basified with 50% NaOH and the resulting mixture extracted twice with 200-mL portions of ether. The combined extracts were washed once with water and then extracted twice with 100-mL portions of 6 N HCl. The extracts were basified, and the oily product was reextracted into ether. After washing with water and drying over anhydrous K_2CO_3, the filtered solution was evaporated in vacuo to yield crude **3** (7.4 g) as a pale yellow oil which was distilled in a Kugelrohr apparatus. Two fractions were taken: bp 170–175 °C (bath) (0.05 mm) (3.7 g) and bp 147–153 °C (bath) (0.01 mm) (1.6 g). Both fractions were colorless viscous oils which crystallized on trituration with pentane: mp 70–71 °C; infrared (Nujol) 3350 cm^{-1} (NH); TLC R_f 0.53 (silica gel F_{254}; eluent, 8% Et_2NH in benzene). Anal. ($C_{19}H_{22}N_2$) C, H, N.

cis-**2,3,4,4a,5,9b-Hexahydro-2-phenethyl-5-propionyl-1*H*-pyrido[4,3-*b*]indole (4).** A solution of propionyl chloride (2.0 mL, 2.1 g, 0.023 mol) in 10 mL of $CHCl_3$ was added dropwise to a stirred solution of **3** (4.4 g, 0.016 mol) and triethylamine (3.5 mL, 0.025 mol) in 75 mL of $CHCl_3$. The reaction mixture was heated at reflux for 30 min, cooled, and washed twice with water. After drying over anhydrous K_2CO_3, evaporation in vacuo left a yellow oil which deposited crystals (3.4 g) from benzene–hexane: mp 105–108 °C. Recrystallization from ethanol gave pure **4** (2.1 g, 27% yield): mp 109–110 °C; infrared (Nujol) 1660 cm^{-1} (amide C=O).

trans-**2,3,4,4a,5,9b-Hexahydro-2-phenethyl-1*H*-pyrido[4,3-*b*]indole (5).** A warm solution of **2** (34.5 g, 0.125 mol) in 300 mL of dioxane was added dropwise to 500 mL of a stirred solution of 1 M BH_3 in THF (Alfa-Ventron) under a nitrogen atmosphere. Vigorous gas evolution was noted during addition. The resulting mixture was then heated at reflux for 3.5 h and then THF was slowly distilled from the mixture and replaced with dioxane until a pot temperature of 96 °C was attained. The resulting mixture was maintained at reflux overnight, then cooled in ice, and cautiously decomposed by addition of 300 mL of 37% HCl. The resulting mixture was heated at reflux for 2 h, cooled, and basified with excess 50% NaOH solution. Most of the volatile solvent was removed on a rotary evaporator, and the residue was then diluted with water to dissolve inorganic salts. It was then extracted with two 250-mL portions of ether, and the combined extracts were then washed with water and in turn extracted with two 250-mL portions of 3 N HCl. The combined acid extracts were washed once with ether and basified, and the precipitated oil was reextracted into ether. The ether solution was dried over anhydrous K_2CO_3, filtered, and evaporated in vacuo to give a solid product which was recrystallized twice from ether–hexane–benzene to give 15.2 g (44%) of **5**: mp 105–107 °C; infrared (Nujol) 3300 cm^{-1} (NH); TLC R_f 0.49 (silica gel F_{254}, 8% Et_2NH in benzene). Anal. ($C_{19}H_{22}N_2$) C, H, N.

trans-**2,3,4,4a,5,9b-Hexahydro-2-phenethyl-5-propionyl-1*H*-pyrido[4,3-*b*]indole (6).** Compound **5** (5.6 g, 0.02 mol) was propionylated in a manner identical with that used to prepare **4**. The crude product was obtained as a waxy solid which was taken up in 75 mL of ethanol and treated with dry HCl. On chilling a solid (3.5 g) separated which was filtered and recrystallized from 125 mL of H_2O to give 2.8 g (38%) of **6**·HCl: mp 280–282 °C dec. Anal. ($C_{22}H_{26}N_2O$·HCl) C, H, N, Cl.

