SYNTHESIS OF NEW DERIVATIVES OF MORPHINE

II. PRODUCTION OF BENZOYLMORPHINES WITH ANALGESIC ACTION AND BENZYLMORPHINE POSSESSING MORPHINE-POTENTIATING ACTIVITY

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A series of new 3-benzoyl and 3-benzyl derivatives of morphine was synthesized for the production of more effective analgesics than morphine. 3-(m-Trifluoromethylbenzoyl)-morphine and 3-(p-Chlorobenzoyl)-morphine had an analgesic action analogous to that of morphine, without any harmful side effects.

Changes in the A and C rings of morphine are usually accompanied by a substantial change in biological activity. It is known that alkylation of the hydroxyl group in the 3-position weakens the analgesic action. Codeine—a 3-O-methyl ester of morphine—possesses only part of the analgetic properties of morphine, and at the same time, gives the same cough-inhibiting effect [3, 4, 7, 8]. The decrease in the pain-relieving effect as a result of 3-O-methylation also is effective in the case of other morphine derivatives. For example, α-isomorphine is a better pain reliever than isocodeine [9], dihydromorphine is better than dihydrocodeine, dihydro-α-isomorphine is better than dihydrocodeine, dihydroxymorphine is better than dihydroxycodeine, and dihydromorphinone is better than dihydrocodeine.

Methylation or acetylation of the hydroxyl group in the 6-position usually increases the pain-relieving activity. For example, dihydrocodeine is a weaker pain-relieving agent than dihydroheterocodeine, while morphine is weaker than heroin [5, 6], dihydromorphine is weaker than diacetyldihydromorphine [2], etc.

Removal of the hydroxyl group in the 6-position or its conversion to a ketone group increases the pain-relieving activity of the basic compound. Thus, dihydromorphine is a weaker pain reliever than dihydrodeoxymorphine-D, dihydrocodeine is weaker than dihydrodeoxycodeine-D [10], dihydromorphine is weaker than dihydromorphinone, and dihydrocodeine is weaker than dihydrocodeinone [11]. Saturation of the double bond in the 7,8-position in all cases leads to the formation of a derivative of dihydromorphine, which has increased pain-relieving activity. For example, dihydromorphine gives a greater pain-relieving effect than morphine, dihydro-α-isomorphine is stronger than isomorphine, dihydrocodeine is stronger than codeine, and dihydroisocodeine is stronger than isocodeine. It is interesting that in the case of diacetylmorphine, the unsaturated form, on the contrary, exerts a stronger pain-relieving action.

Certain methyl and hydroxyl groups, introduced into the alicyclic ring of morphine, increase the pain-relieving action. For example, dihydrohydroxymorphinone [10] is stronger than dihydromorphinone [12], while dihydrohydroxycodeinone [10] is stronger than dihydrocodeinone [12], and 7-methyldihydromorphinone is stronger than dihydromorphinone [2]. At the same time, 6-methylhydromorphine is a weaker analgesic than dihydromorphine [13].

Table 1 presents the most important morphine derivatives in order of increasing pain-relieving activity. The action of morphine is taken as 100%, while the analgesic activity of the remaining derivatives is expressed in percent of the action of morphine.

We have found no literature data concerning the production or pharmacological investigation of other 3-benzoyl or 3-benzyl derivatives of morphine, except for two basic compounds—3-benzoylmorphine and 3-benzylmorphine.

3-Benzoylmorphine was first described by Becket and Wright [7]. The production of 3-benzylmorphine and the determination of its pharmacological properties were done by Mering. Both compounds exert an analgesic effect. The analgesic action of 3-benzylmorphine is almost the same as that of morphine.

