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

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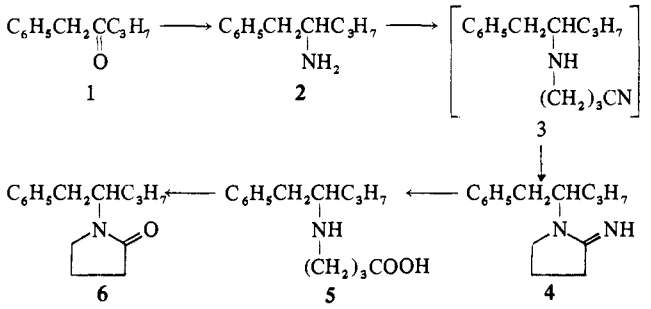
Although prolintane,[1] 1-(α-propylphenethyl)pyrrolidine, has been used as a stimulant drug for over a decade, little is known concerning its metabolism in animal or man. Eberhardt and Debackere[2] demonstrated the presence of possible prolintane metabolites in human urine, but no characterization of 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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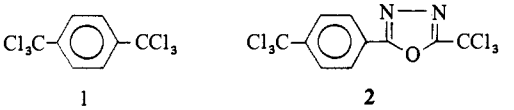
In 1970, it was reported that, in addition to displaying a broad spectrum of anthelmintic activity, α,α,α,α′,α′,α′-hexachloro-*p*-xylene, Hetol (**1**), also possessed substantial suppressive antimalarial properties.[2] Subsequently, certain 2-(trichloromethyl)-5-(trichloromethylphenyl)-1,3,4-oxadiazoles 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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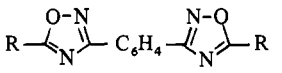
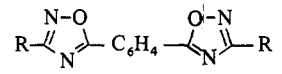
‡For the previous paper in this series see ref 1.

Table I. Bis-1,2,4-oxadiazoles



R	Benzene substitution	No.	Mp, °C	Formula	Analyses[a]	Yield, %	Recrystallization medium and no.
			A. Bis(5-substituted-1,2,4-oxadiazoly)benzenes				
C_6H_5	1,4	**3**	291-293[b]	$C_{22}H_{14}N_4O_2$	C, H, N	26.5	C_6H_5Cl (1)
4-$CF_3C_6H_4$	1,4	**4**	260-261	$C_{24}H_{12}F_6N_4O_2$	C, H, F, N	15.6	EtOH (1)
3-$CF_3C_6H_4$	1,4	**5**	286-287	$C_{24}H_{12}F_6N_4O_2$	C, H, F, N	19.4	Dioxane (2)
4-$CF_3C_6H_4$	1,3	**6**	196-197	$C_{24}H_{12}F_6N_4O_2$	C, H, F, N	44.5	Dioxane-H_2O[c] (1)
3-$CF_3C_6H_4$	1,3	**7**	184-185	$C_{24}H_{12}F_6N_4O_2$	C, H, F, N	39.9	MeOH (1)
CCl_3	1,4	**8**	151-152	$C_{12}H_4Cl_6N_4O_2$	C, H, Cl, N	86.7	MeOH (1)
CCl_3	1,3	**9**	117-118	$C_{12}H_4Cl_6N_4O_2$	C, H, Cl, N	71.4	EtOH (1)
CF_3	1,4	10	87-88	$C_{12}H_4F_6N_4O_2$	C, H, F, N	41.7	MeOH-H_2O[c] (2)
CF_3	1,3	11	72-73	$C_{12}H_4F_6N_4O_2$	C, H, F, N	35.0	MeOH-H_2O[c] (2)
$CClF_2$	1,4	12	71-72	$C_{12}H_4Cl_2F_4N_4O_2$	C, H, Cl, F, N	35.3	MeOH-H_2O[c] (2)
$CClF_2$	1,3	13	51-53	$C_{12}H_4Cl_2F_4N_4O_2$	C, H, Cl, F, N	28.5	MeOH-H_2O[c] (1)
1-Adamantyl	1,4	14	273-274	$C_{30}H_{34}N_4O_2$	C, H, N	21.4	Dioxane-H_2O[c] (1)
			B. Bis(3-substituted-1,2,4-oxadiazoyl)benzenes				