The mother liquor from the above recrystallization was basified with 1 N NaOH and the precipitated oil extracted into ether. After drying over anhydrous K_2CO_3 and evaporation in vacuo, a yellow oil was obtained which was dissolved in 50 mL of pentane and allowed to stand overnight at 0–5 °C. The white crystals which formed were filtered and dried to give 0.25 g of free base: mp 96–98 °C; mmp with **4**, 86–100 °C; infrared (Nujol) 1660 cm^{-1} (amide C=O); ^1H NMR (270 MHz, $CDCl_3$) δ 1.29 (t, J = 6 Hz, 3 H, CH_3), 2.10 [q (J = 12.3 Hz) of d (J = 4.0 Hz), 1 H, H-4ax], 2.57 (q, J = 6 Hz, 2 H, $CHCH_3$), 2.71–2.93 (m, 5 H, overlapping H-3ax and CH_2CH_2), 3.13 [t (J = 12.3 Hz) of d (J = 2.0 Hz), 1 H, H-9b], 3.25 (d, J = 11.8 Hz, 1 H, H-3eq), 3.48 [t (J = 14.7 Hz) of d (J = 4.0 Hz), 1 H, H-4a], 3.60 [d (J = 12.0 Hz of d (J = 2.5 Hz), 1 H, H-1eq]. Anal. ($C_{22}H_{26}N_2O$) C, H, N.

Acknowledgment. We wish to thank Dr. D. H. Smith, Stine Laboratory, E. I. du Pont de Nemours, Inc., Newark Del., Dr. M. Cohen, Mr. H. Dayton, and Ms. M. MacDonald, Endo Laboratories, Inc., Garden City, N.Y., for pharmacological results. G.E.L. thanks the National Research Council of Canada for a postdoctoral fellowship.

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Synthesis of Some Pentazocine Metabolites and Related Compounds

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The syntheses of the trans alcohol **2** and the trans acid **5**, metabolites of pentazocine (**1**), are described. These are essentially devoid of agonist and antagonist activities. Some related oxidation products were also prepared for comparison with products isolated during metabolism studies.

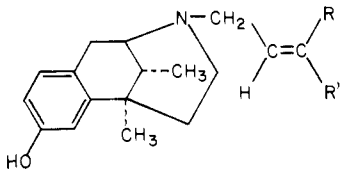
Early studies of the metabolism of pentazocine (**1**) in this Institute by Rosi and Merola[1] using mouse liver homogenates led to the isolation of a sufficient amount of the major metabolite as the acetate derivative to characterize by NMR. The data (see Experimental Section) showed that there was a loss of a side-chain methyl signal from pentazocine and the gain of a CH_2OAc group so that the compound was the acetate of either **2** or **3**, but in the absence of a sample of known configuration, no decision could be reached as to whether the cis alcohol **3** or trans alcohol **2** had been isolated. The present work was undertaken to provide a reference sample for comparison so

Table I. Test Results in mg/kg sc with 95% Confidence Limits

Compd	D'Amour-Smith	AD_{50}[a]	PPQ ED_{50}[b]
1	Inact. at 120	3.9 (2.1-7.4)	2.3 (1.6-3.0)
2		>320	37 (32-43)
5		No dose response	Inact. at 100
7	Inact. at 120	66 (37-119)	
8	Inact. at 60	Inact. at 40	
9	Inact. at 120	1.7 (0.87-3.3)	22 (15-31)
10	Inact. at 120	Inact. at 80	37 (30-45)
11		2.8 (1.9-4.0)	

[a] AD_{50} is the dose causing a 50% decrease in the effect of an approximate ED_{80} dose of meperidine. [b] PPQ ED_{50} is the dose protecting 50% of the animals from writhings elicited by a standard dose of *p*-phenylquinone.

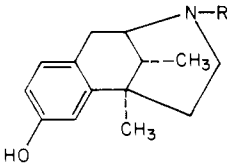
that the structure of the metabolites could be definitely established.



