Prolintane Metabolites. Synthesis of *dl*-1-(α-Propylphenethyl)pyrrolidin-2-one

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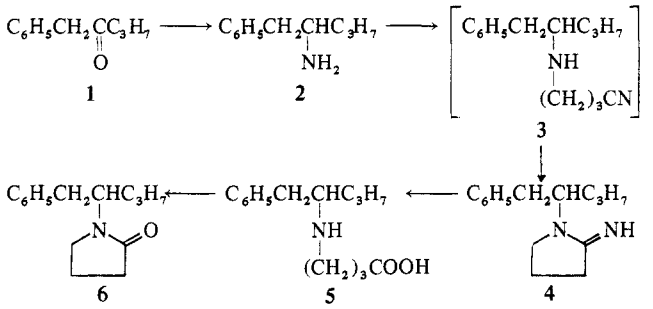
Although prolintane,[1] 1-(α-propylphenethyl)pyrrolidine, has been used as a stimulant drug for over a decade, little is known concerning its metabolism in animal or man. Eberhardt and Debackere[2] demonstrated the presence of possible prolintane metabolites in human urine, but no characterization of these urinary substances was undertaken. The present work was carried out in connection with a study of the metabolism and pharmacology of prolintane. The lactam **6** has been shown to be the single major metabolite of prolintane in a rabbit liver microsomal system, as well as a metabolite in tissues of rats given the drug.[3] Compared to prolintane (ED_{50} 1.8 mg/kg po), the lactam **6** and the amino acid **5** (ED_{50}'s > 32.0 mg/kg po) showed little ability to antagonize the sedative action of tetrabenazine in mice as determined by the method of Vernier, *et al.*[4]



Experimental Section

Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values. Tlc was performed on fluorescent silica gel G plates. All bp are uncorrected; mp were taken on a Thomas-Hoover Uni-Melt capillary mp apparatus and are uncorrected.

Benzyl *n*-propyl ketone (**1**) was prepared by the method of Bredereck and Gompper: bp 113–117° (12 mm); n^{25}D 1.5051; 43% [lit.[5] bp 115–117° (11 mm); 45%]. *dl*-α-Propylphenethylamine (**2**) was prepared from benzyl *n*-propyl ketoxime by reduction with sodium in refluxing ethanol.[6] The oil obtained after work-up was distilled giving 8.71 g (80.5%) of **2**: bp 112–118° (14–15 mm) [lit.[7] bp 118° (15 mm); 67%]. 4-Iodobutyronitrile was prepared by the method of Leonard and Goode: bp 115–116° (16 mm); n^{25}D 1.5369; 68% [lit.[8] bp 109–111° (15 mm), 92%; lit.[9] n^{21}D 1.5358].

***dl*-1-(α-Propylphenethyl)-2-iminopyrrolidine (4).** A homogeneous soln of 5.20 g (0.0267 mole) of 4-iodobutyronitrile and 8.71 g (0.0534 mole) of **2** in 35 ml of C_6H_6 was stirred and refluxed for 21 hr. The resulting two-phase mixt was sepd and the lower oily phase was dissolved in 1.5 *N* HCl (200 ml). After washing with C_6H_6, the aqueous phase was made basic with 40% NaOH. The oil that pptd was extd into C_6H_6, dried ($MgSO_4$), and distd to give 3.70 g (60%) of **4** as a viscous, clear fuming oil: bp 135–136° (1 mm); ir (liq film) 3290 cm^{-1} (NH), 1616 (C=N). The compd had a strong odor resembling pyrrolidine and appeared to absorb CO_2 and H_2O rapidly. No consistent analytical data could be obtained on the compd, and it was used for the next step without further characterization.

***dl*-(α-Benzyl-*n*-butyl)-4-aminobutyric Acid (5).** Into a stainless steel flask was placed 3.00 g (0.013 mole) of **4**, 15.0 g of $Ba(OH)_2 \cdot 8H_2O$, 15 ml of water, and 8 ml of *n*-PrOH. The mixt was stirred and refluxed for 36 hr. Initially, there was a copious evolution of NH_3. The mixt was evapd to dryness *in vacuo*. The residue was extd several times with Me_2CO, and the combined exts were filtered. Concn of the filtrate gave 2.96 g of a clear oil. This oil was dissolved in aqueous EtOH (1:1), and CO_2 gas was bubbled into the soln until it reached pH 7. The pptd $BaCO_3$ was removed by filtration, and the clear filtrate was concd. The residue, on trituration with Me_2CO, crystd as white needles. Recrystn from Me_2CO–EtOH gave 0.79 g (25%) of **5**: mp 137–137.5°; pK_a = 4.00, pK_B = 9.72; equiv wt 253.1 (titrn); R_f 0.60 (*n*-BuOH–AcOH–H_2O, 3:1:1), R_f 0.04 (C_6H_6–dioxane–AcOH, 90:25:4) ninhydrin-developed spots. *Anal.* ($C_{15}H_{23}NO_2$) C, H, N.

***dl*-1-(α-Propylphenethyl)pyrrolidin-2-one (6)** was prepd by heating the amino acid **5** at 70° under reduced pressure or by melting **5**. The product was purified by distn: bp 125–126° (0.05 mm); n^{20}D 1.5256; R_f 0.60 (C_6H_6–EtOH–12 *N* NH_4OH, 95:15:5). *Anal.* ($C_{15}H_{21}NO \cdot 0.05H_2O$) C, H, N, H_2O.

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Hydroxylamine Derivatives as Potential Antimalarial Agents. 3. 1,2,4-Oxadiazoles†,‡

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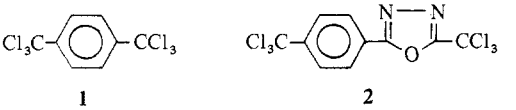
In 1970, it was reported that, in addition to displaying a broad spectrum of anthelmintic activity, α,α,α,α′,α′,α′-hexachloro-*p*-xylene, Hetol (**1**), also possessed substantial suppressive antimalarial properties.[2] Subsequently, certain 2-(trichloromethyl)-5-(trichloromethylphenyl)-1,3,4-oxadiazoles such as **2** were shown to have similar levels of activity as **1** against *Plasmodium berghei* in mice.[3] Therefore, a



series of mono-, bis-, and tris(trihalomethylated-1,2,4-oxadiazoyl)benzenes was synthesized and evaluated for possible activity enhancement. These compounds were prepared by the reaction of an amidoxime with the appropriate acid chloride or anhydride. The physical properties of the bis-(1,2,4-oxadiazoles) are presented in Table I while those of the mono- and tris(1,2,4-oxadiazoles) as well as certain intermediate amidoximes are summarized in Table II.

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‡For the previous paper in this series see ref 1.