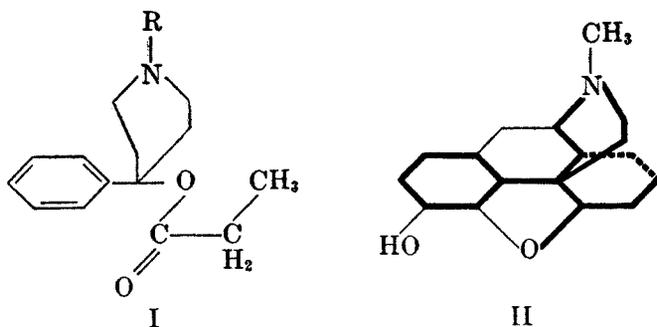


## PIPERIDINE DERIVATIVES. V. 1,3-DIALKYL-4-ARYL-4-ACYLOXYPIPERIDINES

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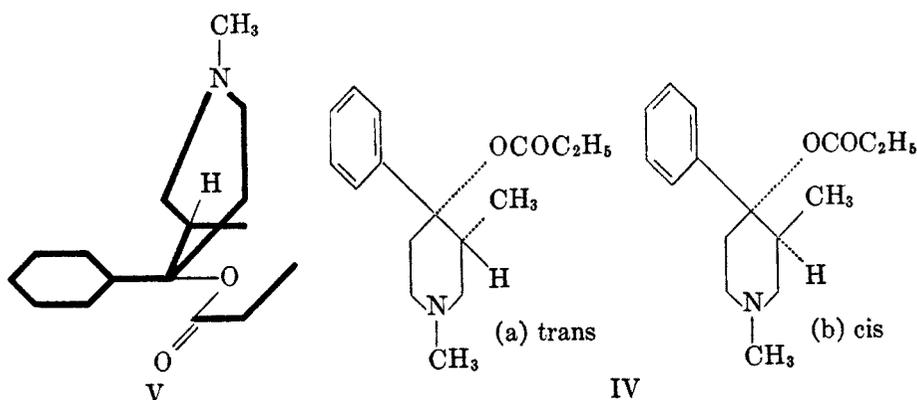
In a previous paper (1) it was shown that 1-alkyl-4-phenyl-4-propionoxy-piperidines of the structure I which simulate, in part, that part of the dihydrodesoxymorphine-D structure II which is shown with heavy solid lines, have a



high analgesic potency, which, although in some instances exceeding that of morphine, does not reach that of dihydrodesoxymorphine-D. This latter has been shown to be 5 to 10 times as active as morphine (2). It could therefore be reversely postulated that the fragment of dihydrodesoxymorphine-D structure responsible for its high activity is that indicated by the heavy solid and possibly the broken lines in II. It therefore became of interest to determine to what extent the remaining parts of the cyclohexane ring in II not simulated by the structure I, that is, the structure denoted by the broken lines, contributes to the analgesic effect of II.

We have previously shown (3) that the substitution of the 4-propionoxy residue by 4-acetoxy residue in the structure I lowers the activity to about  $\frac{1}{25}$  whilst the substitution of the higher member of the series, namely, the butyroxy residue reduces the activity to  $\frac{1}{5}$  of the original. Maintaining this optimal substitution of the propionoxy residue in the structure I, a methyl group has been introduced in the position-3 of the piperidine nucleus yielding two compounds corresponding to the structures IVa and IVb, one of which (IVa) would be spatially related to dihydrodesoxymorphine-D as shown by the heavy print in the structure V. It might be expected that one of the isomers IVa or b might show increased activity whilst the other might be expected to substantially retain the order of activity of the compounds of structure I. This is found to be the case.

By the reaction of phenyllithium on 1,3-dimethyl-4-piperidone a mixture of diastereomeric alcohols was obtained. Fractional crystallization from Skellysolve B did not effect a separation, but in one instance, on letting the crude



liquid residue (as obtained by decomposing the reaction mixture with water, separating the ether layer and distilling off the ether) stand at room temperature for a few days, the  $\alpha$  form, m.p.  $103^\circ$  crystallized out. The filtrate was distilled in vacuum to yield a mixture of the  $\alpha$  and  $\beta$  forms m.p.  $72-85^\circ$ . The  $\alpha$  isomer yielded *dl*- $\alpha$ -1,3-dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride, m.p.  $214-215^\circ$ , whilst the mixed alcohols yielded a mixture of propionate hydrochlorides which could be fractionated into the above mentioned *dl*- $\alpha$ -propionate hydrochloride, m.p.  $214-215^\circ$  (Prep. Nu- 1196)<sup>1</sup> and a lower-melting *dl*- $\beta$ -1,3-dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride, m.p.  $190-192^\circ$  (Prep. Nu-1779).

