pure by GLC of the derivative (IV)[5] (polypropylene glycol capillary column, 150°, helium stream). However, this partly resolved product could be further purified by recrystallization from acetone-ether. The purified product, (–)-N-formyl-β-tyrosine methyl ether, had m.p. 158–161° (decomp.) and $[\alpha]_D = -125°$ (c = 0.52, methanol); the optical purity was at least 91%, determined by GLC of (IVa). From the mother liquor of the cinchonidine salt (or from the less soluble diastereomer of the brucine salts), the partly purified enantiomer IIIb of IIIa was obtained and further purified to at least 95% optical purity: m.p. 158–161° (decomp.) $[\alpha]_D = +130°$ (c = 0.54, methanol).

The dextrorotatory N-formylamino acid (IIIb) (202 mg) was ozonized in 30 ml of 5% aqueous formic acid according to CORRODI and HARDEGGER[6] during 24 h, and the ozonide cleaved by the addition of 2 ml of 30% hydrogen peroxide in 2 ml of formic acid (*20 h, 20°*). From the evaporated reaction mixture, a 24% yield of of D-aspartic acid (V), $[\alpha]_D = -27{,}1°$ (c = 1,77 in 5 *N* HCl) was obtained by recrystallization from water, and identified by the IR-spectrum and by TLC. The dextrorotatory formylamino acid (IIIb) has therefore the (*R*)-chirality.

The levorotatory (*S*)-formyl derivative (IIIa) (91% optical purity) was transformed to the oily methyl ester hydrochloride (VI) by simultaneous deformylation and esterification (abs. methanol saturated with dry HCl; *24 h, 20°*). The ester was reduced with excess lithium aluminium hydride in abs. dioxane (1 h, reflux) to the liquid amino alcohol (VII). The crude product was isolated from the reaction mixture by decomposition with water and extraction with chloroform. The mixture contained a major component (Rf 0.5, TLC with butanol – acetic acid – water 4:1:1; ninhydrin positive) and several unidentified minor impurities (Rf 0.16 up to 0.9). The IR-spectrum showed no absorption in the carbonyl region.

Selective N-acetylation of 85 mg of crude (VII) was carried out with 1 ml of acetic anhydride in 5 ml of methanol (5 h, 20°) to yield the final product (I), which was purified by chromatography on silica gel, recrystallization and sublimation at 0.01 mm Hg and 105–110°; over all yield 15% from IIIa. The m.p. and mixed m.p. were 124–124.5°; $[\alpha]_D = -149°$ (c = 0.47, chloroform). The Rf value (TLC), IR- and NMR-spectrum, showed no difference from those of the natural product, which therefore has the (*S*)-chirality.

Racemic I, prepared in the same manner from racemic II, had m.p. 108°; the NMR-spectrum and IR-spectrum in chloroform were identical with those of the optically active compound. However, the IR-spectra in KBr showed marked differences in the finger-print region.

Summary. (*S*)-3-*p*-methoxyphenyl-3-acetamidopropan-1-ol was isolated from cultures of an actinomycete (*Streptomyces michiganensis*). Its structural determination by spectroscopic means and its synthesis are described.

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14 May 1975.

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The Absolute Configuration of the Enantiomers of Glutethimide and Aminoglutethimide

Aminoglutethimide (Elipten® CIBA) was originally introduced as an anticonvulsant for the treatment of epilepsy. It was subsequently withdrawn because of inhibitory effects on adrenal function[1]. Recently these adrenal effects have been suggested to be of utility in the treatment of metastatic breast cancer[2,3]. Because aminoglutethimide also inhibits ovarian secretion of progesterone, the potential abortifacient properties of aminoglutethimide have been investigated[4–6]. Further chemical studies have also been reported recently[7,8].

In view of this renewed interest in aminoglutethimide, we decided to resolve it and explore the biological properties of its antipodes I and II (levo- and dextro-rotatory, respectively). We postulated that the steroid synthesis inhibiting properties might reside in one antipode and the potency could therefore be enhanced by resolution.

The antipodes were tested in parallel with racemic aminoglutethimide for their effects on adrenal and ovarian steroid secretion in rats. Changes in corticosterone secretion were measured in adrenal vein blood obtained before and after i.v. injection of aminoglutethimide or its antipodes into anesthetized rats. The dextrorotatory antipode II was 2 or 3 times more potent an inhibitor than the racemate, while levorotatory antipode I had very little activity at dose levels 10-fold higher. In gonadotrophin-primed immature female rats[9], antipode II injected i.v. reduced mean plasma progesterone levels by more than 78% and accounted for most of the activity in the racemate.

Resolution of aminoglutethimide, therefore, provided a compound (antipode II) with essentially all of the steroid synthesis inhibiting activity of the racemate.

Glutethimide (Doriden® CIBA and USV) had been previously resolved[10], and biological studies indicated

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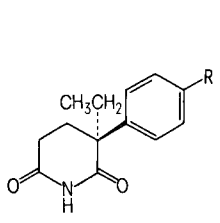
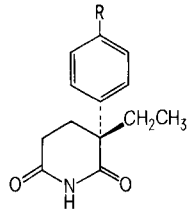
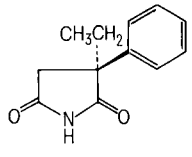
that the dextro-rotatory (+)-antipode IV was 2–3 times more sedative than the levo-rotatory (−) III[11]. Nevertheless, no attempt had been made to assign the absolute configurations to these antipodes III and IV. We now describe the assignment of absolute configuration to the aminoglutethimide antipodes I and II thus, incidentally, also to the glutethimide antipodes III and IV.

