Synthesis of Two Metabolites of (+)-Propoxyphene

William W. Turner,* Richard N. Booher, Stephen E. Smits, and Albert Pohland

The Lilly Research Laboratories, Indianapolis, Indiana 46206. *Received January 17, 1977*

Two minor metabolites of (+)-propoxyphene were prepared in both the (±) and (+) forms. The optically pure forms were synthesized by a degradative route from (+)-propoxyphene. The di-N-demethylated metabolite **10a,b** had weak analgesic activity while the cyclized oxazine metabolite **7a** was inactive.

The metabolism of (+)-propoxyphene (**13**) has been the subject of a number of papers from these laboratories. It was known that N-demethylation was a major metabolic route in man[1] and in several animal species.[2,3] With newer techniques of gas chromatographic–mass spectrometric analysis a number of minor metabolites have recently been identified.[4-6]

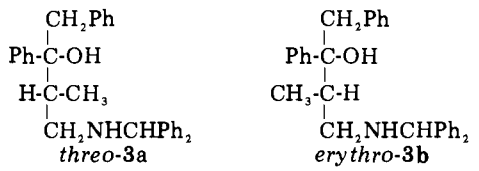
In this paper we wish to report the synthesis of two of these minor metabolites, 6-benzyl-2-ethyl-5,6-dihydro-5-methyl-6-phenyl-4*H*-1,3-oxazine (**7**) and 4-amino-1,2-diphenyl-3-methyl-2-butanol propionate (**10**), the di-N-demethylated analogue of propoxyphene. Both the racemic and (+) isomers of each compound were prepared with the optically pure material resulting from degradation of **13**.

Synthesis. The primary amino alcohol **4** was prepared from propiophenone in four steps. Propiophenone was allowed to react with 38% formalin and concentrated sulfuric acid to give 2-methylacrylophenone (**1**). Heating **1** with benzhydrylamine gave a Michael adduct **2** which was treated with benzylmagnesium chloride to produce two diastereometric racemates **3a,b**. These diastereomers were isolated by fractional crystallization in a 7:1 ratio with the more abundant isomer defined as **3a**. In order to decide which diastereomer corresponded to the (+)-propoxyphene (**13**) stereochemistry, **3a** was catalytically hydrogenated over palladium to give (±)-**4** which was di-N-methylated with formaldehyde and formic acid to give a compound which was identical with α-(±)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol,[7] a precursor of **13** and known to have the threo configuration.[8] By this comparison **3a** and **3b** were shown to have the relative stereochemistry depicted in Chart I. In practice **3a** and **3b** can be differentiated by NMR spectral analysis. The branched methyl group of **3a** appears as a doublet at δ 0.85, whereas the methyl doublet for **3b** appears at δ 1.35. Only **3a**, the threo isomer, was carried on in the synthesis.

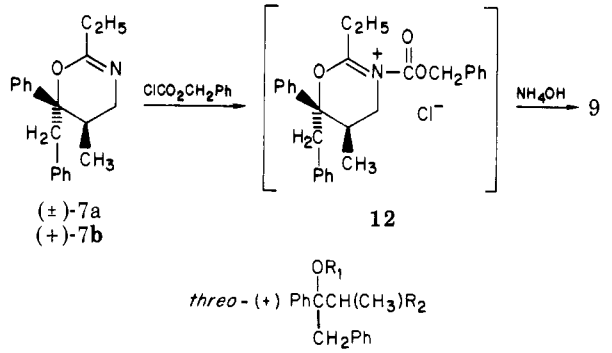
With the primary amino alcohol **4** in hand, a scheme of nitrogen protection, propionylation of the alcohol, and protective group cleavage was followed in the attempt to produce **10**. Reaction of **4** with trichloroethyl chloroformate gave the carbamate **5**. This hindered alcohol proved difficult to esterify. Only starting material was isolated from the reaction of **5** with propionic anhydride in pyridine. Heating **5** for 48 h at 80 °C with the mixed anhydride formed from trifluoroacetic anhydride and propionic acid gave a low yield (17%) of the desired **6**. Unfortunately, the cleavage of the nitrogen-protecting carbamate group in zinc and formic acid in dimethylformamide gave only the oxazine metabolite **7a** with no detectable amount of the open-chain metabolite **10a**. The cyclization could have occurred during a phase of the work-up which had a basic environment. The reaction was repeated using a constantly acidic work-up procedure, but **7a** was still the only isolated product.