1, R = R' = CH_3
2, R = CH_3; R' = CH_2OH
3, R = CH_2OH; R' = CH_3
4, R = CH_3; R' = $COOC_2H_5$
5, R = CH_3; R' = COOH

Chemistry. Chloroacetaldehyde was condensed with the Wittig reagent from carbethoxyethyltriphenylphosphonium bromide to give (*E*)-ethyl 4-chloro-2-methylbutenoate with no evidence for the *Z* isomer.[2] This was allowed to react with 1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-2,6-methano-3-benzazocine to give **4**. Reduction with aluminum hydride gave **2**, the acetate of which gave an NMR identical with the acetate of the metabolite isolated by Rosi and Merola.

Subsequent metabolism studies with other species[1] indicated that another alcohol was produced by oxidation of a terminal methyl group of the pentazocine side chain. Since this differed from the trans alcohol **2**, the only alternative structure that would fit the NMR data (see Experimental Section) would be the cis alcohol **3**.



6, R = H
7, R = $CH_2COOC_2H_5$
8, R = CH_2COOH
9, R = $CH_2CH_2COCH_3$
10, R = $CH_2CH_2C(OH)(CH_3)_2$
11, R = $CH_2C(=O)CH(CH_3)_2$

Initial work with monkeys produced an acidic material which Conway[1] thought could be compound **8**. A sample was made by hydrolysis of the ester **7** which was on hand. However, **8** was not identical with the metabolite, and subsequently it was discovered that the acidic metabolite was **5**. A sample of **5** was prepared by acid hydrolysis of ester **4**. Several preparations gave a product melting at about 235 °C, but one preparation melted at 171–174 °C and differed in solubility. Both of these gave the same elemental analyses and identical infrared spectra in $AsCl_3$ solution. The NMR spectra were also identical. Polymorphism has been observed previously in the benzomorphan series; pentazocine, for example, gives interconvertible hydrochlorides, and May has observed two crystalline modifications for phenazocine.[3]

Several other oxidation products of pentazocine were synthesized as reference samples but were not found to be metabolites. Some workers had inadvertently hydrated pentazocine in acid solution. To supply them with a reference standard, nor base **6** was added to methyl vinyl ketone and treated with methyl Grignard reagent to give **10**.[4]

Ketone **11** was prepared by the alkylation of the nor base **6** with 1-chloro-3-methyl-2-butanone.

Pharmacology. Compounds were assayed for narcotic antagonism of meperidine by the method of Harris and Pierson[5] using a modified D'Amour-Smith thermal stimulus test procedure in the rat. Agonist activity was measured by the D'Amour-Smith assay or by the *p*-phenylquinone writhing tests. The compounds were administered in distilled water. Data are presented in Table I. It will be noted that trans acid **5** is inactive as both an agonist and an antagonist and trans alcohol **2** is essentially inactive as an antagonist and only $^1/_{11}$th as active as pentazocine in the phenylquinone writhing test. Thus, the activity of pentazocine is not due to conversion to these metabolites.

Experimental Section[6]

(*E*)-Ethyl 4-Chloro-2-methyl-2-butenoate. To 18.5 g of monochloroacetaldehyde[7] in 180 mL of CH_2Cl_2 was added dropwise 85.5 g of ethyl 2-(triphenylphosphoranylidene)-propanoate[8] in 300 mL of CH_2Cl_2 over 1 h. The solution was refluxed 2.5 h, concentrated in vacuo, and diluted with 300 mL of hexane to precipitate triphenylphosphine oxide. This was chilled and filtered and the filtrate distilled. After removal of the hexane, the product distilled at 102–104 °C (at 28 mm) to give 26.7 g (70%) of product: NMR ($CDCl_3$, internal Me_4Si) 1.28 (t, J = 7 Hz, 3 H), 4.15 (q, J = 7 Hz; d, J = 8 Hz, 4 H), 6.86 ppm (t, J = 8 Hz; q, J = 1–2 Hz, 1 H). Anal. ($C_7H_{11}ClO_2$) Cl: calcd, 21.80; found, 21.24.

