Azamorphinan and Related Compounds. III.[1] Syntheses of 3-Hydroxy-*N*-substituted-9-azamorphinans[2]

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Three kinds of 3-hydroxy-*N*-alkyl-9-azamorphinan (XX, XXI, and XXII) were synthesized by several methods in order to obtain a potent analgetic agent. The *N*-phenethyl compound XXII was the most effective.

We had reported the syntheses of several types of azabenzomorphans (I–V)[4] and 3-hydroxy-*N*-methyl- (VI)[1a] and 3-methoxy-*N*-alkyl-9-azamorphinans (VII–XII),[1b] prepared in order to obtain drugs acting on the CNS, and we found VI to have a strong analgetic activity. In this paper, we wish to report the demethylation of 3-methoxy-*N*-substituted-9-azamorphinans and the introduction of several kinds of N-substituents in 3-hydroxy-9-azamorphinan (XXVI), in a search for more effective analgetic agents than VI. We also report an alternative synthesis of 3-hydroxy-*N*-phenethyl-9-azamorphinan (XXII) which compound shows a strong analgetic activity and no suppression of withdrawal symptoms in monkeys physically dependent on morphine.

Demethylation of VII and X was carried out with 47% HBr in AcOH or with pyridine·HCl by fusion to give the corresponding 3-hydroxy compounds VI[1a] and XXII, respectively.

Introduction of N-alkyl groups was examined by preparing 3-hydroxy-9-azamorphinan (XXVI) from VIII, acylating and reducing as shown on Scheme I to give XX, XXI, and XXII. The structures of the N,O-diacyl and N-alkyl compounds were identified by spectroscopic methods and microanalyses. On the other hand, monobenzoylation of XXVI with BzCl, followed by reduction, gave the target compound XX, but the yield in this method was inferior to the method *via* the N,O-diacyl compound.

As 3-hydroxy-*N*-phenethyl-9-azamorphinan (XXII) revealed the most effective analgetic activity in this series, we investigated a simple synthesis of this compound. 2-(3-Methoxyphenyl)cyclohexanone (XIVa)[5] was treated with ethyl bromoacetate and the resulting γ-ketocarboxylic acid (XVa) was converted into the octahydrocinnoline derivative XVIa by refluxing with phenethylhydrazine[6] in aq EtOH. XVIa was identified by ir spectrum; reduction with LAH gave the decahydrocinnoline derivative XVIIa, which was subjected to a Pictet–Spengler reaction with formalin and HCl to give 3-methoxy-*N*-phenethyl-9-azamorphinan (X). The structure of X was identified by mmp, ir, and nmr (δ in $CDCl_3$, 4.50 ppm, $C_{10}H_2$) comparisons with an authentic sample.[1b] Demethylation of X afforded XXII in 41% yield.

In order to improve the yield in the demethylation, the synthesis and debenzylation of 3-benzyloxy-*N*-phenethyl-9-azamorphinan (XVIII), whose benzyl group could be easily removed, were examined as follows. Benzyne reaction of 2-benzyloxychlorobenzene with cyclohexanone or its enamine afforded 2-(3-benzyloxyphenyl)cyclohexanone (XIVb),[5] which was condensed with ethyl bromoacetate in the presence of NaH or $NaNH_2$, followed by hydrolysis, to give γ-ketocarboxylic acid XVb. The fusion of XVb with phenethylhydrazine furnished the octahydrocinnoline XVIb, which was reduced with LAH to afford the decahydrocinnoline XVIb in good yield. In this case, further synthetic variation improved the yield of XVI. For this purpose, condensation of carboxylic acid XVa with phenethylhydrazine in dil EtOH in the presence of KOH was carried out to give the octahydrocinnoline derivative XVIb in 92.5% yield. Pictet–Spengler reaction of XVIIb as usual, followed by debenzylation of the resulting 9-azamorphinan (XVIII) with concd HCl in EtOH, gave the expected 3-hydroxy-*N*-phenethyl-9-azamorphinan (XXII) in good yield.