Another protecting group, the benzylcarbamate **8**, was prepared from **4** using benzyl chloroformate. Reaction of **8** with the mixed anhydride acylating mixture gave a very

Chart I



Scheme I



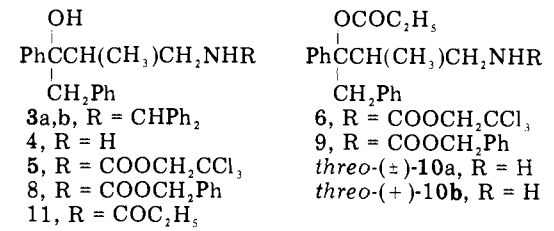
13, $R_1 = COC_2H_5$; $R_2 = CH_2N(CH_3)_2$
14, $R_1 = COC_2H_5$; $R_2 = CO_2H$
15, $R_1 = H$; $R_2 = CH_2OH$

low yield (2%) of the propionate ester **9**. Catalytic hydrogenation of **9** in the presence of palladium in ethanol containing a small amount of chloroform (to generate the HCl salt[9]) gave **10a**·HCl.

Because of the low yield, an improved synthesis of **9** was devised. The propionamide **11** was allowed to react with phosphorus pentachloride to form an intermediate imino chloride which cyclized in situ to **7a**. Treatment of **7a** with benzyl chloroformate in pentane at 0 °C gave a white precipitate. When allowed to warm to room temperature the white solid decomposed to an oil giving a mixture of components upon work-up. When the reaction was quenched at 0 °C with dilute ammonium hydroxide solution the only product isolated was the desired **9**, indicating that the unstable precipitate most likely had the structure **12**.

Resolution attempts using a variety of optically pure acids were unsuccessful with intermediates **3** and **4**, but a degradative procedure starting with **13** finally did succeed in giving the optically pure metabolites. The (+)-propoxyphene **13** was oxidized with potassium permanganate to give the acid **14** which was reduced with borane–methyl sulfide complex and hydrolyzed to give the diol **15**. Treatment of **15** with *p*-toluenesulfonyl chloride provided the primary tosylate which reacted with ammonia to give *threo*-(+)-**4**. The optical purity of *threo*-(+)-**4** was verified by conversion to the known α-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol. The *threo*-(+)-**4** was carried through the procedures of Chart II and Scheme I to give **7b** and eventually **10b**. The preferred salt form of **10** was the highly crystalline maleate. This compound is unstable in solution and has cyclized to **7** during some

Chart II



recrystallization attempts. The free base of **10** cyclizes completely in ether at 0 °C in only a few minutes.

Biological Results. The mouse-writhing analgesic test,[10] with 0.6% acetic acid as the agent to induce writhing, was used to assess the analgesic activities of **7a**, **10a**, and **10b** after subcutaneous administration. No activity was seen with **7a** at 100 mg/kg. With **10a** and **10b** the inhibition of writhing had a very rapid onset, a peak at 5–15 min, and a duration of 30–60 min. The ED_{50} (95% confidence limits) was 51 (40–64) mg/kg for **10a** compared to an ED_{50} of 6.9 (4.1–12) mg/kg for **13**. Although there was insufficient sample for a complete dose–response curve, the data available indicate an ED_{50} of approximately 25 mg/kg for **10b**. The narcotic antagonist naloxone (10 mg/kg) effectively blocked the analgesic activity of both **10a** and **10b**. The subcutaneous injection of **10a** and **10b** appeared to be irritating since the mice scratched at the injection site when concentrations greater than 1.0 mg/mL were used.