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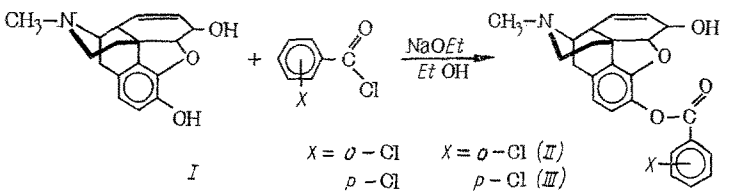
TABLE 1. Pharmacological Properties of Morphine Derivatives

Morphine derivatives	Pain-relieving action (in %)	Duration of pain-relieving action (in min)	Morphine derivatives	Pain-relieving action (in %)	Duration of pain-relieving action (in min)
Pseudocodeine	0.5	145	Morphine	100	129
Morpholinylethylmorphine	1	–	Dihydromorphine	117	154
Diacetyl-N-alkylnormorphine	1	–	Dihydro-α-isomorphine	124	–
N-Propyldihydronormorphine	1	–	Diacetyldihydromorphine	131	–
N-Alkylnormorphine	3	–	Dihydrocodeinone-enol acetate	162	89
Normorphine	5	–	β-Chloromorphide	175	–
Isocodeine	6	–	Diacetylmorphine	233	–
Codeine	15	67	Dihydrohydroxycodeinone	350	169
Dihydrocodeine	17	130	Dihydroheterocodeine	354	117
Dihydroisocodeine	19	147	Methyldihydromorphinone	420	156
6-Methyldihydromorphine	39	140	Dihydromorphinone	700	133
α-Isomorphine	55	148	6-Methyl-Δ^6-deoxymorphinone	1050	–
Dihydrocodeine methyl ester	64	123	Dihydrodeoxymorphine-D	1166	103
Dihydrocodeinone	66	–	Dihydrohydroxymorphinone	1235	122
Dihydrodeoxycodeine-D	72	–			

During our work we produced several derivatives of morphine (I) with substituted benzoyl and benzyl groups.

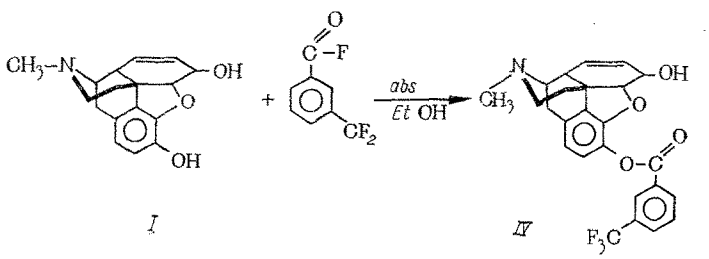
3-Benzoyl derivatives were produced through the sodium salt of morphine, using the corresponding benzoyl halides.

Thus, we obtained 3-(o-chlorobenzoyl)-morphine (II) and 3-(p-chlorobenzoyl)-morphine (III):



I

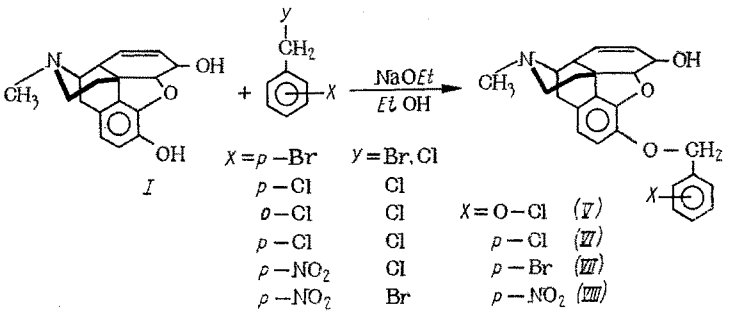
For the production of 3-(m-trifluoromethylbenzoyl)-morphine we used m-trifluoromethylbenzoyl fluoride, which proved to be an unsuitable acylating agent, both according to the Schotten-Baumann method and according to the preceding method, but in absolute ethanol it reacts smoothly with morphine, unambiguously forming 3-(m-trifluoromethylbenzoyl)-morphine (IV):