The decahydrocinnoline XVIIb was debenzylated with HCl and the phenolic base (XIX) thus obtained was subjected to a Pictet–Spengler reaction with formalin and HCl to give XXII.

The analgetic activity of 3-hydroxy-*N*-phenethyl-9-azamorphinan (XXII) was examined by comparison with morphine by a hot plate technique. Male albino mice dd strain (16–21 g) were used. After ip injection of the drugs to 10 animals as one group, the effective ratio till 50 min was calculated by the method of Takagi and Kameyama,[7] and the ED_{50} was calculated by the Lichfield–Wilcoxone method[8] (Table I).

Experimental Section[9]

2-(3-Benzyloxyphenyl)-2-hydroxycarbonylmethylcyclohexanone (XVb).—To a suspension of 8.2 g of 55% NaH in 150 ml of Et_2O was added dropwise 41.0 g of 2-(3-benzyloxyphenyl)-cyclohexanone (XIVb) in 150 ml of PhH with stirring and warming, and, after refluxing for 6 hr, a soln of 29.3 g of ethyl bromo-

(1) (a) Part I: T. Kametani, K. Kigasawa, M. Hiiragi, and N. Wagatsuma, *Chem. Pharm. Bull.*, **16**, 296 (1966); (b) Part II: T. Kametani, K. Kigasawa, M. Hiiragi, K. Wakisaka, and N. Wagatsuma, *ibid.*, **17**, 1096 (1969).

(2) Part CCCLXXX of "Studies on the Syntheses of Heterocyclic Compounds," by T. Kametani.

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(4) (a) T. Kametani, K. Kigasawa, M. Hiiragi, T. Hayasaka, and T. Iwata, *Yakugaku Zasshi*, **84**, 405 (1964); (b) T. Kametani, K. Kigasawa, and M. Hiiragi, *ibid.*, **85**, 871 (1965); (c) T. Kametani, K. Kigasawa, M. Hiiragi, and H. Ishimaru, *Chem. Pharm. Bull.*, **13**, 295 (1965); (d) T. Kametani, K. Kigasawa, and T. Hayasaka, *ibid.*, **13**, 300 (1965); (e) T. Kametani, K. Kigasawa, and M. Hiiragi, *ibid.*, **13**, 1220 (1965). (f) T. Kametani, K. Kigasawa, and T. Hayasaka, *ibid.*, **13**, 1225 (1965).

(5) T. Kametani, *J. Chem. Soc. C*, in press.

(6) J. H. Biel, U. S. Patent 3,000,903; *Chem. Abstr.*, **56**, 1393 (1962).

(7) K. Takagi and T. Kameyama, *Yakugaku Zasshi*, **77**, 871 (1957).

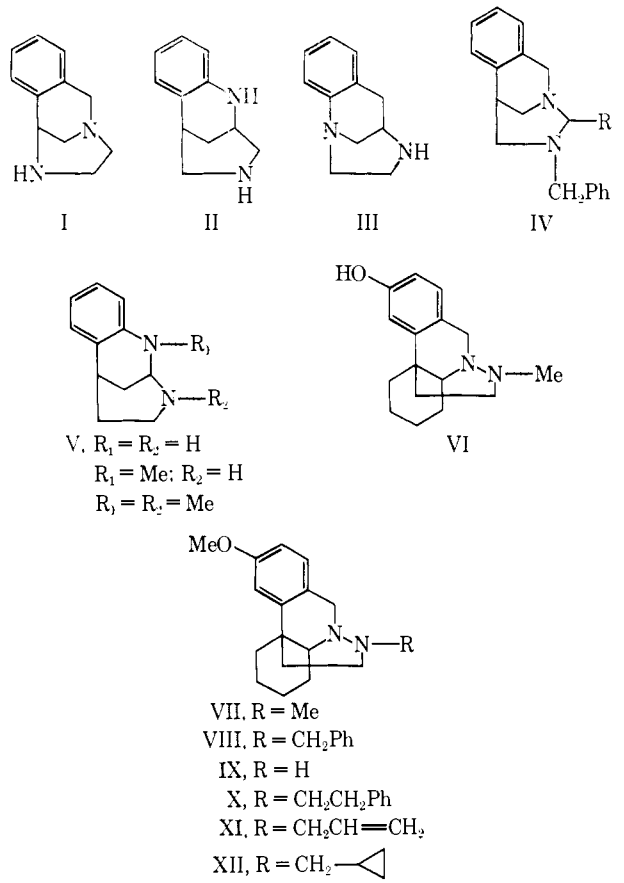
(8) J. T. Lichfield and F. Wilcoxone, *J. Pharmacol.*, **96**, 99 (1949).