CCl_3	1,4	**15**	236-237	$C_{12}H_4Cl_6N_4O_2$	C, H, Cl, N	11.0	Dioxane-H_2O[c] (1)
CCl_3	1,3	**16**	110-111	$C_{12}H_4Cl_6N_4O_2$	C, H, Cl, N	10.0	MeOH-H_2O (1) (80:20)
4-$CF_3C_6H_4$	1,4	17	238-240	$C_{24}H_{12}F_6N_4O_2$	C, H, F, N	69.8	Dioxane-H_2O[c] (1)
4-$CF_3C_6H_4$	1,3	18	186-187	$C_{24}H_{12}F_6N_4O_2$	C, H, F, N	64.8	Dioxane-H_2O[c] (1)
3-$CF_3C_6H_4$	1,4	19	267-268	$C_{24}H_{12}F_6N_4O_2$	C, H, F, N	74.2	C_6H_5Cl (1)
3-$CF_3C_6H_4$	1,3	**20**	151-152	$C_{24}H_{12}F_6N_4O_2$	C, H, F, N	80.6	Dioxane-H_2O[c] (2)

[a] Where analyses are indicated by symbols of the elements, the results were within ±0.4% of the theoretical values. The analyses were performed by Galbraith Laboratories, Knoxville, Tenn. [b] Lennaers and Eloy[5] reported mp 276-277°. [c] By reprecipitation.

Table II. Mono- and Tris(1,2,4-oxadiazoles) and Amidoximes

Name	No.	Mp, °C	Formula	Analyses[a]	Yield, %	Recrystallization medium and no.
3-Trichloromethyl-5-(4-trifluoromethylphenyl)-1,2,4-oxadiazole	**21**	102-103	$C_{10}H_4Cl_3F_3N_2O$	C, H, Cl, F, N	23.7	MeOH-H_2O[b] (1)
1,3,5-Tris(3-trichloromethyl-1,2,4-oxadiazoyl)benzene	**22**	216-219	$C_{15}H_3Cl_9N_6O_3$	C, H, Cl, N	28.2	MeOH-H_2O (1) (95:5)
1,3,5-Tris(5-trichloromethyl-1,2,4-oxadiazoyl)-benzene	**23**	187-190	$C_{15}H_3Cl_9N_6O_3$	C, H, Cl, N	50.0	MeOH-H_2O[b] (1)
2-Trifluoromethylbenzamidoxime	**24**	132-134	$C_8H_7F_3N_2O$	C, H, F, N	30.5	H_2O (2)
3-Trifluoromethylbenzamidoxime	**25**	87-88[c]	$C_8H_7F_3N_2O$	C, H, F, N	42.4	H_2O (2)
4-Trifluoromethylbenzamidoxime	**26**	129-131	$C_8H_7F_3N_2O$	C, H, F, N	62.7	H_2O (2)
3-Methylbenzamidoxime	**27**	88-90[d]	$C_8H_{10}N_2O$	C, H, N	49.0	H_2O (2)
4-Methylbenzamidoxime	**28**	148-150[e]	$C_8H_{10}N_2O$		56.5	H_2O (2)
Trimesamidoxime	**29**	>265 dec	$C_9H_{12}N_6O_3$	C, H, N	79.4	DMSO-H_2O[b]

[a] *Cf.* footnote *a*, Table I. [b] By reprecipitation. [c] Ainsworth, *et al.*,[6] reported mp 83-85°. [d] Ainsworth, *et al.*,[6] reported mp 120-121°. [e] Clarke[7] reported mp 147°.

