Similarly, the methiodide of the methyl ether of III gave VI whose n.m.r. spectrum is shown in Figure 3.

7-Methoxy-1-methylnaphthalene.[7] **A. From IX.**—Compound IX (3 g.) in 25 ml. of alcohol was treated with 1–2 g. of $NaBH_4$. After gas evolution had ceased, aqueous NaOH was added, and the mixture was extracted with ether. Evaporative distillation (150°, 0.1 mm.) of the residue from drying and evaporation of the ether gave 2.5 g. of the **2-carbinol** corresponding to IX (C, H analysis correct), retention time[14] 5 min. at 148°. This carbinol (0.5 g.) and 0.5 g. of 10% palladium–charcoal were kept at 300–315° for 30 min. to give 20% yield of hydrocarbon which was purified through its picrate, m.p. 110–114°. The free hydrocarbon X, m.p. 43–45° from ligroin (30–60°), had a retention time[14] of 2 min. at 145° whose n.m.r. pattern ($CDCl_3$), TMS reference standard, showed 6 protons in the 6.9–7.9-p.p.m. region, 3 methoxy protons at 3.95 p.p.m. and 3 C-methyl protons at 2.6 p.p.m.; λ_{max}^{EtOH} 332, 317, 288, 277, 266, 232 mμ (ε 1800, 1360, 3400, 4200. 2450, 105,000).

B. From VII.—Similar aromatization of 0.3 g. of VII with 0.2 g. of 10% palladium–charcoal gave a mixture from which a fraction could be isolated with physical properties identical with those given above for authentic X.

Cyclization of I with 85% Phosphoric Acid.—The hydrochloride[3] of the methyl ether of I (10 g.) and 50 ml. of 48% HBr were refluxed for 20 min., cooled, and made alkaline with NH_4OH. Three extractions with $CHCl_3$ and evaporation of the extracts left 9.0 g. of crude I, which with 40 ml. of 85% H_3PO_4 was kept at 185–190° (bath temperature) for 35 hr. The cooled solution was made basic with NH_4OH and extracted four times with a total of 250 ml. of $CHCl_3$. Drying and evaporation of the $CHCl_3$ left 7.8 g. of solid which was digested for 10 min. with 200 ml. of boiling acetone while the volume decreased to 175 ml. The mixture was cooled to −15° during 2 hr. to give 4.9 g. of II,[2a,3] m.p. 240–245°. The filtrate was evaporated to dryness and the residue evaporatively distilled (0.05 mm.). The 2.4 g. of semisolid was digested with boiling acetone (final volume 5–7 ml.). Cooling to −15° gave 2.2 g. of III,[2a,3] m.p. 195–205° identified by its infrared spectrum (Figure 1) and hydrochloride salt. Occasionally, another crystalline modification separated whose infrared spectrum was that shown by IIIa, Figure 1. The two were interconvertible and gave the same HCl salt.[2a,3]

(14) Research Specialties gas chromatograph, 6-ft. coiled glass column, SE 30, Chromosorb W (60–80 mesh).

Structures Related to Morphine. XXXI.[1] 2′-Substituted Benzomorphans

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Several 2′-nitro-, 2′-amino-, and 2′-halo-α- and -β-5,9-dialkyl-2-methyl-6,7-benzomorphans have been synthesized. In general these compounds are less potent as analgetics and more acutely toxic than corresponding 2′-H or 2′-OH derivatives. Comparable substitution in the morphine and morphinan series has not been reported. New analgetic ED_{50} values for Caesarian-Derived General Purpose mice are given; they are approximately half those obtained with previously used General Purpose mice which were kept under less sanitary conditions.

The 2′-hydroxy group[2] in various benzomorphans and related compounds has been found to enhance analgetic potency and reduce toxicity when compared with their 2′-H analogs.[3] To our knowledge, compounds with substituents other than hydroxyl, or derivatives thereof, in the comparable position in the benzomorphans, morphine, or the morphinans have not been examined. It seemed of interest, as part of our program on the role of the substituent in analgetic effect, to prepare 6,7-benzomorphans having nitro, fluoro, chloro, and amino as the 2′-substituent.