(9) All melting points were measured in capillary tubes in a bath and are not corrected. Nmr spectra were taken on a Hitachi H-60 and JNM-NH-60 (Me_4Si).

TABLE I

Compd	ED_{50}, mean value (mg/kg)	95% Fiducial limit (mg/kg)
XXII	11.6	9.6–14.0
Morphine	4.0	2.9–5.6

CHART I



acetate in 30 ml of PhH was added dropwise to the reaction mixture. Refluxing was continued for a further 3 hr with stirring. To the cooled reaction mixture was added H_2O to decompose the excess of NaH, and the organic layer was sepd and washed with (satd aq NaCl), dried (Na_2SO_4), and evapd to leave 49 g of Et ester of XVb as a reddish brown oil [ir ν_{max}^{liquid} cm^{-1}, 1720 and 1705 (C=O)]. The crude ester was refluxed with a mixture of 18 g of NaOH, 150 ml of EtOH, and 150 ml of H_2O for 1.5 hr and then EtOH was distd off. The residue was washed (Et_2O) and the aq layer was acidified (concd HCl) to ppt 13.5 g (30.1%) of colorless needles, which were recrystd from EtOH to give XVb as colorless needles: mp 143–145°; ir ν_{max}^{KBr} cm^{-1}, 1720 and 1710 (C=O); nmr δ (in $CDCl_3$–CCl_4) 4.96 (2 H, s, OCH_2Ph). *Anal.* ($C_{21}H_{22}O_4$) C, H.

3-Keto-4a-(3-methoxyphenyl)-2-phenethyl-2,3,4,4a,5,6,7,8-octahydrocinnoline (XVIa).—To a mixture of 25 g of γ-ketocarboxylic acid (XVa), 8.0 g of KOH, 50 ml of H_2O, and 60 ml of EtOH was added a soln of 21 g of phenethylhydrazine·HCl in 30 ml of H_2O and the mixture was heated on a water bath for 10 hr. The sepd crystals were collected and recrystd from MeOH to give 15.8 g (45.7%) of XVIa as colorless prisms: mp 120–121° (lit.[10] mp 119°); ir ν_{max}^{KBr} cm^{-1}, 1660 (C=O).

4a-(3-Benzyloxyphenyl)-3-keto-2-phenethyl-2,3,4,4a,5,6,7,8-octahydrocinnoline (XVIb).—(a) A mixture of 11.3 g of γ-ketocarboxylic acid (XVb) and 5.5 g of phenethylhydrazine was heated at 185–195° for 3 hr in a current of N_2 and the H_2O generated during the reaction was removed. The cooled reaction mixture was triturated with EtOH to afford 9.7 g (66.5%) of colorless crystals, which were recrystd from EtOH to give (XVIb) as colorless prisms: mp 100–102°; ir ν_{max}^{KBr} cm^{-1}, 1670 (C=O); nmr δ (in $CDCl_3$) 2.90 (2 H, t, J = 8.0 Hz, NCH_2CH_2Ph), 3.94 (2 H, t, J = 8.0 Hz, NCH_2CH_2Ph), 4.93 (2 H, s, OCH_2Ph). *Anal.* ($C_{29}H_{30}O_2N_2$) C, H, N.

(10) K. Mitsubashi and S. Shiotani, *Yakugaku Zasshi*, **80**, 1348 (1960).

