Recent Discoveries in the Search for Non-Opiate Analgetics

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Dedicated to Professor John C. Sheehan on the occasion of his sixty-fifth birthday.

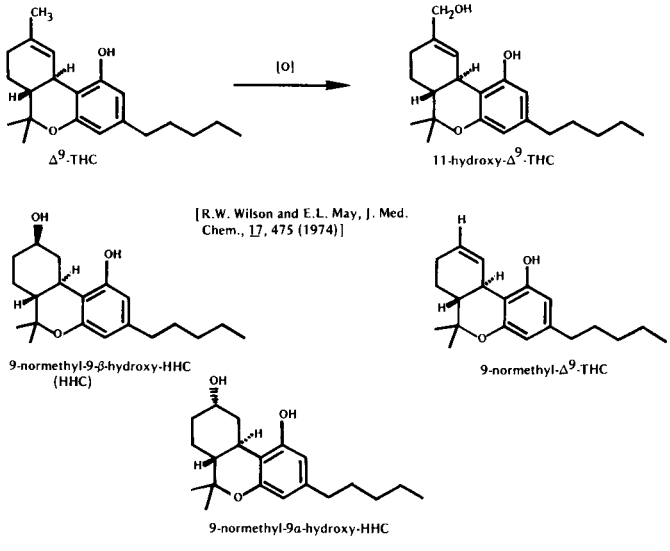
A novel phenanthridine, nantradol (**1**), resulted from a search to dissect out analgetic activity from the cannabinoid molecule. Nantradol possesses two to seven times greater potency than morphine across a battery of analgetic tests. Despite this morphine-like profile, nantradol does not bind to the opiate receptor. Nantradol has a total of five asymmetric centers and was studied as a 50:50 mixture of two diastereomers, both of which possess the *trans* 6a, 10a stereochemistry and have β-oriented substituents at positions 6 and 9. Evidence is provided that, in common with the opiates, the analgetic actions of nantradol are stereospecific, the majority of the activity residing in a single levorotatory isomer. The stereospecificity and potency of the analetic effects of the nantradol series suggests a highly specific interaction at an as yet unidentified receptor.

J. Heterocyclic Chem., **17**, 1817 (1980).

Sir:

Various preparations from the plant *Cannabis satavia*, including marihuana and hashish, have been used for nearly 5000 years for a variety of social and medicinal properties including pain relief (1,2). Until quite recently, reports of the analgetic activity of the natural cannabinoids in animals and man could best be described as equivocal (3-7). The availability of the proposed active constituents in *Cannabis sativa*, Δ^9-tetrahydrocannabinol (8) (Δ^9-THC) and Δ^8-tetrahydrocannabinol (9) (Δ^8-THC), in pure form has made possible more definitive studies. Initial results indicated that oral Δ^9-THC (10 and 20 mg.) provides pain reduction equivalent to codeine (60 and 120 mg.), however, marked sedation was observed at the higher dose of Δ^9-THC (10-12). While studies to date do not hold much promise for the use of Δ^9-THC as an analgetic, recent discoveries of synthetic cannabinoids having enhanced analgetic activity in animals and man have renewed impetus to the exploration of these families (13).

PROTOTYPE CANNABINOID-RELATED STRUCTURES



In 1974, Wilson and May (14) postulated that the analgetic activity of Δ^8- and Δ^9-THC was due to their respective 11-hydroxy metabolites. They provided rather elegant support for this hyopthesis by demonstrating that the 9-normethyl derivatives (15), which cannot be transformed into the 11-hydroxy metabolites, lack significant analgetic activity but elicit a dog static ataxia and cardiovascular profile nearly identical to those of Δ^8- and Δ^9-THC. Of equal importance was their observation that (−)−9−nor−9−β−hydroxyhexahydrocannabinol (HHC) had analgetic activity in the mouse hot plate test nearly equal to that of morphine (16,17). These findings encouraged the belief that there are precise structural requirements for analgetic activity which are divergent from those features eliciting other CNS and cariovascular effects.

In pursuit of the hypothesis that analgetic activity is a discrete dissociable feature of the cannabinoid molecule, we began a program in 1975 aimed at designing a molecule which would incoroprate structural features necessary for analgesia and, hence, would distinguish it both structurally and pharmacologically from the known potent analgetics. This search ultimately led to nantradol hydrochloride (18) (**1**, CP-44,001-1).