The 2′-nitro compounds (II, Va, and Vb) were prepared by nitration of the known α- and β-5,9-diethyl-2-methyl-6,7-benzomorphan (I and IVa)[3] and β-2,5,9-trimethyl-6,7-benzomorphan (IVb),[4] respectively; amino analogs (III and VI) were obtained by catalytic reduction of the corresponding nitro compounds (see Chart I). The 2′-chloro (Xa) and 2′-fluoro (Xb) compounds could be obtained best *via* total synthesis by the Grewe[5] method. An alternative procedure for Xa based on the Stevens rearrangement[6] of 1-*p*-chlorobenzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridinium chloride gave IXa in low yield along with two isomeric products whose structures are being investigated.

The cyclization of IXa to Xa could be readily effected with hot HBr, while IXb and this reagent gave poor yields of Xb. Hot phosphoric acid was effective in cyclizing IXb, although a troublesome by-product was formed simultaneously. Pure Xb could be obtained, ultimately, only by use of preparative thin layer chromatography.

For proof of structure, Xa and Xb were degraded to 1,2-dimethylnaphthalene (XIIIa) and 7-fluoro-1,2-dimethylnaphthalene (XIIIb), which were purified through their picrates.[5] The constitution of XIIIb rests upon its elemental and spectral analyses. Ultraviolet and n.m.r. spectra indicated the naphthalene nucleus, and the n.m.r. spectrum showed the presence of two methyl groups on an aromatic nucleus (2.48 and 2.52 p.p.m.) and a complex pattern for the five protons in the aromatic region, centered at 7.5 p.p.m. The combined data are clearly consistent with the structure XIIIb. Elemental analysis of the picrate of the product obtained by palladium-on-charcoal aromatization of XIIa showed the, perhaps not unexpected, loss of chlorine. The physical properties of this picrate were identical with the known 1,2-dimethylnaphthalene picrate. The n.m.r. spectrum of XIIIa was similar to XIIIb, having the two methyl groups at 2.45 and

(1) Paper XXX: B. C. Joshi, C. F. Chignell, and E. L. May, *J. Med. Chem.*, **8**, 694 (1965).

(2) The 2′-position in benzomorphan compounds is comparable to the 3-position in morphine and the morphinans.

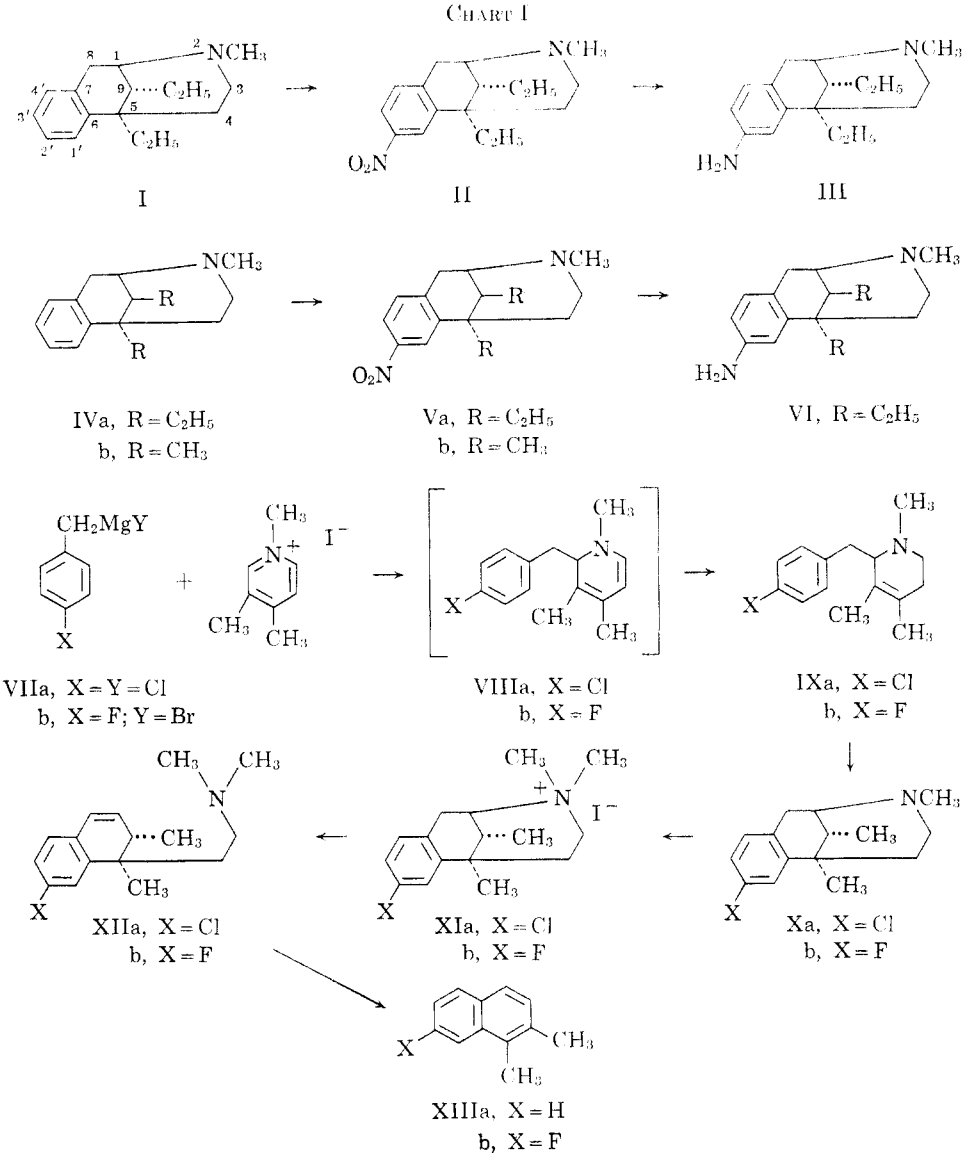
(3) A. E. Jacobson and E. L. May, *J. Med. Chem.*, **7**, 409 (1964); see ref. 2 therein.