Resolution of the *dl*- $\alpha$ -ester was attempted with *d*-tartaric acid. Resolution did not take place because the readily crystallizable diastereo compound, the *dl*- $\alpha$ -ester-*d*-acid tartrate, formed immediately.

The *dl*- $\beta$ -ester on treatment with *d*-tartaric acid yielded two acid tartrate monohydrates, one melting at  $163-165^\circ$  (Prep. Nu-1831) and the other melting in a range from  $95-103^\circ$  (Prep. Nu-1832). On treatment with *l*-malic acid, the *dl*- $\beta$ -ester also yielded two acid malates, one melting at  $134-135^\circ$  and the other melting at  $114-115^\circ$ . No configuration has been assigned to these salts since the optical rotation of the hydrochlorides which can be derived from them is in all cases inappreciable. The rotation of the tartrates and malates must be ascribed entirely to the anion in each case, since the bases have apparently no optical rotation. It is believed that resolution has occurred since the melting points and solubilities of the salts in each case are different, and whilst polymorphism cannot be entirely excluded from consideration, we have not in any case observed any transformation of one salt to the other under a variety of conditions.

*Pharmacological results.* Using the modified version of the method of Ercoli and Lewis (3) for the determination of analgesic activity in rats the activities expressed in relation to morphine are: morphine, 1.0; amidone, 1.5; Prep. 1196, 0.97; Prep. 1779, 5.5; Prep. 1831, 3.5; and Prep. 1832, 7.9 by the subcutaneous

<sup>1</sup> These designations are given since the compounds have been submitted to pharmacological and clinical trials under these numbers.

route. Orally the activities expressed in relation to amidone were: amidone, 1.0; Prep. 1196, 1.4; Prep. 1779, 4.3; Prep. 1831, 3.9 and Prep. 1832, 5.1. The pharmacological results will be published in detail elsewhere. These results would suggest that Prep. Nu-1779 would be more closely related to dihydrodesoxymorphine-D than Prep. Nu-1196, since the former has an analgesic activity which is of the order of that of dihydrodesoxymorphine-D whereas the latter has only about  $\frac{1}{8}-\frac{1}{10}$  of this activity. Hence the structure IVa is provisionally ascribed to *dl*- $\beta$ -1,3-dimethyl-4-phenyl-4-propionoxypiperidine and the structure IVb to the corresponding *dl*- $\alpha$ -compound.

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## EXPERIMENTAL

*1,3-Dimethyl-4-phenyl-4-hydroxypiperidine.* One liter of dry ether and 15 g. of lithium wire cut into small pieces were placed in a 3-liter round-bottom flask provided with a condenser, stirrer, and dropping-funnel. Bromobenzene (172 g.) was placed in the dropping-funnel and 10 cc. added at one time to the flask. Gentle warming was employed until the reaction started and then the bromobenzene was added from the dropping-funnel at such a rate that the ether refluxed vigorously. At the end of the reaction the dropping-funnel was rinsed with 100 cc. of ether and the flask cooled to  $-5^{\circ}$ . One hundred twenty-seven grams of 1,3-dimethyl-4-piperidone (4) was added slowly from the funnel, maintaining the temperature at  $-5^{\circ}$ . After the addition, the contents were stirred for 1 hour at room temperature. The flask was cooled in an ice-bath and 200 cc. of water was added slowly from the funnel with continued stirring. The ether layer was separated and dried over potassium carbonate. After the removal of the ether the residue was distilled *in vacuo* and the fraction boiling at  $130^{\circ}/2$  mm. pressure was collected. This product was dissolved in 300 cc. of *n*-hexane (Skellysolve B), and on standing in the ice-box the product crystallized, yielding 150 g. of colorless crystals m.p.  $72-85^{\circ}$ . This is a mixture of diastereomeric alcohols. On one occasion, before distilling the crude mixture, it was kept at room temperature for 5 days. During that time crystallization of the  $\alpha$ -form set in. The crystals were filtered, washed with Skellysolve B, and recrystallized from Skellysolve B, m.p.  $103^{\circ}$ ; yield 75 g.

*Anal.* Calc'd for  $C_{13}H_{19}NO$ : C, 76.09; H, 9.27.

Found: C, 76.17; H, 9.05.