Nantradol is a structurally novel analgetic that possesses a number of pharmacological and structural features which distinguish it from both the opiates and cannabinoids (19-23). Despite two to seven times greater potency than morphine across a battery of analgetic tests in animals traditionally responsive to the opiates, nantradol is devoid of interactions at the opiate receptor and its analgetic actions are not reversed by naloxone. Notable structural differences from the cannabinoids are the absence of a pyran oxygen, the presence of a weakly basic nitrogen and the introduction of an oxygen containing C-3 side chain. Nantradol has a total of five asymmetric centers; however, owing to its defined stereochemistry at

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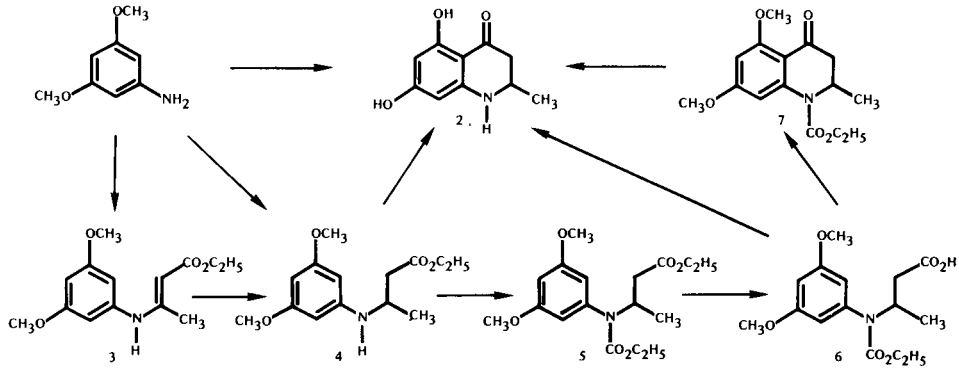
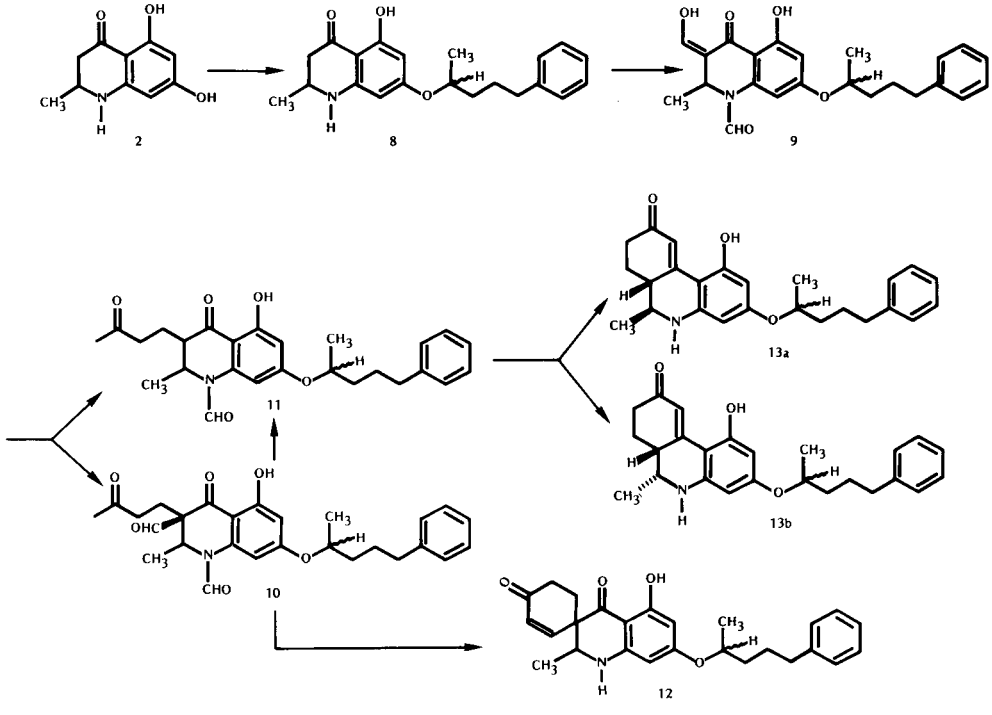
SCHEME I