(4) J. H. Ager, S. E. Fullerton, E. M. Fry, and E. L. May, *J. Org. Chem.*, **28**, 2470 (1963).

(5) (a) R. Grewe and A. Mondon *Chem. Ber.*, **81**, 279 (1948); (b) E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957); (c) E. L. May and J. H. Ager, *ibid.*, **24**, 1432 (1959).

(6) S. E. Fullerton, J. H. Ager, and E. L. May, *ibid.*, **27**, 2554 (1962).

CHART I



2.58 p.p.m., and the complex 6-aromatic proton pattern centered at about 7.5 p.p.m.

TABLE I

COMPARISON OF ANALGETIC ACTIVITY OF 2′-SUBSTITUTED BENZOMORPHANS

2-Methyl-6,7-benzomorphan	ED_{50}, mg./kg. s.c.
α-5,9-Diethyl- (I)[a]	2.5
2′-hydroxy-[b]	2.1
2′-nitro- (II)[c]	9.4
2′-amino- (III)[d]	18.7
β-5,9-Diethyl- (IV)[a]	2.1
2′-hydroxy-[b]	0.2
2′-nitro- (Va)[c]	25.0
2′-amino- (VI)[d]	13.2
β-5,9-Dimethyl- (IVb)[e]	2.5
2′-hydroxy-[f]	0.3
2′-nitro-[c] (Vb)	11.1
α-5,9-Dimethyl-[f]	13.5
2′-hydroxy-[f]	1.2
2′-chloro- (Xa)[c]	47.0
2′-fluoro- (Xb)[c]	22.7
Morphine[a]	1.2

[a] HCl salt; see ref. 3. [b] HCl salt; see ref. 7. [c] HCl salt: LD_{50} *ca.* 100 mg./kg. for Vb, *ca.* 200 mg./kg. for Xb. [d] ·2HBr salt; LD_{50} *ca.* 200 mg./kg. [e] HBr salt; see ref. 4. [f] HCl salt; see ref. 12.

The structure of the amino compound VI and thus its nitro precursor (Va), neither of which was previously characterized,[3] follows from its conversion to the known β-5,9-diethyl-2′-hydroxy-2-methyl-6,7-benzomorphan.[3,7] Structures II and III were assigned by analogy.[3,5]

The analgetic activities of II, III, Va, Vb, VI, Xa, and Xb were determined by the hot plate method.[8] These are compared with similar data for the related 2′-H and 2′-OH compounds, and with morphine in Table I.[9] It is apparent that replacement of the 2′-OH or 2′-H with nitro, amino, chloro, and fluoro consider-

(7) J. H. Ager and E. L. May, *J. Org. Chem.*, **27**, 245 (1962).

(8) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953). We are indebted to Dr. Nathan Eddy, Mrs. Louise Atwell, and Mrs. Wendy Ness for these data which have been derived by probit analysis.