Although both **7b** and **10b** have been found in man in small amounts after the administration of **13**, the weak analgesic activity of these two compounds in mice suggests that they do not contribute significantly to the pharmacological effects of **13**.

Experimental Section

All compounds were identified by NMR. Where analyses were indicated by symbols of the elements, the microanalytical results were within ±0.4% of the theoretical values. Melting points are uncorrected.

2-Methylacrylophenone (1). Concentrated sulfuric acid (85 mL) was cautiously added to a solution of propiophenone (134 g, 1.0 mol) and 37% aqueous formaldehyde (595 mL) in 425 mL of 1,4-dioxane. The reaction mixture was refluxed 18 h, cooled to room temperature, and poured into 1 L of H_2O. This mixture was extracted with two portions (1 L) of Et_2O. The combined Et_2O extracts were dried ($MgSO_4$) and the solvent was removed in vacuo to give a yellow oil which was distilled to provide 52.5 g [80–90 °C (0.7 mm)] (36%) of 1: NMR ($CDCl_3$) δ 2.05 (s, 3 H, $-CH_3$), 5.6 (s, 1 H, =CH), 5.9 (s, 1 H, =CH), 7.3–7.9 (m, 5 H, ArH).

***threo*- and *erythro*-(±)-4-Diphenylmethylamino-1,2-diphenyl-3-methyl-2-butanol (3a,b).** A mixture of 1 (52.5 g, 0.36 mol) and benzhydrylamine (65.9 g, 0.36 mol) was heated on a steamplate for 18 h. A benzyl Grignard reagent was prepared by standard techniques from magnesium turnings (19.2 g, 0.8 mol) and benzyl chloride (101.6 g, 0.8 mol) in Et_2O. The viscous solution containing **2** was removed from the steamplate and diluted with benzene (100 mL). This solution was added dropwise to Grignard reagent and stirred for 20 h at room temperature. The mixture was poured into ice and dilute aqueous HCl. The precipitate was collected by filtration and recrystallized from ethyl acetate and methanol to give 60 g (36%) of **3a**·HCl: mp 127–130 °C; NMR (Me_2SO-d_6) δ 0.85 (d, 3 H, $-CH_3$), 2.9–3.9 (m, 5 H), 5.5 (s, 1 H, $NCHAr_2$), 7.1–7.9 (m, 20 H, ArH). Further concentration of the filtrate gave **3b**·HCl (8.0 g, 5%): mp 164–167 °C; NMR (Me_2SO-d_6) δ 1.35 (d, 3 H, $-CH_3$), 2.5–3.2 (m, 5 H), 5.4 (s, 1 H, $-NCHAr_2$), 7.1–7.9 (m, 20 H, ArH). A small sample of **3a** was di-N-methylated with formaldehyde and formic acid to give the known α-(±)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol hydrochloride whose melting point compared favorably with the literature value: mp 230–232 °C (lit.[7] mp 231–232 °C).

***threo*-(±)-4-Amino-1,2-diphenyl-3-methyl-2-butanol (4).** A mixture of **3a** (101 g, 0.22 mol) and 5% Pd on carbon in EtOH (880 mL) was shaken at room temperature under 55 psi of H_2 for 16 h. The catalyst was removed by filtration and the solvent was evaporated in vacuo. The residue was dissolved in H_2O and washed with Et_2O. The H_2O layer was made basic with concentrated NH_4OH and extracted with two portions (100 mL) of Et_2O. The combined organic fractions were dried ($MgSO_4$) and the solvent was removed in vacuo to yield 44 g (78%) of *threo*-(±)-4 as a thick oil: NMR ($CDCl_3$) δ 0.80 (d, 3 H, $-CH_3$), 1.7–2.2 (m, 1 H, –CH–), 2.5–3.6 (m, 7 H), 7.0–7.6 (m, 10 H, ArH).