SCHEME II

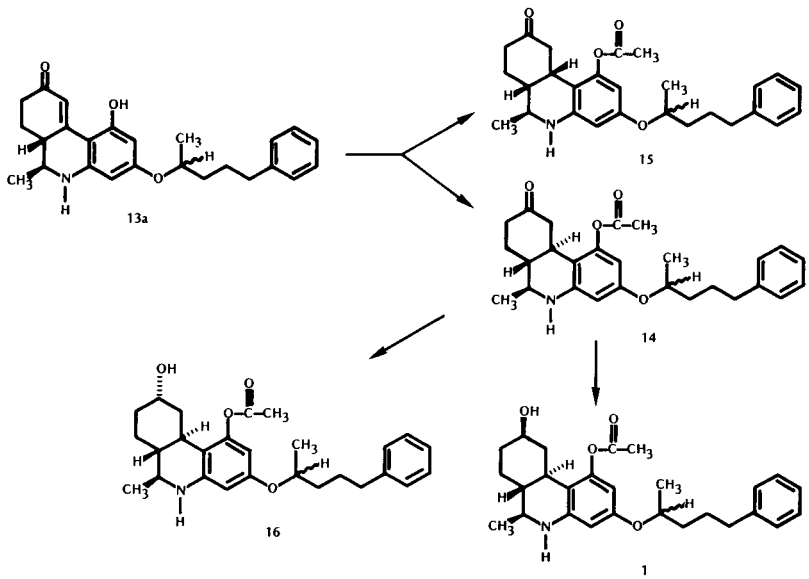


positions 6, 6a, 9, 10a, it is an approximately equal mixture of only four of the possible 32 isomers and has been studied in both animals and man as a 50:50 mixture of two pairs of racemic diastereoisomers, both of which possess the *trans* 6a, 10a stereochemistry and have β-oriented substituents at positions 6 and 9.

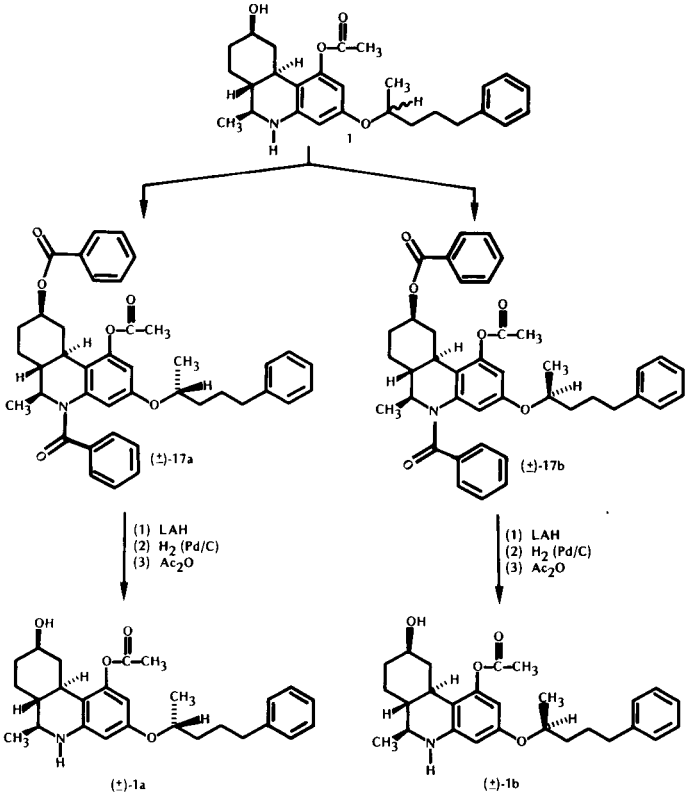
Nantradol was synthesized from commercially available 3,5-dimethoxyaniline (23). The key intermediate, bicyclic ketone **2**, was prepared by the reductive amination of ethyl acetoacetate with 3,5-dimethoxyaniline in acetic acid followed by ring closure and deprotection with either 48% hydrobromic acid or sulfuric acid. Regiospecific alkylation of **2** with (±)-1-methyl-4-phenylbutanol mesylate yielded **8**. Elaboration of **8** into the tricyclic phenanthridine system was achieved by utilizing the Robinson annelation procedure as shown in Scheme II. Dissolving metal reduction of **13a** followed by regiospecific *O*-acetylation provided the *trans* **14** and *cis* **15** ketones (Scheme III). Reduction of **14** with sodium borohydide in ethanol at 0° furnished nantradol (**1**) along with a small amount of the C-9 epimer **16**.