(9) During the 12-year period prior to December 1962, ED_{50} values of 2.1 mg./kg. (subcutaneous) for morphine and of 14.0 mg./kg. for codeine have been obtained consistently and used as standards. Since that time our Animal Production Section has been providing healthier, faster growing mice, called Caesarian-Derived General Purpose (CDGP) mice, by use of more sanitary food and quarters, inclusion of HCl in the drinking water, and nearly sterile birth. These indeed healthier animals are, however, more sensitive to analgetic drugs than the previously used General Purpose (GP) mice as shown (repeated assays) in Table II for several well-known analgetics. For further information the Animal Production Section of these Institutes may be consulted.

TABLE II

ANALGETIC ED_{50} VALUES FOR CDGP COMPARED WITH GP MICE[a]

Compd.	ED_{50}, mg./kg. s.c. CDGP mice	ED_{50}, mg./kg. s.c. GP mice
Morphine·HCl	1.2	2.1
Codeine·HCl	7.5	14.0
Meperidine·HCl	4.7	9.9
Levorphanol tartrate	0.2	0.5
Metazocine·HCl	1.2	3.0
Etazocine·HCl	2.1	4.2

[a] See ref. 9.

ably reduces analgetic effectiveness. This reduction is much more pronounced in the α- than in the β-series.

Experimental[10]

α-2′-Nitro-2-methyl-5,9-diethyl-6,7-benzomorphan (II) Hydrochloride.—α-Methyl-5,9-diethyl-6,7-benzomorphan (I, 2.1 g.)[3] in glacial acetic acid (15 ml.) was added dropwise to an ice-cold mixture of fuming HNO_3 (31 ml.) and glacial acetic acid (18 ml.). The mixture was stirred overnight at 25°, and the solvent was removed *in vacuo*. Ice, water, and NH_4OH were added to the oily residue, and the basic solution was extracted with chloroform. The extract was dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. The product was converted to the hydrochloride salt (acetone–ether–HCl gas) which was recrystallized from a mixture of acetone, methanol, and ether to give 2.1 g. (75%), m.p. 256–257° dec.

Anal. Calcd. for $C_{17}H_{25}ClN_2O_2$: C, 62.85; H, 7.76; N, 8.62. Found: C, 63.06; H, 8.00; N, 8.66.

β-2′-Nitro-2-methyl-5,9-diethyl-6,7-benzomorphan (Va) Hydrochloride.—The nitration procedure outlined for II gave comparable yields of Va hydrochloride from IVa[3]; m.p. 256–258° dec.

Anal. Calcd. for $C_{17}H_{25}ClN_2O_2$: C, 62.85; H, 7.76; N, 8.62. Found: C, 62.80; H, 7.65; N, 8.52.

α-2′-Amino-2-methyl-5,9-diethyl-6,7-benzomorphan (III) Dihydrobromide.—The 2′-nitro compound II (2.1 g.) in methanol (100 ml.) was hydrogenated over 5% Pd–$BaSO_4$ in a Parr hydrogenation apparatus. The product was filtered, and the solvent was removed *in vacuo*. The oily residue was made basic with dilute NH_4OH and extracted with chloroform, and the organic solution was dried ($MgSO_4$). After filtration the solvent was removed *in vacuo*, and the product was distilled to give a light yellow oil (1.4 g.). A hydrobromide salt was prepared and recrystallized from a mixture of acetone, methanol, and ether, yielding 1.35 g. of III (50% calcd. as the dihydrobromide), m.p. 299–302° dec.

Anal. Calcd. for $C_{17}H_{28}Br_2N_2$: C, 48.59; H, 6.72. Found: C, 48.60; H, 6.57.

β-2′-Amino-2-methyl-5,9-diethyl-6,7-benzomorphan (VI) Dihydrobromide.—The 2′-nitro compound Va was hydrogenated by the procedure outlined for III, to give VI dihydrobromide, m.p. 245–248° dec.

Anal. Calcd. for $C_{17}H_{28}Br_2N_2$: C, 48.59; H, 6.72. Found: C, 48.55; H, 6.40.

A **dipicrate** was prepared (in alcohol) from the free base; m.p. 203–204°.

Anal. Calcd. for $C_{29}H_{32}N_8O_7$: C, 46.87; H, 4.50; N, 15.62. Found: C, 47.21; H, 4.70; N, 15.40.