Each of these compounds was evaluated for antimalarial activity against *P. berghei* in mice.[4,§] As shown in Table III, compounds **8**, **9**, **12**, and **16** gave mean survival time increases of greater than 100% and may therefore be considered active. However, none of these were found to be more potent than **1**. In addition, **10** and **24** gave modest increases in survival time (3.3 and 4.5 days, respectively) at the 640 mg/kg level, while the others were inactive.

Experimental Section

Amidoximes. Terephthal- and isophthalamidoxime were prepared as described earlier,[1] while trichloroacetamidoxime was obtained by the literature method.[8] The remaining amidoximes, **24-29**, were synthesized by refluxing the appropriate nitrile with a stoichiometric amount of NH_2OH in EtOH for 1-4 days. In the case of **29**, however, it was necessary to repeat the procedure with a newly prepared NH_2OH solution in order to obtain a complete conversion.

(5-Substituted-1,2,4-oxadiazoyl)benzenes (3-14 and 23). Compounds **4-7**, **14**, and **23** were prepared by the reaction of terephthalamidoxime, isophthalamidoxime, or **29** and 2 equiv of the appropriate acid chloride in DMF at 100° (**14**) or at reflux for 18 hr. In the case of **3**, a 2.5:1 molar ratio was employed at reflux temperature. For compounds **6** and **7**, 2 equiv of pyridine was used, and the reaction mixtures were refluxed in dioxane for 18 hr.

Compounds **8**, **9**, and **23** were prepared according to the method of Sousa, *et al.*, involving the use of molten CCl_3COOH as the solvent and 2 moles of $(CCl_3CO)_2O$ per amidoxime group.[9] Compounds **10-13** were synthesized by allowing the appropriate amidoxime and anhydride in DMF to react at ambient temperature, followed by heating at reflux (10 and 11) or *ca.* 100° (**12** and **13**) for 24 hr.

(3-Substituted-1,2,4-oxadiazoyl)benzenes (15-22). Compounds **15**, **16**, **21**, and **22** were prepared by allowing stoichiometric amounts of trichloroacetamidoxime and the appropriate acid chloride in DMF to react at ambient temperature and then heating at 100° for 3 hr (**15**), at 100° for 18 hr (**22**), or at reflux for 18 hr (**16** and **21**). The

§ Testing of all compounds was carried out by Dr. L. Rane of the University of Miami.

Table III. Antimalarial Testing Data (*P. berghei* in Mice)

Compd	Dose, mg/kg	Mean survival time, days[a]	Δ survival time, days	Mortality
8	20	6.6	0.4	5/5
	40	7.0	0.8	5/5
	80	10.0	3.8	5/5
	160	16.6	10.4	5/5
	320	19.6	13.4	5/5
	640	20.2	14.0	5/5
9	20	6.4	0.3	5/5
	40	6.4	0.3	5/5
	80	6.6	0.5	5/5
	160	9.6	3.5	5/5
	320	14.0	7.9	5/5
	640	14.8	8.7	5/5
12	20	6.4	0.3	5/5
	40	6.4	0.3	5/5
	80	6.6	0.5	5/5
	160	6.6	0.5	5/5
	320	7.0	0.9	5/5
	640	18.4	12.3	5/5
16	20	6.2	0.1	5/5
	40	6.4	0.3	5/5
	80	6.4	0.3	5/5
	160	9.6	3.5	5/5
	320	10.8	4.7	5/5
	640[b]	16.0	9.9[c]	

[a] Mean survival time of controls: 6.2 for **8**; 6.1 for **9**, **12**, and **16**. [b] Four mice survived for 60 days; mice which survive for 60 days are considered cured. [c] Data for uncured mice.

preparation of **15** was also conducted in the presence of 2 equiv of pyridine in refluxing DMF for 3 hr. Similar results were obtained, and the yield was only slightly improved. The procedure employed for preparing 1,3-bis[3-(3-trifluoromethylphenyl)-1,2,4-oxadiazoyl]-benzene (**20**), which is the same as that employed for **17**–**19**, is as follows. To a solution of 3.5 g (0.017 mole) of **25** in 50 ml of dioxane and 1.4 g (0.017 mole) of pyridine was added a solution of 1.7 g (0.0085 mole) of isophthaloyl chloride in 50 ml of dioxane. After refluxing for 18 hr, the hot solution was decanted from a red oil, and the dioxane was removed *in vacuo*. Analytical purity was achieved by two reprecipitations from dioxane by H_2O.