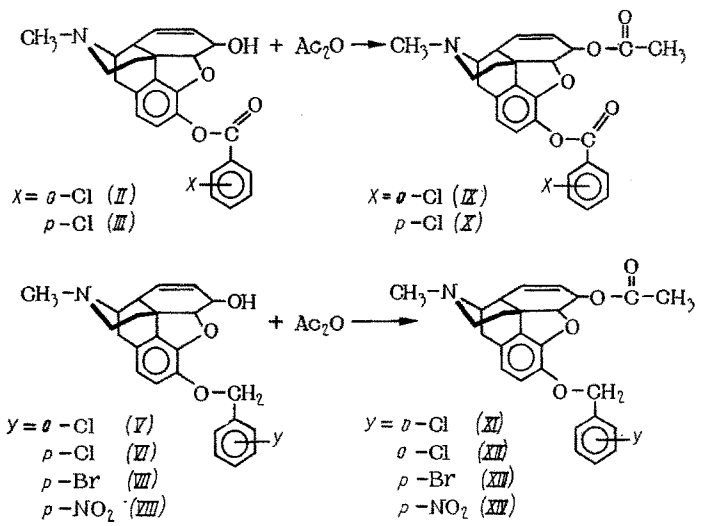
I IV

The Williamson method is the most suitable for synthesizing various 3-benzylmorphines. According to this method, morphine is dissolved in ethanol containing the equivalent amount of sodium ethoxide, and the morphine reacts with various benzyl halides at the boiling point of the alcohol. In our experience, the maximum yield is ensured by p-nitrobenzyl bromide. o- and p-chlorobenzyl or bromobenzyl halides give practically the same yields (55-65%).

Using the Williamson method we succeeded in synthesizing 3-(o-chlorobenzyl)-morphine (V), 3-(p-chlorobenzyl)-morphine (VI), 3-(p-bromobenzyl)-morphine [VII], and 3-(p-nitrobenzyl)-morphine (VIII):



We also studied 6-acetylation of certain 3-benzoyl and 3-benzyl derivatives of morphine, which we synthesized. Various acetyl derivatives, for example, 3-(o-chlorobenzoyl)-6-acetylmorphine (IX), 3-(p-chlorobenzoyl)-6-acetylmorphine (X), 3-(o-chlorobenzyl)-6-acetylmorphine (XI), 3-(p-chlorobenzyl)-6-acetylmorphine (XII), 3-(p-bromobenzyl)-6-acetylmorphine (XIII), and 3-(p-nitrobenzyl)-6-acetylmorphine (XIV), could be produced by the classical method of acetylation in almost quantitative yields:



EXPERIMENTAL *

3-(o-Chlorobenzoyl)-morphine (II). A 28.53-g portion (0.1 mole) of morphine, dried over Al_2O_3, was dissolved with cooling and intensive mixing in an atmosphere of nitrogen in ethanol, containing sodium ethoxide, from 0.1 g-atom of Na. The final volume of the solution was about 600 ml. After half an hour of mixing, 19.25 g (0.11 mole) o-chlorobenzyl chloride was added drop-wise, and the mixture boiled for 4 h. The course of the reaction was followed by thin-layer chromatography. After the end of the reaction the solvent was removed and the dry residue extracted with chloroform. After evaporation of the chloroform we obtained unpurified II, which was recrystallized from 75% methanol. Weight of the crystalline product 21.6 g (51%). Mp 163-164°. Calculated, %: N 3.31. $C_{24}H_{22}O_4NCl$. Found, %: N 3.41.

3-(p-Chlorobenzoyl)-morphine (III). A 28.53-g portion (0.1 mole) of morphine was reacted according to II with 19.25 g (0.11 mole) p-chlorobenzoyl chloride. The unpurified product was recrystallized from 50% ethanol. Weight of the crystalline product 33.1 g (78%). Mp 210°. Calculated, %: N 3.31. $C_{24}H_{22}O_4NCl$. Found, %: N 3.35.