β-2′-Nitro-2,5,9-trimethyl-6,7-benzomorphan (Vb) Hydrochloride.—β-2,5,9-Trimethyl-6,7-benzomorphan (IVb)[4] was nitrated as described in the preparation of II to give Vb hydrochloride, m.p. 241–243° dec., after recrystallization from a mixture of acetone and ether.

Anal. Calcd. for $C_{15}H_{21}ClN_2O_2$: C, 60.70; H, 7.13. Found: C, 60.62; H, 7.46.

A **picrate** was prepared from the free base; m.p. 212° dec.

Anal. Calcd. for $C_{21}H_{23}N_5O_9$: N, 14.31. Found: N, 14.24.

2-*p*-Chlorobenzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine (IXa) Picrate.—Etheral *p*-chlorobenzylmagnesium chloride (VIIa, 0.4 mole) was prepared from *p*,α-dichlorotoluene by the Grignard procedure and added rapidly to a vigorously stirred suspension of 1,3,4-trimethylpyridinium iodide (0.2 mole) in ether. The mixture was stirred for 1.5 hr. and the produt (VIIIa) was obtained by the usual procedures[3] and reduced in a mixture of methanol (250 ml.) and 1 *N* NaOH (100 ml.) with $NaBH_4$ (15 g.). The mixture was stirred overnight at 60°. The usual working procedure[3] gave about 40 g. of a reddish brown oil which was fractionally distilled through a spinning-band column. The desired IXa, a colorless oil, was collected at 103–107° (0.03 mm.), yield 17 g. The oil was found to be homogenous by v.p.c. and t.l.c. A picrate was prepared and recrystallized from a mixture of acetone and ethanol; m.p. 157–158°.

Anal. Calcd. for $C_{21}H_{23}ClN_4O_7$: C, 52.67; H, 4.84; N, 11.70. Found: C, 52.76; H, 5.04; N, 11.46.

The n.m.r. spectrum of IXa was consistent with the proposed structure. It showed a 6-proton apparent singlet at 1.58 p.p.m. for the two methyl groups on a double bond, the N-methyl singlet at 2.31 p.p.m., and a 4-proton singlet for the phenyl protons at 7.15 p.p.m.

α-2′-Chloro-2,5,9-trimethyl-6,7-benzomorphan (Xa).—The tetrahydropyridine (IXa, 15 g.) was dissolved in hydrobromic acid (48%, 450 g.) to give a clear brown solution. It was stirred at 145° for 65 hr. to give a fairly clear, darker brown mixture with a small amount of gum. The usual working procedure[3] was followed to give a brown oil, 14 g. The oil was distilled (118–125°, 0.1 mm.) to give the free base Xa.

Anal. Calcd. for $C_{15}H_{20}ClN$: C, 72.13; H, 8.07. Found: C, 72.09; H, 7.91.

A **picrate** was prepared and recrystallized from a mixture of ethanol and acetone; m.p. 208–210°.

Anal. Calcd. for $C_{21}H_{23}ClN_4O_7$: C, 52.67; H, 4.84; N, 11.70. Found: C, 52.93; H, 4.97; N, 11.98.

The picrate was reconverted to the free base which was distilled and converted to the hydrochloride, m.p. 254–255°.

Anal. Calcd. for $C_{15}H_{21}Cl_2N\cdot 1.5H_2O$: C, 57.50: H, 7.72; Cl, 11.32; active H, 1.29. Found: C, 57.58; H, 7.85; Cl, 11.61; active H, 1.17.

The n.m.r. spectrum of the free base was consistent with the desired structure. It showed a doublet at 0.82 p.p.m. (J = 7 c.p.s.) for the 9α-methyl, and a singlet at 1.35 p.p.m. for the 5-methyl.[11]

α-2′-Chloro-2,5,9-trimethyl-6,7-benzomorphan (XIa) methiodide was prepared according to the usual procedures[12]; m.p. 264–265°.

Anal. Calcd. for $C_{16}H_{23}ClIN$: C, 49.06; H, 5.92. Found: C, 49.17; H, 5.63.

1,2-Dimethylnaphthalene (XIIIa) Picrate.—The methiodide (XIa) was treated with 10% NaOH at reflux temperature[4,7] to give XIIa (0.9 g.). This oil was mixed intimately with 5% Pd–C (0.9 g.) and heated to 320° for 30 min. The cooled mixture was extracted with ether and gave, after dilute HCl extraction of the combined ethereal solution, an oil (0.19 g.). A picrate (80 mg.) was prepared from the oil; m.p. 128–130°. It was identical with that of the known 1,2-dimethylnaphthalene[5b] (melting point and mixture melting point). Individual and mixture v.p.c. showed identical retention times of 1.9 min. The infrared and n.m.r. spectra corroborated the structure.