The filtrate was distilled in *vac.* at  $130^{\circ}/2$  mm. The distillate, a mixture of the  $\alpha$  and  $\beta$  forms, was crystallized from Skellysolve B, m.p.  $72-85^{\circ}$ ; yield 75 g.

*1,3-Dimethyl-4-phenyl-4-propionoxypiperidine.* 1,3-Dimethyl-4-phenyl-4-hydroxypiperidine (229 g.) m.p.  $72-85^{\circ}$  was dissolved in a mixture of 350 cc. of pyridine and 350 cc. of propionic anhydride. The solution was refluxed for 3 hours and the solvents were distilled off *in vacuo* from a steam-bath using a water-pump. The residue, after cooling, was mixed with 200 cc. of water and basified with 20% sodium hydroxide solution to bring the pH to 9-10. The separated oil was extracted with ether, the ether solution dried over potassium carbonate, filtered, and hydrogen chloride gas bubbled in until no more hydrochloride separated. The solid, after drying in a vacuum desiccator over sodium hydroxide, was crystallized from about 600 cc. of acetone containing a little methanol. One hundred forty-five grams of colorless crystals, m.p.  $212-214^{\circ}$  was obtained in the first crop. This fraction has been named the  $\alpha$  form.

*Anal.* Calc'd for  $C_{18}H_{23}NO_2 \cdot HCl$ : C, 64.53; H, 8.06.

Found: C, 64.58; H, 7.88.

The filtrate was concentrated to 250 cc. and allowed to stand in the ice-box overnight. A second crop of crystals was obtained which on recrystallization three times from acetone melted at  $190-192^{\circ}$ . This has been designated the  $\beta$  form; yield 107 g.

*Anal.* Calc'd for  $C_{16}H_{23}NO_2 \cdot HCl$ : C, 64.53; H, 8.06.

Found: C, 64.88; H, 7.99.

*Resolution with d-tartaric acid.* Five grams of  $\beta$ -dl-1,3-dimethyl-4-phenyl-4-propionyloxy-piperidine was converted to the free base with sodium carbonate. The oil was extracted with ether, and the ether solution dried over potassium carbonate. The ether was distilled off and the residue dissolved in 50 cc. of acetone containing 2.5 g. of *d*-tartaric acid. The solution was concentrated to 25 cc., and on standing in the ice-box crystallization occurred. The crystals were filtered off and recrystallized from methyl ethyl ketone (Prep. Nu 1831). Yield 3.5 g., m.p. 163–165°,  $[\alpha]_D^{25} +13.1^\circ$  (3% solution in methanol).

*Anal.* Calc'd for  $C_{16}H_{23}NO_2 \cdot C_4H_6O_6 \cdot H_2O$ : C, 55.94; H, 7.22.

Found: C, 55.98; H, 6.90.

The filtrate from the original crystallization was concentrated to dryness and the viscous residue was dissolved in methyl ethyl ketone. On standing in the ice-box crystallization occurred. The crystals were filtered and recrystallized two times from isopropanol (Prep. Nu 1832), m.p. 95–103°  $[\alpha]_D^{25} +12.8^\circ$  (3% solution in methanol).

*Anal.* Calc'd for  $C_{16}H_{23}NO_2 \cdot C_4H_6O_6 \cdot H_2O$ : C, 55.94; H, 7.22.

Found: C, 55.29; H, 7.20.

*Resolution with l-malic acid.* Seventeen and one-half grams of the  $\beta$ -dl-ester base was added to a solution of 9 g. of *l*-malic acid in 50 cc. of acetone. On standing in the ice-box crystallization occurred. The crystals were filtered off and recrystallized from acetone; yield 12 g., m.p. 134–135°  $[\alpha]_D^{25} -2.26^\circ$  (5% in  $H_2O$ ).

*Anal.* Calc'd for  $C_{16}H_{23}NO_2 \cdot C_4H_6O_5$ : C, 60.76; H, 7.34.

Found: C, 60.83; H, 7.34.

The filtrate from the original crystallization was concentrated to dryness and the residue dissolved in 10 cc. of water. On standing in the ice-box crystallization occurred. The crystals were filtered off, dried, and crystallized from acetone, m.p. 114–115°;  $[\alpha]_D^{25} -2.74^\circ$  (5% solution in water).

*Anal.* Calc'd for  $C_{16}H_{23}NO_2 \cdot C_4H_6O_5$ : C, 60.70; H, 7.34.

Found: C, 60.60; H, 7.43.

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