(b) A mixture of 1.0 g of γ-ketocarboxylic acid, 0.62 g of phenethylhydrazine·HCl, 0.21 g of KOH, 3 ml of EtOH, and 3 ml of H_2O was refluxed for 3 hr. After the reaction, an oil formed was sepd by decantation and triturated with EtOH, followed by recrystn, to give 1.2 g (92.5%) of colorless prisms (XVIb), which were identical with the sample prepared by method a.

4a-(3-Methoxyphenyl)-2-phenethyldecahydrocinnoline (XVIIa)·HCl.—A soln of XVIa in 150 ml of dioxane was added dropwise to a suspension of 15 g of LAH in 200 ml of dry dioxane with stirring and refluxing during 0.5 hr and the mixture was refluxed for 6 hr. Excess LAH was decompd with H_2O under cooling and the organic layer was sepd, dried (K_2CO_3), and satd with HCl gas. Solvent was removed by distn to leave crystals, which were recrystd from *i*-PrOH–Et_2O to give 23.3 g (70.6%) of XVIIa·HCl as colorless needles: mp 209–211° dec; ir ν_{max}^{KBr} cm^{-1}, 3160 (NH). *Anal.* ($C_{23}H_{31}ON_2Cl$) C, H, N.

4a-(3-Benzyloxyphenyl)-2-phenethyldecahydrocinnoline (XVIIb)·HCl.—To a suspension of 15 g of LAH in 100 ml of dry dioxane was added dropwise 9 g of XVIb in 100 ml of dioxane with stirring and the mixture was refluxed for 5.5 hr. After reaction, excess LAH was decompd with 30% aq NaOH with ice-cooling and the organic layer was collected, dried (K_2CO_3), and satd with HCl gas. Dioxane was distd to leave a yellow caramel, which was recrystd from *i*-PrOH–Et_2O to give 3.95 g (41.5%) of XVIIb·HCl as colorless needles: mp 203–206°; ir ν_{max}^{KBr} cm^{-1}, 3160 (NH). *Anal.* ($C_{29}H_{35}ClN_2O$) C, H, N.

3-Methoxy-*N*-phenethyl-9-azamorphinan (X)·HCl.—A mixture of 20 g of XVIIa·HCl, 60 ml of H_2O, 60 ml of 37% CH_2O, 100 ml of EtOH, and 10 ml of concd HCl was heated on a water bath for 4 hr and then EtOH was distd off. The residue was basified (10% aq NaOH) and extracted with $CHCl_3$. The extract was washed (H_2O), dried (K_2CO_3), and evapd to leave an oil, which was dissolved in Et_2O and satd with HCl gas to leave 18.7 g (90.8%) of X·HCl as colorless needles after recrystn from *i*-PrOH–Et_2O: mp 179–180.5°; nmr δ (in $CDCl_3$) 4.50 (2 H, s, $ArCH_2N$). The ir spectrum (KBr) and mp were identical with those of an authentic sample.[1b]

3-Benzyloxy-*N*-phenethyl-9-azamorphinan (XVIII)·HCl.—A mixture of 2 g of XVIIb·HCl, 1 ml of concd HCl, 6 ml of 37% CH_2O, 6 ml of EtOH, and 6 ml of H_2O was refluxed on a water bath for 4 hr and the solvent was distd to leave a pale brown caramel, which was recrystd from EtOH–Et_2O to give 1.35 g (65.9%) of XVIII·HCl as colorless prisms: mp 201–203°; ir ν_{max}^{KBr} cm^{-1}, 3405 (OH of H_2O of crystn). *Anal.* ($C_{30}H_{35}ClN_2O\cdot 0.5H_2O$) C, H, N.

4a-(3-Hydroxyphenyl)-2-phenethyldecahydrocinnoline (XIX)·HCl.—A soln of 450 mg of XVIIb·HCl in 30 ml of concd HCl and 30 ml of EtOH was refluxed for 1.5 hr. The solvent was removed by distn to leave a solid, which was recrystd from EtOH to give 320 mg (88.5%) of XIX·HCl as colorless needles, mp 233–235°. *Anal.* ($C_{22}H_{29}ClN_2O$) C, H, N.