3-(m-Trifluoromethylbenzoyl)-morphine (IV). A 28.53-g portion (0.1 mole) of morpholine base was suspended in 900 ml of absolute ethanol. During ice-cooling and mixing, 21.13 g (0.11 mole) of m-trifluoromethylbenzoyl fluoride was added drop-wise to the suspension, then the reaction mixture was mixed at room temperature for 2 h, the salt precipitated filtered off, and the solvent distilled off. IV was purified through

*All the melting points cited are uncorrected.

the hydrochloride and crystallized from ethanol, yield 23.3 g of a product with mp 155-156°. Calculated, %: N 3.06. $C_{25}H_{22}O_4NF_3$. Found, %: N 3.12.

3-(o-Chlorobenzyl)-morphine (V). A 28.53-g portion (0.1 mole) of morphine base was suspended in 600 ml of ethanol. Sodium ethoxide from 0.1 g-atom of Na was added to the suspension in an atmosphere of nitrogen. After dissolving, 17.71 g (0.11 mole) of o-chlorobenzyl chloride was added in an atmosphere of nitrogen at room temperature and mixed. After 2 h mixing, the solution was boiled with a reflux condenser for 4 h, the precipitated salt filtered off, and the filtrate evaporated to dryness under vacuum. The dry residue was treated with chloroform. After removal of the solvent, the product was extracted twice with 150-ml portions of a 2% sodium hydroxide solution. The residue was dissolved in chloroform, the solution dried over sodium sulfate, and after removal of the solvent, the substance obtained was converted to the tartrate in absolute ethanol. The bitartrate of V was recrystallized twice from 96% ethanol. Yield 63%, mp 174-180°. Calculated, %: N 2.51. $C_{24}H_{24}O_3NCl$ (V). Found, %: N 2.45.

3-(p-Chlorobenzyl)-morphine (VI) was produced analogously to V. Yield 40%, mp 128-130°. Calculated, %: N 3.14. $C_{24}H_{24}O_3NCl$. Found, %: N 3.15.

3)p-Bromobenzyl)-morphine (VII) was produced analogously to V. Yield 48%, mp 152°. Calculated, %: N 2.85. $C_{24}H_{24}O_3NBr$. Found, %: N 2.84.

3-(p-Nitrobenzyl)-morphine (VIII) was produced analogously to V. Yield 65%, mp 103-104°. Calculated, %: N 6.57. $C_{24}H_{24}O_5N_2$. Found, %: N 6.56.

3-(o-Chlorobenzoyl)-6-acetylmorphine (IX). A 42.38-g portion (0.1 mole) of II was added to 200 ml of freshly redistilled acetic anhydride. After heating for 1 h on a boiling water bath, it was poured out onto ice and neutralized with a 10% solution of ammonia. The IX deposited was filtered, washed with cold water, and recrystallized from methanol. mp 141-142°. Yield 92%. Calculated, %: N 3.00. $C_{26}H_{24}O_5NCl$. Found, %: N 3.03.

3-(p-Chlorobenzoyl)-6-acetylmorphine (X) was produced analogously to IX. The unpurified product was recrystallized from 70% ethanol. Yield 90%, mp 167-168°. Calculated, %: N 3.00. $C_{26}H_{24}O_5NCl$. Found, %: N 3.10.

3-(o-Chlorobenzyl)-6-acetylmorphine (XI) was produced analogously to IX. Recrystallized from 70% ethanol. Yield 74%, mp 113-115°. Calculated, %: N 3.10. $C_{26}H_{26}O_4NCl$. Found, %: N 3.10.

3-(p-Chlorobenzyl)-6-acetylmorphine) (XII) was produced analogously to IX. Crystallized from 70% ethanol. Yield 60%, mp 125-126°. Calculated, %: N 3.10. $C_{26}H_{26}O_4NCl$. Found, %: N 2.99.

3-(p-Bromobenzyl)-6-acetylmorphine (XIII) was produced analogously to IX. Crystallization from methanol. Yield 93%, mp 135°. Calculated, %: N 2.89. $C_{26}H_{26}O_4NBr$. Found, %: N 3.04.

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