Ethyl (*E*)-4-[(2α,6α,11*R)-(±)-1,2,3,4,5,6-Hexahydro-8-hydroxy-6,11-dimethyl-2,6-methano-3-benzazocine]-2-methyl-2-butenoate (4).** A mixture of 28.0 g of nor base **6**, 650 mL of DMF, 325 mL of THF, 28.0 g of $NaHCO_3$, and 26.7 g of (*E*)-ethyl 4-chloro-2-methyl-2-butenoate was stirred at 50–60 °C for 9 h, filtered, concentrated in vacuo, and partitioned between H_2O and Et_2O. The Et_2O layer was washed with H_2O, dried, filtered, and scratched to induce crystallization. Filtration gave 43.4 g of colored product. This was washed with Et_2O to remove the color to give 36.1 g (81.7%), mp 139–141.5 °C. A sample, recrystallized from Et_2O, melted at 144.0–146.0 °C. Anal. ($C_{12}H_{29}NO_3$) C, H, N.

(2α,6α,11*R)-(±)-1,2,3,4,5,6-Hexahydro-3-[(*E*)-4-hydroxy-3-methyl-2-butenyl]-6,11-dimethyl-2,6-methano-3-benzazocin-8-ol (2).** A mixture of 13.0 g of $LiAlH_4$ in THF was cooled in an ice bath while 9.0 mL of 100% H_2SO_4 followed by 18.9 g of **4** in THF was dripped in. After stirring 1.5 h, 26 mL of H_2O in THF was added. The inorganic salts were removed by filtration and the filtrate was concentrated in vacuo. The residue was recrystallized from EtOAc, filtered, and washed well with Et_2O with some loss to give 7.6 g, mp 155–160 °C. Recrystallization from EtOAc raised the melting point to 161–163 °C. Anal. ($C_{19}H_{27}NO_2$) C, H, N. NMR ($CDCl_3$, internal Me_4Si) for pentazocine (**1**) showed signals at 0.85 (d, 3 H, C_{11}-Me), 1.25 (s, 3 H,

C_6-Me), and 1.68 ppm [s, 6 H, $=C(CH_3)_2$]. NMR ($CDCl_3$, internal Me_4Si) for **2**: 0.83 (d, 3 H, C_{11}-Me), 1.28 (s, 3 H, C_6-Me), 1.80 (s, 3 H, side chain Me), and 4.04 ppm (s, 2 H, CH_2O). R_f in EtOAc–Et_3N (9:1) = 0.23 on silica plates.

Acetylation of **2** with acetic anhydride and pyridine gave a compound whose R_f, IR, and NMR were identical with the major metabolite from mouse liver. NMR ($CDCl_3$, internal Me_4Si) for acetylated **2** showed signals at 0.83 (d, 3 H, C_{11}-Me), 1.25 (s, 3 H, C_6-Me), 1.67 (s, 3 H, side chain Me), 2.02 + 2.22 (s, 6 H, 2 × CH_3CO), and 4.42 ppm (s, 2 H, CH_2O).

(2α,6α,11R*)-(±)-1,2,3,4,5,6-Hexahydro-3-[(*Z*)-4-hydroxy-3-methyl-2-butenyl]-6,11-dimethyl-2,6-methano-3-benzazocin-8-ol (3). Cherniak[1] isolated this product as the major metabolite from the incubation of pentazocine with rat liver microsomes and supplied us with a small sample for spectral study. The IR curve was essentially identical with that of the *E* isomer **2**. The NMR ($CDCl_3$, internal Me_4Si) showed signals at 0.84 (d, 3 H, C_{11}-Me), 1.32 (s, 3 H, C_6-Me), 1.83 (s, 3 H, side chain Me), and 4.18 ppm (s, 2 H, CH_2O). R_f in EtOAc–Et_3N (9:1) = 0.35 on silica plates.

(*E*)-4-[(2α,6α,11R*)-(±)-1,2,3,4,5,6-Hexahydro-8-hydroxy-6,11-dimethyl-2,6-methano-3-benzazocinyl]-2-methyl-2-butenoic Acid (5). High-Melting Form. Ester **4** (2.4 g) was refluxed 1 h with 24 mL of concentrated HCl and concentrated in vacuo. The residue was boiled with Me_2CO to induce crystallization and the solvent evaporated. Recrystallization from isopropyl alcohol–Et_2O gave 2.1 g, mp 229–232 °C. A second preparation in which the product was dissolved in excess Me_2CO, concentrated, chilled, and filtered gave a product melting at 233–236 °C. Anal. ($C_{19}H_{25}NO_3$·HCl) C, H, Cl.