Anal. Calcd. for $C_{18}H_{15}N_3O_7$: C, 56.11; H, 3.92. Found: C, 56.0; H, 3.91.

2-*p*-Fluorobenzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine (IXb).—Ethereal *p*-fluorobenzylmagnesium bromide (VIIb, 0.25 mole) was prepared from *p*-fluoro-α-bromotoluene (50 g.) by the Grignard procedure and added rapidly to a suspension of 1,3,4-trimethylpyridinium iodide (62.5 g.) in ether. This reaction and the subsequent reduction of the product VIIIb with $NaBH_4$ as described in the preparation of IXa, gave a yellow oil, 16 g.

(10) Melting points were taken in a capillary (Hershberg apparatus, total immersion thermometers). Microanalyses were performed in the Microanalytical Services Section of this Institute. The thin layer chromatography procedures, both analytical and preparative, were carried out using silica gel G (Merck, Darmstadt), with a solvent system of ethanol–dioxane–benzene–NH_4OH, 5:40:50:5.[2] The products were detected by spraying with potassium iodoplatinate reagent. A Research Specialties vapor phase chromatograph was used with a 6-ft. coiled glass column, 0.25-in. o.d., packed with 5% SE-30 on 80–100 mesh Chromosorb G, DMCS. It was equipped with a flame ionization detector. The chromatograph was run isothermally at a column temperature of 165°. N.m.r. spectra were taken on a Varian Model A 60 spectrophotometer in $CDCl_3$ solution, using tetramethylsilane as the internal standard.

(11) S. E. Fullerton, E. L. May, and E. D. Becker, *J. Org. Chem.*, **27**, 2144 (1962).

(12) J. H. Ager, S. E. Fullerton, and E. L. May, *J. Med. Chem.*, **6**, 322 (1963).

The oil was found to be homogenous by v.p.c. and t.l.c., and its n.m.r. spectrum was identical with that of the corresponding 2-*p*-chlorobenzyl compound IXa, except for the phenyl region. A complex 4-proton pattern was obtained centering at about 7 p.p.m.

Anal. Calcd. for $C_{15}H_{20}FN$: C, 77.21; H, 8.64. Found: C, 77.29; H, 8.76.

α-2′-Fluoro-2,5,9-trimethyl-6,7-benzomorphan (Xb).—The tetrahydropyridine (IXb, 6.5 g.) was cyclized in 85% phosphoric acid (80 g.) at 185° for 45 hr. to give 6 g. of a dark brown oil. Both v.p.c. and t.l.c. indicated that the oil was a mixture of two components. Neither fractional distillation through a spinning-band column nor purification through a picrate derivative gave satisfactory separation of the compounds. The oil (2.0 g.) was successfully purified by preparative t.l.c., applying about 220 mg. of the mixture in 1 ml. of chloroform to each of 9 plates. The individual components were detected by spraying a corner of the plate, whereupon the individual silica gel containing components were scraped off the plates. They were extracted three times each with $CHCl_3$ and ether after adding dilute NH_4OH to an aqueous suspension of the silica gel, since the compounds would not be removed from the silica gel without adding the base. A pale yellow oil was obtained from the extraction of the lower band. It was distilled to give 1.2 g. of a colorless oil (Xb). This was shown to be homogenous by t.l.c. and v.p.c. The n.m.r. spectrum was consistent with the structure of the desired product and very similar to the spectrum of Xa.

Anal. Calcd. for $C_{15}H_{20}FN$: C, 77.21; H, 8.64. Found: C, 77.05; H, 8.41.

A **hydrochloride** salt was prepared and recrystallized from a mixture of acetone and ether; m.p. 88–92°, followed by partial resolidification and complete melting at 208–212° dec.

Anal. Calcd. for $C_{15}H_{21}ClFN \cdot 1.5H_2O$: C, 60.69; H, 8.15; N, 4.71; active H, 1.37. Found: C, 60.19; H, 8.09; N, 4.59; active H, 1.41.

The **methiodide** of XIb melted at 260–261° dec.