***threo*-(±)-2,2,2-Trichloroethyl *N*-(3,4-Diphenyl-2-methyl-3-butanol)carbamate (5).** Trichloroethyl chloroformate (7.1 g, 0.033 mol) was added dropwise to a stirred solution of 4 (8.5 g, 0.033 mol) and triethylamine (3.4 g, 0.033 mol) in benzene (100 mL) and the reaction mixture was refluxed for 6 h. The cooled solution was poured into dilute aqueous HCl and extracted with two portions (50 mL) of Et_2O. The Et_2O extracts were dried ($MgSO_4$) and concentrated in vacuo to give 12 g of solid which was recrystallized from Skelly B and acetone to yield 10.6 g (75%) of *threo*-(±)-**5**: mp 107–109 °C. Anal. ($C_{20}H_{22}Cl_3NO_3$) C, H, N, Cl.

***threo*-(±)-2,2,2-Trichloroethyl *N*-(3,4-Diphenyl-2-methyl-3-butanol propionate)carbamate (6).** A mixture of propionic acid (2.7 mL) and trifluoroacetic anhydride (5.1 mL) was kept at room temperature for 30 min and then diluted with 15 mL of toluene. This solution was added dropwise to an ice bath cooled slurry of 5 (10.6 g, 0.025 mol) and triethylamine (5.7 mL) in 6 mL of toluene. The reaction mixture was heated at 70 °C for 18 h. Longer periods of heating produced more dehydration product. After cooling to room temperature, the solution was diluted with Et_2O and washed with 10 mL of H_2O. The organic phase was then washed with two portions of saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated in vacuo to give 6 g of a foam. Crystallization from Skelly B and acetone gave 3.1 g (17%) of *threo*-(±)-**6** as a white solid: mp 112–113 °C. Anal. ($C_{23}H_{26}Cl_3NO_4$) C, H, Cl, N.

(±)-6-Benzyl-2-ethyl-5,6-dihydro-5-methyl-6-phenyl-4*H*-1,3-oxazine (7a). Method A. A solution of 6 (2.5 g, 0.005 mol) in 8 mL of dimethylformamide and 0.45 mL (0.02 mol) of formic acid was cooled to 10–15 °C with an ice bath. Zinc dust (1.0 g, 0.015 mol) was added in two portions maintaining the temperature below 20 °C. After the addition was complete the reaction mixture was cooled to 5 °C and stirred for 30 min. The ice bath was removed and the reaction was stirred for an additional 1.5 h. After the solids were removed by filtration, the filtrate was poured into a mixture of ice and dilute aqueous HCl solution and washed with Et_2O. The cooled aqueous layer was adjusted to pH 8 with NH_4OH and was quickly extracted with two portions (50 mL) of Et_2O. The combined Et_2O extracts were washed with H_2O, dried over $MgSO_4$, and treated with anhydrous HCl. Removal of the solvent in vacuo provided 1.1 g (67%) of **7a**·HCl as a hygroscopic foam: IR ν ($CHCl_3$) 1680 cm^{-1}; pK_a 6.33; NMR ($CDCl_3$) δ 0.9 (d, 3 H, $-CH_3$), 1.3 (t, 3 H, $-CH_3$), 2.5–4.3 (m, 7 H), 6.8–7.6 (m, 10 H, ArH).

Method B. The reaction procedure of method A was repeated through the point at which the zinc was removed by filtration. At this point, 2 mL of H_2O was added to the filtrate and H_2S gas was bubbled through the solution until the white precipitate ceased to form. After the solid was separated by filtration, several drops of concentrated HCl were added and the solvent was removed in vacuo to leave a foam residue. Analysis by NMR and IR only showed the presence of **7a**·HCl.