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Book Reviews

Iatrogenic Diseases. P. F. D'Arcy and J. P. Griffin. Oxford University Press, London, New York. 1972. vi + 208 pp. 24.5 × 19 cm. Cloth $19.95. Paperback $13.50.

Adverse reactions are encountered with every drug and with almost every nutrient in a certain proportion of individuals. In some cases, doses of drugs approaching toxic levels must be used to achieve therapeutic success; in other cases, reaction to a drug is genetically determined. Hepatic or renal disease can interfere with metabolism and excretion of normal doses of drugs, and thus increase the retained drug concentrations to toxic amounts. Some individuals have a low threshold to normal pharmacological actions of drugs. Others develop hypersensitivity with ensuing pathological symptoms, or idiosyncrasy to a given class of agents. When drug combinations are used in therapy, one drug may suppress the hepatic microsomal enzymes needed for the metabolic removal of the other agent(s). Or else, a drug may induce biosynthesis of such enzymes, which leads to increased rates of metabolism of the other agent in the combination, sometimes with catastrophic physiological results. Even the metabolism of many foods is influenced by various drugs.

The clinically observable symptoms of all these adverse reactions are called iatrogenic diseases. The present volume presents a summary of the epidemiological aspects of iatrogenic disease, and gives a fully documented report on all types and cases of drug-induced pathology listed in the medical literature. The adverse reactions are arranged according to the organ or tissue where they are manifested. Biochemical causation is stressed wherever possible. Generic drug names are used in the text but a convenient and comprehensive cross index to American, British, and Continental proprietary drug names is appended. The book should be of the greatest value to medical practitioners, but it will serve pharmacologists and biochemists equally well. It should also be read by drug safety administrators and trial lawyers because it lists toxic reactions clearly but places their incidence in proper perspective in regard to the therapeutic advantages of each drug.

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Chemical Oxidations with Microorganisms. By Gunther S. Fonken and Roy A. Johnson. Marcel Dekker, New York, N. Y. 1972. vii + 292 pp. 17 × 24 cm. $19.50.

The organic chemist who lacks microbiological training will be glad to find, in the concluding chapter of this book, detailed directions for experimental procedures for reactions involving microbial cultures. All too often chemists are deterred from undertaking exquisitely specific and stereospecific microbial oxidations because they do not have the "feel" for such operations. The equipment, its sterilization, the securement and use of the cultures, solvents, and reaction and work-up methods are all set forth with great clarity.

The body of the book discusses 12 types of microbial oxidations, according to the structures of the substrates. They include hydroxylation of nonactivated carbon bonds, allylic, olefinic, and aromatic hydroxylations, aromatic ring opening, Baeyer–Villiger and β-oxidations, dehydrogenations, oxidation of amines, sulfur compounds, oxidative dealkylations, etc. All reactions are richly illustrated and referenced. It will not be surprising if this book serves as a catalyst to draw many organic chemists to the use of microbes as chemical reagents.

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Advances in Drug Research. Vol. 6. Edited by N. J. Harper and A. B. Simmonds. Academic Press, London, New York. 1971. vi + 256 pp. 23.4 × 15.7 cm. $15.00.

This volume contains four excellent reviews. Two of them are essentially pharmacological, namely, Activities and Sites of Antinociceptive Action of Morphine-like Analgesics (by A. Herz and A. J. Teschemacher) and Molecular Aspects of the Storage and Uptake of Catecholamines (by N. Kirshner, S. M. Schanberg, and R. M. Ferris). Another review deals with Mass Spectrometry in Drug Research (by B. J. Millard). It reexplains briefly principles and scope of mass spectroscopy and selects as illustrative examples relatively