SYNTHESIS OF A FANTASTIC ANALGESIC N-CYCLOPROPYLMETHYL-3-HYDROXY-9-AZAMORPHINAN

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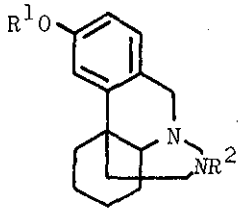
Optical resolution of dl-N-cyclopropylmethyl-3-hydroxy-9-azamorphinan (1) was successfully effected with O,O-dibenzoyl-d-tartaric acid or (2R : 3R)-2'-nitrotartranilic acid as the resolution agent. The optically active compounds thus obtained were tested for their analgesic activity and antagonistic effect of morphine analgesia.

Previously, we reported the several synthetic methods of the 9-azamorphinan ring system[1] and found this type of compounds to have an analgesic activity. Especially, dl-N-cyclopropylmethyl-3-hydroxy-9-azamorphinan (1) was found to be about twice as potent as pentazocine in the analgesic activity, but to show no side effects such as addiction.[1d] Therefore, we have examined the pharmaceutical activity of the optically active compound of 1 and attempted to accomplish the

optical resolution of 1. Here we wish to report the successful resolution of 1 and also the analgesic activity of the optically active compounds.

Firstly, we investigated the optical resolution of compounds (1, 2, and 3) in several solvents by using O,O-dibenzoyl-d-tartaric acid,[2] which was widely used as a resolution agent in morphinan system compounds, and (2R : 3R)-2'-nitrotartranilic acid,[3] which was developed as an effective resolution agent by Montzke, Pindell and Matishella.[3] Both of them effected successfully the resolution of 1 in acetone and in 90 % ethanol while cooling in refrigerator to give the crystalline salt of optically active isomer. Furthermore, (+)-binaphthyl phosphoric acid[4] was used as the resolution agent, but gave the negative result. The optical rotation of (+)-isomer (d - 1) and (-)-isomer (l - 1) was each $[\alpha]_D^{27^\circ}$: + 101.6° and $[\alpha]_D^{27^\circ}$: - 102.4°, respectively.



1 : R^1=H, R^2=CH_2-◁

2 : R^1=$COCH_3$, R^2=CH_2-◁

3 : R^1=$CH_2C_6H_5$, R^2=CH_2-◁

4 : R^1=R^2=H

5 : R^1=R^2=CO-◁

Similarly, 3-hydroxy-9-azamorphinan (4)[1c] was resolved with (2R : 3R)-2'-

nitrotartranilic acid in 90 % ethanol to give the optically active compounds, d - 4 $[\alpha]_D^{26}$ + 34.0 and l - 4, $[\alpha]_D^{26}$: - 34.0. (+)-3-Hydroxy-9-azamorphinan (d - 4) was subjected to a Schotten-Baumann reaction with cyclopropylcarbonyl chloride in the presence of 10 % sodium hydroxide in ether at room temperature for 1 hr and the resulting N-acylated compound (d - 5) was reduced with lithium aluminum hydride in refluxing dioxane to give (+)-N-cyclopropylmethyl-3-hydroxy-9-azamorphinan (d - 1), which was identical with the sample prepared by direct resolution of 1 in the comparisons of m.p., ir spectrum and optical rotation.

Pharmacology. Table I showed the results of screening for the analgesic activities of the racemate and the optically active compounds of 1 by the acetic acid (intraperioneal injection of 0.1 ml/10 g body weight of 1.0 % acetic acid) induced stretching method.[5]

Male albino mice dd strain (18.0 - 22.0 g) were used. After these compounds were administered subcutaneously to five groups of animals consisting of ten mice

Table I. Effective Ratio and ED_{50} by Lichfield-Wilcoxone Method

Method	Compd	ED_{50}, Mean value	95 % Fiducial limit
	dl - 1	mg/kg	mg/kg
Stretching	dl - 1	1.63	0.99 - 2.7
	d - 1	ca. 80	
	l - 1	0.45	0.22 - 0.91
	Pentazocine	2.40	1.56 - 3.70

per group, the effective ratio until 60 min was examined and ED_{50} was calculated by the Lichfield-Wilcoxone method.[6]

An antagonistic effect of morphine analgesia (ED_{100}, 16 mg/kg, s c) was calculated by Haffner method,[7] in which ten male mice dd strain per group were used and the results were summarized in Table II.

Table II. Comparison of the Antagonistic Effect of Morphine Analgesia by Haffner Method

Compd	AD_{50} mg/kg, S. C.	95 % Fiducial limit mg/kg
dl - 1	4.70	4.55 - 4.87
d - 1	20	
l - 1	2.20	1.80 - 3.30
Levallorphan	0.24	0.16 - 0.36

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