Method C. Phosphorus pentachloride (10.1 g, 0.048 mol) was added in one portion to a mixture of 11 (10.0 g, 0.032 mol) and triethylamine (6.8 mL, 0.048 mol) in benzene (100 mL) cooled by an ice bath. After 3 h the ice bath was removed and stirring was continued for 16 h. The reaction mixture was poured into ice and dilute NaOH solution and extracted with two portions of Et_2O. The Et_2O was dried ($MgSO_4$) and concentrated in vacuo to yield 8.5 g of an oil. The oil was converted to the perchloric acid salt and recrystallized from acetone and ether to give 5.43 g (43%) of **7a** perchlorate: mp 138–140 °C. Anal. ($C_{20}H_{24}ClNO_5$) C, H, N.

In a similar manner *threo*-(+)-11 (14.5 g, 0.047 mol) was treated with phosphorus pentachloride to provide 10 g of oil which was

chromatographed on 50 g of silica (Grace). The column was eluted with benzene and ethyl acetate (9:1) to give 5.2 g (38%) of the free base of **7b**. No crystalline salt form was found.

***threo*-(±)-Benzyl *N*-(3,4-Diphenyl-2-methyl-3-butanol)-carbamate (8).** Benzyl chloroformate (19.5 g, 0.114 mol) was added dropwise to a stirred solution of *threo*-(±)-4 (29.0 g, 0.114 mol) and triethylamine (11.4 g, 0.114 mol) in benzene (300 mL) at room temperature. After 6 h the reaction mixture was poured into dilute aqueous HCl solution and extracted with two portions (100 mL) of Et_2O. The Et_2O extracts were dried ($MgSO_4$) and concentrated in vacuo to give 39.0 g of oil which were crystallized from Skelly F and ether to provide 24 g (54%) of *threo*-(±)-8: mp 70–72 °C. Anal. ($C_{25}H_{27}NO_3$) C, H, N.

***threo*-(±)-Benzyl *N*-(3,4-Diphenyl-2-methyl-3-butanol propionate)carbamate (9). Method A.** A mixture of propionic acid (2.7 mL) and trifluoroacetic anhydride (5.1 mL) was kept at room temperature for 30 min and then diluted with 15 mL of toluene. This solution was added dropwise to an ice bath cooled slurry of *threo*-(±)-8 (9.7 g, 0.025 mol) and triethylamine (5.7 mL) in 6 mL of toluene. The reaction mixture was heated at 84 °C and monitored by NMR. The reaction was stopped at 72 h when hydroxy elimination products began to appear. After cooling to room temperature the solution was diluted with Et_2O and washed with 10 mL of H_2O. The organic phase was then washed with two portions of saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated in vacuo to give 7.0 g of oil which was chromatographed in 50 g of silica (Grace). The column was eluted with benzene–ethyl acetate (19:1). The pure fraction was crystallized from Skelly F and ether to afford 0.268 g (2%) of *threo*-(±)-9: mp 97–98 °C. Anal. ($C_{28}H_{31}NO_4$) C, H, N.

Method B. Benzyl chloroformate (4.3 g, 0.025 mol) was rapidly added to a stirred solution of the free base of **7a** (3.7 g, 0.013 mol) in pentane (15 mL) at 0 °C. A white precipitate immediately formed. After 3 min a dilute NH_4OH solution (10 mL) was added and the reaction mixture was extracted with Et_2O (20 mL). The Et_2O extract was washed with dilute HCl solution, dried ($MgSO_4$), and concentrated in vacuo to afford 6 g of an oil. The oil was chromatographed on 50 g of silica (Grace). The column was eluted with benzene–ethyl acetate (19:1) giving a pure fraction which was crystallized from Skelly B and ether to yield 2.7 g (47%) of *threo*-(±)-9: mp 97–99 °C. Anal. ($C_{28}H_{31}NO_4$) C, H, N.

In a similar manner **7b** (5.0 g, 0.017 mol) treated with benzyl chloroformate gave 2.2 g (29%) of *threo*-(+)-9 as an oil.