Anal. Calcd. for $C_{16}H_{23}FIN$: C, 51.21; H, 6.18. Found: C, 51.45; H, 6.44.

3,4-Dihydro-1,2-dimethyl-1-(2-dimethylaminoethyl)-7-fluoronaphthalene (XIIb).—Methiodide XIb (1.7 g.) and 20 ml. of refluxing (1–2 hr.) 10% NaOH gave from ether extraction 1.2 g. of a colorless oil. Its n.m.r. spectrum, identical with that of XIIa except for the 3-proton aromatic region, showed singlets at 1.25 (5-CH_3) and 2.12 p.p.m. (N-CH_3), doublets at 0.87 (J = 7 c.p.s., 9-CH_3) and 6.32 p.p.m. (J = 9 c.p.s., α-styrene-type proton), and a quartet centered at 5.82 p.p.m. (β-styrene proton due to coupling with both the α-styrene and allylic hydrogen).

Anal. Calcd. for $C_{16}H_{22}FN$: C, 77.69; H, 8.96. Found: C, 77.95; H, 8.75.

1,2-Dimethyl-7-fluoronaphthalene (XIIIb) Picrate.—Compound XIIb (0.9 g.) as described for the aromatization of XIIa, gave, after distillation (125°, 0.1 mm.), 0.23 g. of colorless XIIIb (whose ultraviolet spectrum indicated a naphthalene structure) contaminated with a product that absorbed in the 0.8–1.2-p.p.m. region of the n.m.r. spectrum. A picrate was prepared and recrystallized from acetone–ethanol; m.p. 101–102°.

Anal. Calcd. for $C_{18}H_{14}FN_3O_7$: C, 53.60; H, 3.50; N, 10.42. Found: C, 53.84; H, 3.72; H, 10.43.

Analgesics. Some Substituted 2,3-Dihydro-4-quinolones[1]

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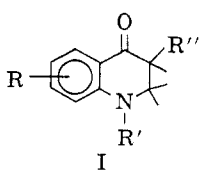
A number of substituted 2,3-dihydro-4-quinolones were prepared by the cyclization of the corresponding β-anilinopropionic acids. Several of these possessed analgesic activity. 1-(*p*-Toluenesulfonyl)-2,3-dihydro-4-quinolone and its 8-methoxy analog were converted to their enamines by reaction with pyrrolidine and alkylated with ethyl acrylate. The resulting products were hydrolyzed to yield 3-(2,3-dihydro-4-quinolone)propionic acid and its 8-methoxy analog. Derivatives of these compounds were examined for analgesic activity.

A series of substituted 2,3-dihydro-4-quinolones (I) were synthesized and examined for biological activity. These compounds were selected for study because of structural resemblances to morphine, meperidine, and other synthetic analgesics, and because the ring system provided a number of opportunities for molecular modification. In this study such modification included (1) replacement of the hydrogen atom on the heterocyclic nitrogen atom by alkyl, alkenyl, or aralkyl groups; (2) substitution on the aromatic ring; and (3) substitution on the carbon atom at the 3-position of I.



I

R = CH_3, Cl, OCH_3, or OC_2H_5
R′ = H, alkyl, allyl, or benzyl
R″ = CH_2CH_2COR'''

The desired 2,3-dihydro-4-quinolones (Table I) with substituents on the heterocyclic nitrogen atom or on the aromatic ring were prepared by the cyclization of the corresponding substituted β-anilinopropionic acids or by alkylation of substituted 2,3-dihydro-4-quinolones.

The required β-anilinopropionic acids were readily obtained by the addition of the substituted anilines to propiolactone[2] (Table II). This synthesis proved particularly advantageous when an N-alkylaniline was used and appeared simpler than the two-step synthesis which involved addition of the amine to an acrylic ester, followed by hydrolysis to give the β-anilinopropionic acid.[3] When the β-anilinopropionic acids were heated in polyphosphoric acid, satisfactory yields of the quinolones were obtained. Studies using thin layer chromatography indicated that at temperatures higher than those specified for the condensation, appreciable quantities of substituted anilines were formed. These undoubtedly resulted

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(2) T. L. Gresham, J. E. Jansen, F. W. Shaver, R. A. Bankert, and F. T. Fiedorek, *J. Am. Chem. Soc.*, **73**, 3168 (1957).

(3) W. S. Johnson, E. L. Woroch, and B. G. Buell, *ibid.*, **71**, 1901 (1949).