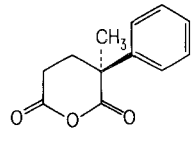




I R = NH_2 *l*-aminoglutethimide II R = NH_2 d-aminoglutethimide
III R = H *l*-glutethimide IV R = H d-glutethimide

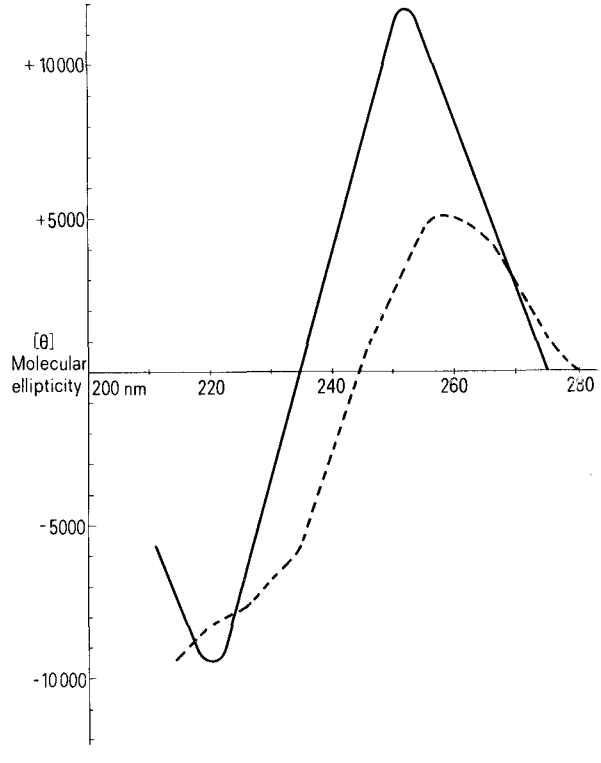


V



VI

Aminoglutethimide was resolved via recrystallization from methanol of the tartarate salts. Use of (+)-tartaric acid yielded the (+)-tartarate salt of (+)-aminoglutethimide II ($[\alpha]_D^{25}$ = +79° [MeOH]) after 5 recrystallizations. Use of (−)-tartaric acid provided the (−)-tartarate salt of (−)-aminoglutethimide I ($[\alpha]_D^{25}$ = −80° [MeOH]). Liberation of the bases via treatment of aqueous solutions



C. D. curves of (−)-glutethimide III and (−)-2-phenyl-2-ethyl succinimide V. ——, *S*(−)2-phenyl-2-ethyl succinimide V (taken from KNABE[7]); – – – –, (−)-glutethimide III.

of the tartarates with equivalent aqueous sodium carbonate gave (+)-aminoglutethimide II (m.p. 114–5° $[\alpha]_D^{25}$ = +163.1° [MeOH]) and (−)-aminoglutethimide I (m.p. 114–5° $[\alpha]_D^{25}$ = −163.6° [MeOH]), respectively. A portion of (−)-aminoglutethimide I was treated as a chilled solution in dilute HCl with aqueous sodium nitrite solution. The diazotization mixture was poured into hypophosphorous acid and allowed to stand overnight at 0°. After workup, the crude product was chromatographed on silica gel eluted by chloroform-ethyl acetate (4:1). Eluted in the initial fractions was (−)-glutethimide III. This was recrystallized from hexane to give material m.p. 97–8° ($[\alpha]_D^{25}$ = −184° [MeOH]) (lit.[10], m.p. 102–3° $[\alpha]_D^{20}$ = −181° [MeOH]). The CD curve of this (−)-glutethimide III (CD) (C1. 235 mg/ml in MeOH) $[\theta]_{280}$O; $[\theta]_{257}$ + 5000; $[\theta]_{244}$ O; $[\theta]_{225}$ − 7700) was compared with the CD curve of *S* (−)2-ethyl-2-phenyl-succinimide V, which was published by KNABE[12], see Figure. This comparison indicates that the position of the CD maxima and their signs are essentially the same for both compounds. The absolute configuration of *S*(−)-2-ethyl-2-phenyl-succinimide V has been rigorously proven by chemical correlations back to the natural amino acids. Therefore, we can confidently assign the *S*-configuration[13] to (−)-glutethimide III. Confirmation of this assignment can be made by a comparison of the ORD curve of (−)-glutethimide III ORD[(C, 1.235 mg/ml MeOH)] $[\Phi]_{460}$ − 600; $[\Phi]_{300}$ − 2,200; $[\Phi]_{250}$ − 11,300; $[\Phi]_{225}$ − 15,900), which is essentially a plain negative curve with a small Cotton effect centered at 270 nm, with the plain negative ORD curve reported for *S*(−)-2-methyl-2-phenyl-glutaric anhydride VI[14]. The absolute configuration of 2-methyl-2-phenyl-glutaric anhydride was established by chemical degradation and correlation with 2-methyl-2-phenyl butanoic acid of known absolute configuration[14].

With the assignment of the *S*-configuration to (−)-glutethimide III, the *S*-configuration can be assigned to the (−)-aminoglutethimide I from which it was derived, as the removal of the aromatic amino group leaves the chiral center unaffected. Thus, the *R*-configuration can be assigned to (+)-aminoglutethimide II, the enantiomer possessing the steroid synthesis inhibiting activity.

Summary. Aminoglutethimide (Elipten® CIBA) was resolved into the optical antipodes I and II. The endocrinological properties and the absolute configuration of both enantiomers I and II were determined. Most of the steroidal synthesis inhibition was found in the (+) enantiomer II. On the basis of circular dichroism, the *R*-configuration was assigned to the (+) enantiomer II.

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