***threo*-(±)-4-Amino-1,2-diphenyl-3-methyl-2-butanol Propionate (10a).** A mixture of *threo*-(±)-9 (0.25 g) and 5% Pd on carbon in ethanol (100 mL) and chloroform (2 mL) was shaken at room temperature under 40 psi of H_2 for 3 h. The catalyst was removed by filtration and the solvent was evaporated in vacuo to leave a solid residue of 160 mg (82%) of **10a**·HCl: IR ($CHCl_3$) ν 1740 cm^{-1}; pK_a 9.4. The **10a**·HCl (1.0 g, 0.003 mol) was dissolved in saturated $NaHCO_3$ solution (5 mL) and quickly extracted with Et_2O (10 mL). The Et_2O extract was immediately poured into a solution of maleic acid (0.34 g, 0.003 mol) in ethyl acetate (10 mL) and crystals formed within 1 min. The solid was collected by filtration to yield 0.88 g (69%) of **10a** maleate: mp 133–134 °C; pK_a 9.2; NMR (Me_2SO-d_6) δ 0.90–1.30 (m, 6 H, $2CH_3$), 2.1–2.7 [m, 3 H, –CH– and –C(=O)CH_2], 3.3 (d, 2 H, $-CH_2N$), 3.8 (s, 2 H, $-CH_2Ar$), 6.2 (s, 2 H, HC=CH), 7.0–7.5 (m, 10 H, ArH). Anal. ($C_{24}H_{29}NO_6$) C, H, N.

Similarly *threo*-(+)-9 (2.2 g, 0.005 mol) was hydrogenated to give 125 mg (8%) of **10b** maleate: mp 127–128 °C; $[\alpha]^{25}_D$ +31.7° (*c* 1, MeOH). Anal. ($C_{24}H_{29}NO_6$) C, H, N.

***threo*-(±)-*N*-(3,4-Diphenyl-2-methyl-3-butanol)propionamide (11).** Propionyl chloride (2.8 g, 0.03 mol) was added dropwise to a solution of *threo*-(±)-4 (6.5 g, 0.026 mol) and triethylamine (3 g, 0.03 mol) in benzene (50 mL). After 6 h at room temperature the mixture was washed with first a dilute HCl solution and then a dilute NaOH solution. The benzene layer next was washed with two portions of H_2O, dried ($MgSO_4$), and concentrated in vacuo to yield 8.0 g (86%) of *threo*-(±)-11 as an oil: NMR ($CDCl_3$) δ 0.85 (d, 3 H, $-CH_3$), 1.1 (t, 3 H, $-CH_3$), 2.1 (m, 1 H, –CH–), 2.2 [q, 2 H, $-CH_2C(=O)$], 2.8 (s, 1 H, –OH), 3.2–3.6 (m, 4 H), 6.6 (m, 1 H, –NH), 6.8–7.4 (m, 10 H, ArH).

In a similar manner *threo*-(+)-4 (12.5 g, 0.049 mol) was treated with propionyl chloride to give 14.5 g (95%) of *threo*-(+)-11.

***threo*-(+)-3,4-Diphenyl-2-methyl-3-propionoxybutanoic Acid (14).** A solution of (+)-propoxyphene (**13**) (33 g, 0.1 mol) in acetone (500 mL) was added rapidly to potassium permanganate (95 g, 0.6 mol) and calcium sulfate dihydrate (52 g, 0.3 mol) in 1 L of H_2O. The reaction temperature rose to 60 °C and 300 mL of cold H_2O and 500 mL of acetone were added. After stirring at room temperature for 3 h, the reaction mixture was cooled with an ice bath and concentrated HCl was carefully added until the solution reached pH 2. Next solid sodium bisulfite was added until the solution and precipitate were white. This reaction mixture was extracted twice with Et_2O (1 L). The Et_2O solution was extracted with dilute NaOH solution (500 mL) and this aqueous layer was made acidic with dilute HCl solution. The aqueous acid solution was extracted with two portions (200 mL) of Et_2O which were dried ($MgSO_4$) and concentrated in vacuo to yield 8 g of oil. The oil was crystallized from Skelly B and ether to give 6 g (18%) of *threo*-(+)-14: mp 104–107 °C. Anal. ($C_{20}H_{22}O_4$) C, H.