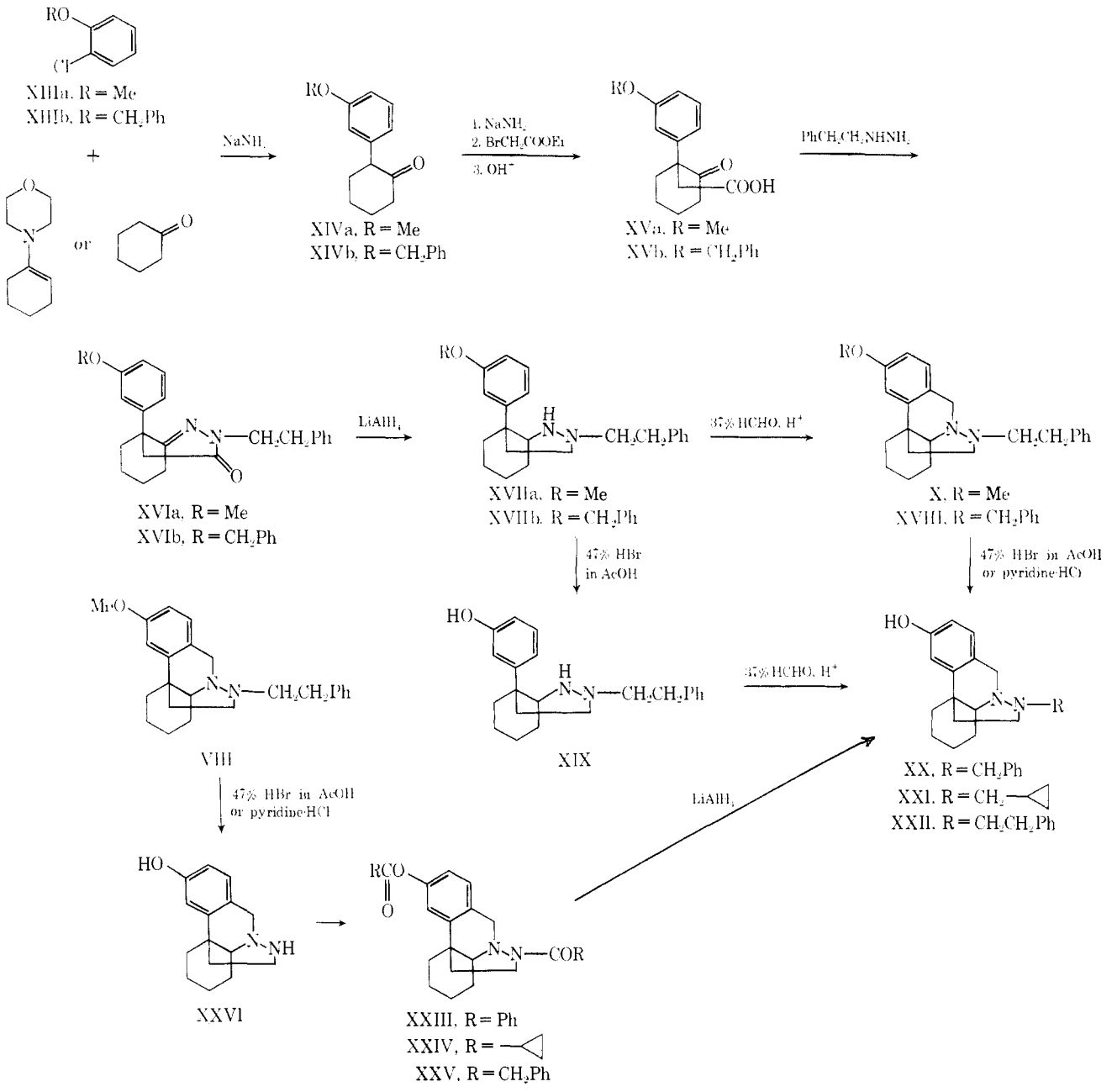
3-Hydroxy-*N*-phenethyl-9-azamorphinan (XXII).—(A) A mixture of 4.0 g of X·HCl, 160 ml of 47% HBr, and 160 ml of AcOH was refluxed for 1.5 hr in an oil bath (bath temp 135–145°), and the mixture was condensed to 50 ml *in vacuo*. The residue was basified (28% NH_4OH) and extracted ($CHCl_3$). The extract was washed (H_2O), dried (Na_2SO_4), and evapd to leave a solid, after trituration with Et_2O, which was recrystd from EtOH to give 14.3 g (41.0%) of XXII as colorless prisms: mp 178–180°; ir ν_{max}^{KBr} cm^{-1}, 2700–2200 (N^+H). XXII·HCl was recrystd from EtOH–Et_2O to give colorless needles: mp 239–241° dec; ir ν_{max}^{KBr} cm^{-1}, 3230 (OH); nmr (δ in $CDCl_3$) 3.98 (2 H, broad s, $ArCH_2N$). *Anal.* ($C_{23}H_{29}ON_2Cl$) C, H, N.

