolysate deposited shiny plates, mp 100–110°. These were filtered and recrystallized from dilute EtOH to yield crystals, mp 118–119°. The ir spectrum showed that this was the **amide** of the acid VIII. *Anal.* ($C_{11}H_{15}NO_2$) C, H, N. Acid hydrolysis of VII gave the same amide in 32% yield.

2-(3-Methoxyphenyl)-2-methyl-1-propanol (IX).—The acid VIII (9.7 g, 0.05 mole) was reduced with 2.85 g (0.075 mole) of $LiAlH_4$ in Et_2O. After 1 hr of refluxing, the mixture was

(6) N. B. Eddy, C. F. Tolchberry, and J. E. Lieberman, *J. Pharmacol. Exptl. Therap.*, **98**, 121 (1950).

(7) G. Woolfe and A. D. MacDonald, *ibid.*, **80**, 300 (1944).

(8) E. Siegmund, R. Cadmus, and G. Lu, *Proc. Soc. Exptl. Biol. Med.*, **95**, 729 (1957).

(9) L. O. Randall and J. J. Selitto, *Arch. Intern. Pharmacodyn.*, **111**, 409 (1957).

(10) L. C. Miller and M. L. Tainter, *Proc. Soc. Exptl. Biol. Med.*, **57**, 271 (1944).

(11) Another simplification of the morphine structure containing the essential structural features has been prepared by E. L. May and J. G. Murphy, *J. Org. Chem.*, **20**, 1197 (1955). This compound and its methyl ether also showed no noteworthy analgetic activity.

(12) W. T. Smith, Jr., and J. T. Sellas, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 702.

(13) In two other runs, the yields of product were 65% at 135° for 4 days and 81% (3-mole run) at 145° for 4 days.

worked up to give 9.0 g of an oil which, on redistillation, yielded 8.0 g (89%) of a colorless liquid, bp 100° (0.6 mm), n^{24}D 1.5264. Glpc showed the purity to be 99+%; nmr ($CDCl_3$), δ 1.51 [6 H, $(CH_3)_2C$], 1.63 (1 H, OH), 3.57 (2 H, CH_2), 3.80 (3 H, CH_3O), 6.72–7.25 (4 H, aromatic, *meta* substitution). *Anal.* ($C_{11}H_{16}O_2$) C, H.

The alcohol IX, with dry HCl, PBr_3 in Et_2O, or $SOCl_2$ in C_6H_6 gave complex mixtures.

3-(3-Methoxyphenyl)-3-methylbutyronitrile (X).—At 0°, 46.0 g (0.402 mole) of $MeSO_2Cl$ was added dropwise to a solution of 65.6 g (0.364 mole) of IX in 262 ml of dry C_5H_5N. The mixture was allowed to warm to room temperature overnight and poured into 500 ml of H_2O. The suspension was extracted with three 100-ml portions of Et_2O. The extracts were washed once with cold H_2O, cold 10% HCl, and cold H_2O, then dried over $MgSO_4$. Distillation of the solvent in a rotary evaporator left 88.0 g of a colorless, oily mesylate. The ir spectrum (neat, film) showed no OH absorption bands in the 3000–3500-cm^{-1} region. This crude mesylate (83 g, 0.322 mole) was heated and stirred with 19.7 g (0.402 mole) of NaCN and 322 ml of DMSO at 95–100° for 4 days. The cooled mixture was poured into 1 l. of H_2O and extracted with three 250-ml portions of 1:1 Et_2O–C_6H_6 from which, after the usual work-up, 57 g of an amber oil was obtained. Distillation (15-cm Vigreux column) yielded 22.6 g (37%) of colorless oil, bp 99° (0.18 mm), n^{24}D 1.5215. Glpc showed the product to be 98.3% pure; nmr ($CDCl_3$), δ 1.48 [6 H, $(CH_3)_2Cl$, 2.58 (2 H, CH_2), 3.80 (3 H, CH_3O), and 6.7–7.5 (4 H, aromatic). *Anal.* ($C_{12}H_{15}NO$) C, H, N.

3-(3-Methoxyphenyl)-3-methylbutylamine (XI) Hydrochloride.—Nitrile X, 22.6 g (0.12 mole) in 25 ml of Et_2O, was added dropwise to a stirred suspension of 5.7 g (0.15 mole) of $LiAlH_4$ in 150 ml of Et_2O. After 1.5 hr of refluxing, the mixture was cooled and decomposed with H_2O, and 3 g of filteraid was added; the suspension was filtered through a bed of filteraid. From the filtrate, after removal of the solvent, 23 g (nearly quantitative) of a colorless oil, homogeneous by tlc, was obtained. A sample of this oil was converted to the hydrochloride, as described for IV·HCl. The salt was recrystallized from *i*-PrOH–EtOAc: mp 170–171°; ν_{max}^{Nujol} 3000–2925 (broad), 2000, and 1595 cm^{-1}. *Anal.* ($C_{12}H_{19}NO$·HCl) C, H, Cl.