***threo*-(+)-3,4-Diphenyl-2-methyl-1,3-butanediol (15).** Borane–methyl sulfide complex (95%) (20 mL, 0.2 mol) was added dropwise to a solution of *threo*-(+)-14 (21.0 g, 0.065 mol) in tetrahydrofuran (200 mL) at room temperature. After 16 h methanol was added dropwise to the reaction mixture until the bubbling ceased. The solvent was removed in vacuo giving a clear oil. The oil was suspended in 1 N NaOH solution (200 mL) and ethanol was added until the solution became totally miscible. After 16 h at room temperature the solvent was removed in vacuo. The residue was dissolved in H_2O (200 mL) and Et_2O (200 mL). The Et_2O layer was dried ($MgSO_4$) and concentrated to afford 14.0 g (85%) of *threo*-(+)-**15** as an oil: NMR ($CDCl_3$) δ 0.8 (d, 3 H, $-CH_3$), 1.8–2.4 (m, 1 H, –CH–), 3.1–4.0 (m, 6 H), 6.8–7.4 (m, 10 H, ArH).

***threo*-(+)-4-Amino-1,2-diphenyl-3-methyl-2-butanol (4).** To a cooled pyridine solution (200 mL) of *threo*-(+)-**15** (14.0 g, 0.055 mol) was added *p*-toluenesulfonyl chloride (21 g, 0.11 mol) and the reaction mixture was refrigerated for 18 h. The solution was poured into cold H_2O and extracted with Et_2O. The Et_2O was washed with cold dilute HCl solution, dried ($MgSO_4$), and concentrated to a lesser volume in vacuo. Skelly B was added until the solution was cloudy and crystals formed. Filtration gave 19.0 g of solid: mp 106–108 °C. The solid was placed in a high-pressure reaction vessel with anhydrous liquid ammonia (150 mL) and heated at 60 °C for 13 h. The reaction mixture was collected in ethanol and the solvent was removed in vacuo. The residue was dissolved in H_2O and extracted with Et_2O. The Et_2O was dried ($MgSO_4$) and concentrated to yield 6.5 g (51%) of *threo*-(+)-4 as an oil. A small portion of the oil was converted to the maleic acid salt: mp 122–123 °C; $[\alpha]^{25}_D$ +13.1° (*c* 1, EtOH). This small sample was di-N-methylated with formaldehyde and formic acid to give the known α-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol hydrochloride whose optical rotation compared favorably with the literature value: $[\alpha]^{25}_D$ +53.2° (*c* 1, H_2O) [lit.[11] $[\alpha]^{25}_D$ +54.9° (*c* 1, H_2O)].

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Experimental Antiulcer Drugs. 2. 2-Substituted 2,4,5,6-Tetrahydro-1,3,4,6,6-pentamethylcyclopenta[*c*]pyrrole-4-carboxamides[1]

Rudolf Oesterlin, Malcolm R. Bell,* Ruthann H. McGarry, Allan G. Hlavac,

Department of Chemistry

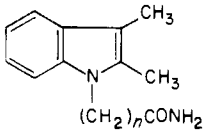
James C. Bradford, and Janis Rozitis, Jr.

Department of Toxicology, Sterling-Winthrop Research Institute, Rensselaer, New York 12144. *Received November 22, 1976*

Condensation of a 1-substituted 2,5-dimethylpyrrole **6** with 2 mol of 2-amino-2-methylpropionitrile in hot acetic acid yielded a 2-substituted 2,4,5,6-tetrahydro-1,3,4,5,6,6-pentamethylcyclopenta[*c*]pyrrole-4-carbonitrile (**4**). Hydrolysis of the nitriles to the amides gave a group of compounds which were active as antisecretory agents in the pyloric-ligated rat. Outstanding in this respect was the 2-phenyl derivative **5b**, the most active compound in the series. It did not possess anticholinergic properties. In contrast to the indoles and pyrroles reported earlier, **5b** demonstrated marked activity in blocking gastric acid secretion in the histamine-stimulated dog.