(B) A mixture of 4.0 g of X·HCl and 20 g of pyridine·HCl was heated at 200–210° for 5 min in a current of N_2. After cooling, 40 ml of H_2O was added to the reaction mixture which was basified (28% NH_4OH) and extracted ($CHCl_3$). The extract was washed (H_2O), dried ($MgSO_4$), and evapd to leave a residue, which was subjected to column chromatography on 40 g of $SiO_2\cdot xH_2O$ using $CHCl_3$ as an eluant. The first eluate gave 2.0 g of the starting material and the second one afforded 1.0 (28.6%) of XXII, which was identical by mp and ir spectral comparisons with the sample prepared by method A.

(C) A soln of 1.3 g of XVIII·HCl in 70 ml of concd HCl and 70 ml of EtOH was refluxed for 1 hr on a water bath. After evapn of the solvent, the residue was recrystd from EtOH–Et_2O to give 0.9 g (85.5%) of XXII·HCl which was identical in all aspects with an authentic sample.

(D) A mixture of 230 mg of XIX·HCl, 0.2 ml of concd HCl,

SCHEME I



1.2 ml of 37% CH_2O, 2 ml of EtOH, and 1.2 ml of H_2O was refluxed for 5 hr, and the solvent was removed by distn to give 150 mg (63.0%) of XXII·HCl as colorless needles after recrystn from EtOH–Et_2O, mp 239–241°, which showed the same physical data as those of an authentic sample.

3-Hydroxy-9-azamorphinan (XXVI).—(A) A soln of 4.2 g of VIII·HCl in 50 ml of 47% HBr and 50 ml of AcOH was heated at 140–150° in an oil bath, and condensed to 10 ml *in vacuo*. To the residue was added 100 ml of $CHCl_3$ and the mixture was basified (28% NH_4OH). The organic layer was sepd, washed (H_2O), dried (Na_2SO_4), and evapd to leave a yellow caramel, which was recrystd from *i*-PrOH to give 1.5 g (67.5%) of XXVI as colorless prisms: mp 270–271° dec; ir ν_{max}^{KBr} cm^{-1}, 2800–2250 (NH); nmr (δ in CF_3COOH) 4.46 and 4.87 (each 1 H, d, J = 17.5 Hz, ArC**H**$_2$N). *Anal.* ($C_{15}H_{29}ON_2$) C, H, N.

(B) Pyridine·HCl (20 g) which was dried by fusion at 250° was added to 3.8 g of VIII·HCl and the resulting mixture was heated at 210–220° for 15 min. Then 10% aq NaOH (50 ml) was added to the cooled mixture and this was washed (Et_2O) and acidified (concd HCl). The aq soln was basified (28% NH_4OH) and extracted ($CHCl_3$). The extract was washed (H_2O), dried (Na_2SO_4), and evapd to leave a solid after trituration with EtOH, which was recrystd from EtOH to afford 0.84 g (35.0%) of XXVI as colorless prisms, mp 270–271° dec. This product was identical with an authentic sample prepared by method A by mmp and spectral comparisons.