One of the outstanding features of potent analgetics is their stereospecificity of action. The substantial potency exhibited by nantradol suggests that it may be acting specifically to produce its analgetic effects, and, in fact, Wilson and May (14) previously found that the analgetic activity of HHC was stereospecific with regard to the tri-

SCHEME III

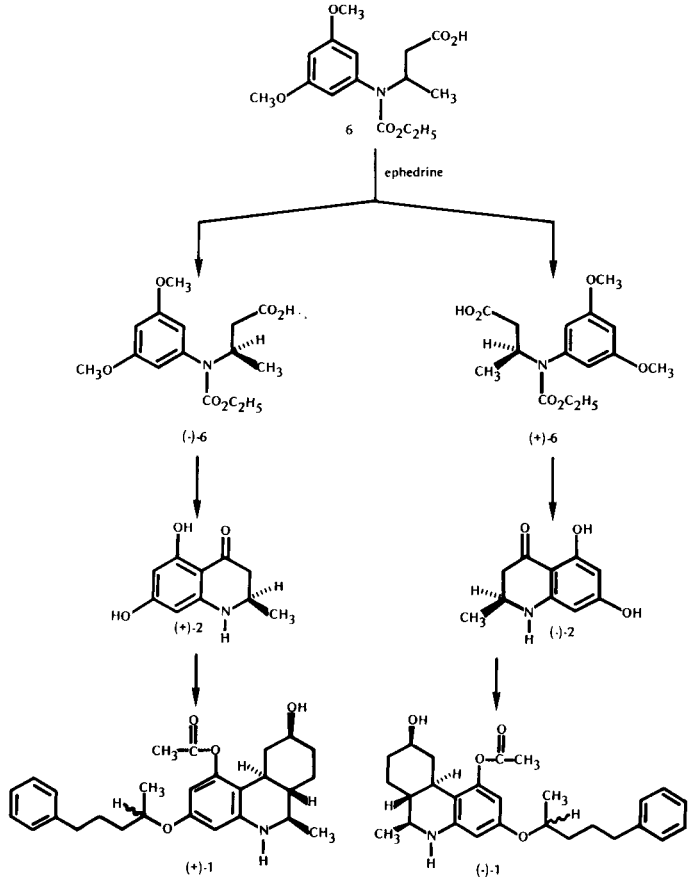


SCHEME IV



of racemic diastereoisomers present in essentially equal amounts, the first step toward identifying the most active isomer was the separation of nantradol into its component diastereoisomers which we have designated diastereoisomers **1a** and **1b**. (It should be noted that the correct

SCHEME V



cyclic nucleus. However, besides substantial differences in the nucleus of HHC and nantradol, the C-3 side chain of HHC contains no asymmetric centers. In the case of nantradol, we have introduced an asymmetric center in the C-3 side chain to this region of the molecule (20,23). Since as synthesized above, nantradol was a mixture of two pairs

relative and absolute configurations of the racemic and optically active diastereoisomers in Schemes IV and V are properly depicted. The assignments were ultimately based on the x-ray structure of (−)−**1b**). Treatment of nantradol with an excess of refluxing benzoyl chloride, followed by fractional recrystallization, gave the purified diastereoisomers **17a** and **17b** which were separately converted to **1a** and **1b** by a successive reduction and selective protection sequence shown in Scheme IV. Diastereoisomer **1a** was found to be at least 10-fold more potent than its C-3 side chain diastereoisomer **1b** in analgetic tests. This was an important new discovery since HHC had no asymmetric center in the side chain. These results clearly suggested that **1a** contained the enantiomer responsible for the majority of nantradol's analgetic activity.

Preparation and identification of the active chiral form was achieved by resolution of a precursor to **2** and ring closure to the *levo* and *dextro* isomers of **2** which were converted into the *levo* and *dextro* forms of **1** as illustrated in Scheme V. Analgetic evaluation revealed that *levo* **1** possessed one hundred times greater potency than its *dextro* counterpart. It was therefore obvious that the *levo* form of **1a** is largely responsible for the analgetic activity of nantradol and indeed, separation of **1a** into its two optically active components demonstrated that the levorotatory isomer, (−)−**1a** (CP-50,556-1, levonantradol-hydrochloride) (24), possessed the expected four- and two-fold potency advantage over nantradol and (±)-**1a**, respectively.

Despite the presence of a nitrogen and a morphine like spectrum of analgetic activity, we have shown that nantradol does not bind to the opiate receptor and its analgetic effect is not reversed by naloxone. Further support for the noninvolvement of the opiate receptor in the actions of nantradol is our finding that (−)−**1a** (levonantradol) shows no increase in binding to the opiate receptor versus nantradol (20,23). The demonstration that levonantradol hydrochloride [(−)−**1a**] produces potent opiate-like analgesia stereospecifically but without acting at the opiate receptor suggests that this new series of analgetics acts stereospecifically at a novel, and as yet unidentified, receptor. Confirmation of analgesia in man for the nantradol series, coupled with information regarding tolerance development, side effects, and abuse potential, would provide a new avenue of exploration in the analgetic field.

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