3-(3-Methoxyphenyl)-3,N,N-trimethylbutylamine (XII) Hydrochloride.—Six grams (0.0311 mole) of XI was treated with 7.13 g (0.156 mole) of HCO_2H and 7.57 g (0.093 mole) of 37% CH_2O, as described for V. After 18 hr of refluxing, 3.5 ml of 12 *N* HCl was added, and the solution was taken to dryness in a rotary evaporator. The white solid thus obtained was slurried in EtOAc and collected by filtration to yield 6.2 g of XII·HCl. This product was recrystallized twice from *i*-PrOH–EtOAc: mp 146–147°; ν_{max}^{Nujol} 3000 (broad), 2650, 2550, 2470, 1600, and 1580 cm^{-1}; nmr (DMSO-d_6), δ 1.32 [6 H, $(CH_3)_2C$], 1.71–3.0 [8 H, $CH_2N(CH_3)_2$], 3.80 (3 H, CH_3O), 6.6–7.5 (4 H, aromatic). *Anal.* ($C_{13}H_{23}NO$·HCl) C, H, Cl.

3-(3-Hydroxyphenyl)-3,N,N-trimethylbutylamine Hydrochloride (XIII·HCl).—Compound XII (5.15 g, 0.02 mole) was refluxed with 150 ml of 48% HBr for 5 hr. The acid was removed in a rotary evaporator leaving a solid residue which was dissolved in 25 ml of H_2O. This solution was made alkaline with NH_4OH, then extracted four times with 15-ml portions of Et_2O. The Et_2O extracts were washed with H_2O and dried over K_2CO_3. The solvent was distilled under reduced pressure, leaving 4.0 g of an amber oil. It was dissolved in 20 ml of *i*-PrOH and excess dry HCl in Et_2O was added. A brown solid, 3.8 g, mp 198–202°, was obtained. Three recrystallizations from *i*-PrOH gave 1.4 g of XIII·HCl as white crystals: mp 201.5–202°; ν_{max}^{KBr} 3280, 3000, 2675, 2520, 2490, 1610, and 1590 cm^{-1}; nmr (DMSO-d_6), 1.28 [6 H, $(CH_3)_2C$], 2.03 (2 H, CH_2), 2.70 [8 H, $CH_2N(CH_3)_2$], 6.8–7.4 (4 H, aromatic), 9.42 (1 H, OH), and 10.23 (1 H, NH^+). *Anal.* ($C_{13}H_{21}NO$·HCl) C, H, Cl.

Acknowledgment.—The microanalyses were obtained by Dr. F. Scheidl and his associates of our Microanalytical Laboratory. The ir spectra were obtained by Mr. S. Traiman and the nmr spectra by Dr. T. Williams of our Physical Chemistry Department, under the direction of Dr. P. Bommer.

Antiinflammatory 2-Aryl-1,3-indandiones[1a]

JOSEPH G. LOMBARDINO AND EDWARD H. WISEMAN

Medical Research Laboratories, Chas. Pfizer & Co., Inc., Groton, Connecticut 06340

Received August 18, 1967

Previously reported antiinflammatory activity for 2-phenyl-1,3-indandione (1) was confirmed in rats. Compound 1 also inhibits blood coagulation *in vivo*, by inhibiting the hepatic synthesis of prothrombin. However, at the time of measurement of antiedema activity (3 hr post-carrageenin injection) neither 1 nor the other anticoagulants warfarin, bishydroxycoumarin, or 2-pivalyl-1,3-indandione had induced a coagulation defect; of these four compounds only 1 had antiinflammatory activity. The aim of this program was the separation of antiinflammatory from anticoagulant activity in some 2-arylindandiones. All compounds were tested in the rat for inhibition of carrageenin-induced paw edema and for inhibition of prothrombin synthesis. Results showed most unclear unsubstituted 2-aryl-1,3-indandiones to be inhibitors in both tests; however, fairly large *meta* substituents on the 2-aryl function diminished anticoagulant activity. In addition, certain substituents in the indane ring successfully removed anticoagulant activity while retaining antiinflammatory activity in many cases. The acidity of those compounds with antiinflammatory activity was found to be restricted to a fairly narrow range.

The property of 2-aryl-1,3-indandiones to inhibit blood coagulation has been thoroughly studied and has led to three analogs with clinically useful anticoagulant activity.[1b] Over the course of some 20 years the greatest amount of interest has centered around the parent 2-phenyl-1,3-indandione (**1**) and its effect on blood prothrombin levels. Extensive structure–activity relationships have been developed[2–7] for analogs of **1** in an attempt to improve the therapeutic index of anticoagulant activity. In addition to anticoagulant

(1) (a) Presented in part before the Medicinal Division at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 12, 1967, Abstract No. P-19; (b) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," 3rd ed, The MacMillan Co., New York, N. Y., 1965, pp 1450–1458.

(2) (a) L. Fontaine, M. Odievre, Y. Achet, and B. Drevon, *Therapie*, **16**, 34 (1961); (b) L. Fontaine, M. Grand, Y. Quentin, and S. Merle, *Med. Pharmacol. Exp.*, **13**, 137 (1965).

(3) (a) S. L. Shapiro, K. Geiger, and L. Freedman, *J. Org. Chem.*, **25**, 1860 (1960); (b) S. L. Shapiro, K. Geiger, J. Youlus, and L. Freedman, *ibid.*, **26**, 3580 (1961).

(4) D. Molho, Proceeding of the International Conference on Thrombosis and Embolism, Basel, 1954, p 193.

(5) J. Cavallini, A. Milla, A. Grumelli, and F. Ravenna, *Farmaco, Sci. Ed.*, **10**, 710 (1955).

(6) P. Hrneiar, *Chem. Zvesti*, **16**, 96 (1962); *Chem. Abstr.*, **59**, 2731 (1963).

(7) H. Kabat, E. F. Stoblman, and N. I. Smith, *J. Pharmacol. Exp. Ther.*, **80**, 160 (1944).