3-Benzyloxy-*N*-benzoyl-9-azamorphinan (XXIII).—To a soln of 1.0 g of XXVI in 150 ml of $CHCl_3$ was added 1.4 g of BzCl in the presence of 0.4 g of NaOH and 100 ml of H_2O at room temp with stirring. After stirring for a further 1 hr, the organic layer was sepd and washed (10% aq NaOH and H_2O), dried (K_2CO_3), and evapd to leave crystals after trituration with hexane. The compd was recrystd from *i*-PrOH to give 0.76 g (41.0%) of XXIII as colorless prisms: mp 180–182°; ir ν_{max}^{KBr} cm^{-1} 1725 and 1640 (C=O). *Anal.* ($C_{29}H_{28}N_2O_3$), C, H, N.

3-Cyclopropionyloxy-*N*-cyclopropionyl-9-azamorphinan (XXIV).—A 5% aq NaOH soln (50 ml) was added to a suspension of 2.4 g of XXVI in 100 ml of Et_2O and then to this mixture was added with shaking 2.0 g of cyclopropionyl chloride. After shaking for 1 hr, the organic layer was sepd and washed (10% aq NaOH and H_2O). The dried (K_2CO_3) solvent was removed by distn to give an amorphous powder, which was recrystd from *i*-PrOH to afford 1.4 g (37.6%) of XXIV as colorless prisms: mp 175–177°; ir ν_{max}^{KBr} cm^{-1}, 1745 and 1640 (C=O).

3-Phenacetyloxy-*N*-phenacetyl-9-azamorphinan (XXV).—Phenacetyl chloride (3 g) was added to a suspension of 1.5 g

of XXVI in 200 ml of Et_2O and 300 ml of 5% aq NaOH with shaking at room temp, and the shaking was continued for a further 1 hr. The organic layer was sepd, washed (10% aq NaOH and H_2O), dried (K_2CO_3), and evapd to leave 2.6 g (88.1%) of XXV as a colorless oil: ir ν_{max}^{liquid} cm^{-1}, 1755 and 1645 (C=O).

3-Hydroxy-*N*-benzyl-9-azamorphinan (XX).—A suspension of 0.5 g of XXIII and 1.0 g of LAH in 100 ml of dry dioxane was refluxed for 6 hr and then the excess of LAH was decompd with H_2O. The organic layer was collected by decantation, dried ($MgSO_4$), and evapd to leave a solid, after trituration with hexane, which was recrystd from PhH–hexane to give 0.25 g (67.6%) of XX as colorless needles, mp 124–125°. XX·HCl was recrystd from EtOH to afford colorless needles: mp 245° dec; ir ν_{max}^{KBr} cm^{-1}, 3200 (OH); nmr δ (in CF_3COOH), 4.68 (2 H, s, $NCH_2C_6H_5$). *Anal.* ($_{22}H_{27}ClN_2O$), C, H, N.

3-Hydroxy-*N*-cyclopropylmethyl-9-azamorphinan (XXI).—A suspension of 1.3 g of XXIV and 1 g of LAH in 80 ml of dry THF was refluxed for 7 hr, and the excess of LAH was decompd with H_2O. The organic layer was collected by decantation, dried ($MgSO_4$), and evapd to leave a yellow oil, which was solidified on trituration with Et_2O and recrystd from EtOH–Et_2O to afford 0.8 g (78.4%) of XXI as colorless prisms: mp 172–174°; ir ν_{max}^{KBr} cm^{-1}, 2750–2200 (N^+H); nmr δ (in $CDCl_3$) 4.07 (2 H, s, $ArCH_2N$), 8.26 (1 H, broad s, OH). *Anal.* ($C_{19}H_{26}ON_2$) C, H, N.

3-Hydroxy-*N*-phenethyl-9-azamorphinan (XXII).—A suspension of 2.6 g of XXV and 3.0 g of LAH in 200 ml of dry dioxane was refluxed for 6 hr and the excess LAH was decompd with H_2O. The organic layer was separated by decantation, dried ($MgSO_4$), and evapd to leave a colorless oil, which was solidified by trituration with Et_2O and then recrystd from EtOH to give 1.03 g (50.0%) of XXII as colorless prisms, mp 178–180°. This sample was identical with a standard sample in all aspects.