In the first paper of this series[2] we reported the gastric antisecretory activity of 2,3-dimethylindole-1-alkanamides (**1**) and 2,3,4,5-tetramethylpyrrole-1-acetamide (**2**) in the pyloric-ligated rat and the lack of gastric antisecretory activity of this class of compounds in the histamine-stimulated dog. A candidate antiulcer drug should have demonstrated activity in at least two species[3] and thus we continued our efforts to solve the problem of the lack of carryover of activity from the rat to the dog in this class of compounds.

The fact that the length of the alkanamide chain could be varied (n = 1, 2, or 3 in **1**) without an appreciable change



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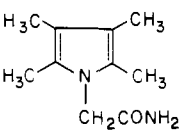
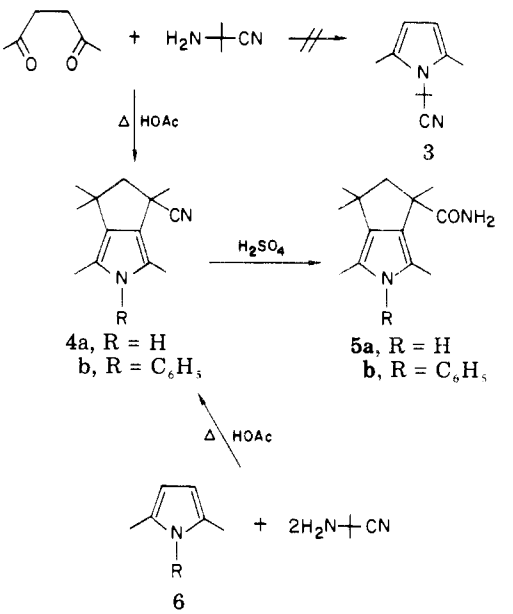


2

in the antisecretory activity suggested that the activity of these compounds was mediated by 2,3-dimethylindole, a theoretical metabolite of all the indole-1-alkanamides. N-Dealkylation is a common metabolic transformation[4] and probably results from enzymatic hydroxylation at the carbon atom adjacent to the nitrogen atom, followed by spontaneous cleavage of the resulting carbinolamine. 2,3-Dimethylindole was found to be active in the rat but appeared to be considerably less active than the parent amides and was only modestly active in the dog. We therefore turned our attention to the construction of indole and pyrrole derivatives with a metabolically stable alkanamide side chain.

An obvious candidate structure is one in which hydroxylation is blocked by replacement of the presumably metabolically labile hydrogen atoms by methyl groups. With the objective of preparing an example of this structural type in the pyrrole series, we attempted the condensation of 2,5-hexanedione with 2-amino-2-methylpropionitrile in hot acetic acid in the hope of obtaining **3** (Scheme I). The reaction took an unexpected course and resulted instead in the formation of the cyclopentapyrrolecarbonitrile **4a**. The same product resulted

Scheme I



upon condensation of 2,5-dimethylpyrrole (**6**, R = H) with 2-amino-2-methylpropionitrile. Although the corresponding carboxamide **5a** was not active in the rat, the *N*-phenyl derivative **5b** proved to be highly active in this species (Table I). Furthermore, compound **5b** was effective in blocking histamine-induced gastric acid secretion in the dog in contrast to **1** and **2** which are inactive in this model. We were encouraged, therefore, to investigate the chemistry and structure–activity relationships in the cyclopentapyrrole-4-carboxamide series.

Chemistry. The structure of the cyclopentapyrrole **4a** was supported by its spectral data, in particular the NMR spectrum. Confirmation of the structural assignment was provided by conversion to the aldehyde **7** (eq 1), followed by Wolff–Kishner reduction to the hexamethylcyclopentapyrrole **8** whose NMR spectrum showed the presence of the four equivalent methyl groups at C-4 and C-6. A pathway to the cyclopentapyrroles may be written if it is