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Potential Antiinflammatory Agents. Aralkoxyhydrouracils and Aralkoxyhydantoins[1]

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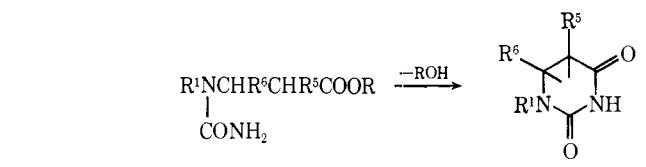
A number of 1-aralkoxyhydrouracils and 1-aralkoxyhydantoins were prepared and evaluated as antiinflammatory agents. The hydrouracils were synthesized by a novel route from *N*-aralkoxyurethans and α,β-unsaturated carboxamides or from *N*-aralkoxyureas and α,β-unsaturated carboxylic esters. The hydantoins were prepared from *N*-aralkoxyureas by alkylation with bromo- or chloroacetic acid, followed by cyclization of the resultant α-ureido acids. The three most active 1-aralkoxyhydrouracils showed activities intermediate between those of aspirin and phenylbutazone against kaolin-induced inflammation of the rat foot. No consistent relationship could be found between the activities of the compounds described herein and the activities of their 1-aralkyl analogs.

Our long-standing interest in hydroxylamine derivatives,[2] bolstered by the finding that certain 1-aralkylhydrouracils possess antiinflammatory activity,[3] led us to investigate the synthesis and biological activity of a series of 1-aralkoxyhydrouracils (Table I) and 1-aralkoxyhydantoins (Table II). We first attempted to synthesize the 1-aralkoxyhydrouracils by the classical reaction sequence shown in Scheme I.[4]

SCHEME I



When R^1 is alkyl, the β-amino ester starting material may be prepared by addition of an amine to an α,β-unsaturated ester, by aminomethylation of an appropriately substituted malonic ester followed by decarboxylation, or by reduction of an enamine of a β-keto ester. However, when R^1 is aralkoxy, we found that only benzyloxyamine and a few ring-substituted benzyloxyamines could be added to ethyl acrylate and these amines failed to add to methyl methacrylate. The aminomethylation reaction and enamine reduction also failed to yield the esters needed for cyclization to C-5 and C-6 substituted 1-aralkoxyhydrouracils.

Since the classical sequence (Scheme I) proved to have limited utility in the aralkoxy series, we employed a synthetic route which utilized aralkoxyurethans or aralkoxyureas instead of aralkoxyamines (see Scheme II). This route provided the C-5 and C-6 substituted 1-aralkoxyhydrouracils as well as the C-5 and C-6 unsubstituted members in good yield.

The reaction of I with II depicted in Scheme II and the reaction of aralkoxyamines with acrylic esters both involve a Michael-type addition of a nucleophilic agent to an activated unsaturated system, yet the latter reaction is much more limited in scope than the former. Since the addition is a reversible reaction, we believe this difference is due to the tendency for the adduct III to undergo cyclization driving the addition step toward completion. The amino ester formed by addition of an aralkoxyamine to an acrylic ester cannot cyclize. It is unlikely that the observed difference in scope is a consequence of differences in the strengths of the nucleophilic agents involved.

[1] A portion of this material was presented at the Second International Congress of Heterocyclic Chemistry, Montpellier, France, July 7–11, 1969.

(2) B. J. Ludwig, F. Dürsch, M. Auerbach, K. Tomeczek, and F. M. Berger, *J. Med. Chem.*, **10**, 556 (1967).

(3) F. M. Berger, F. Dürsch, and B. J. Ludwig, U. S. Patent 3,325,360 (1967); *Chem. Abstr.*, **68**, 49642 (1968).

(4) See D. J. Brown, "The Pyrimidines," Interscience, New York, N. Y., 1962, pp 434–435, for a discussion.