Low-Melting Form. A solution of 6.9 g of ester **4** was refluxed 2 h with 70 mL of concentrated HCl, concentrated in vacuo, and recrystallized from Me_2CO to give 6.2 g, mp 171–174 °C. The NMR curves were identical for the high- and low-melting forms as were the IR curves in $AsCl_3$. However, there were minor differences in the IR curves taken in KBr pellets. Anal. ($C_{19}H_{25}NO_3$·HCl) Cl.

Ethyl (2α,6α,11R*)-(±)-1,4,5,6-Tetrahydro-8-hydroxy-6,11-dimethyl-2,6-methano-3-benzazocine-3(2*H*)-acetate (7). A mixture of 21.7 g of **6**, 12.6 g of $NaHCO_3$, and 12 mL of ethyl bromoacetate in 150 mL of DMF was stirred and refluxed 5 h, filtered, and concentrated in vacuo to a crystalline mass. This was dissolved in Et_2O–H_2O. Upon scratching, the product reprecipitated. It was filtered and washed well with water to give 20.1 g, mp 128–130.5 °C. Recrystallization from 135 mL of MeOH and 100 mL of H_2O with treatment with charcoal gave 17.8 g of white crystals, mp 131–132 °C. Anal. ($C_{18}H_{25}NO_3$) C, H, N.

(2α,6α,11R*)-(±)-1,4,5,6-Tetrahydro-8-hydroxy-6,11-dimethyl-2,6-methano-3-benzazocine-3(2*H*)-acetic Acid (8). A solution of 3.2 g of ester **8** in 10 mL of concentrated HCl and 10 mL of H_2O was refluxed 1.5 h, concentrated in vacuo, taken up in 25 mL of HOAc, and brought to turbidity with ether (ca. 5 mL). The crystals were filtered, washed with HOAc and EtOH, and dried to give 2.8 g, mp 232–235 °C. Anal. ($C_{16}H_{21}NO_3$·HCl) C, H, Cl.

4-[(2α,6α,11R*)-(±)-1,2,3,4,5,6-Hexahydro-8-hydroxy-6,11-dimethyl-2,6-methano-3-benzazocin-3-yl]-2-butanone (9). A solution of 10.8 g of nor base **6** in 150 mL of pyridine and 3.8 g of methyl vinyl ketone was heated 1 h on the steam bath and concentrated in vacuo. The residue was crystallized from EtOAc to give 11.2 g, mp 121–127 °C. Recrystallization from EtOH gave 5.3 g, mp 128–131 °C. Anal. ($C_{18}H_{25}NO_2$) C, H, N. A second preparation, recrystallized from EtOH, had the same melting point, but recrystallization from isopropyl alcohol raised the melting point to 142–145 °C. Anal. ($C_{18}H_{25}NO_2$) C, H.

(2α,6α,11R*)-(±)-1,2,3,4,5,6-Hexahydro-3-(3-hydroxy-3-methyl)butyl-6,11-dimethyl-2,6-methano-3-benzazocin-8-ol (10). Reaction of ketone **9** with excess methyl magnesium iodide in ether gave **10**,[4] mp 157–159 °C (from EtOH). Anal. ($C_{19}H_{29}NO_2$) C, H, N.

1-[(2α,6α,11R*)-(±)-1,2,3,4,5,6-Hexahydro-8-hydroxy-6,11-dimethyl-2,6-methano-3-benzazocin-3-yl]-3-methyl-2-butanone (11). Nor base **6** was alkylated with 1-chloro-3-methyl-2-butanone in DMF in the presence of $NaHCO_3$ (cf. preparation of **4**) to give a product melting at 131–134 °C (from EtOH). Anal. ($C_{19}H_{27}NO_2$) C, H, N.

Acknowledgment. We are indebted to Mrs. A. K. Pierson for pharmacological test results and to Miss C. Martini and Dr. R. Kullnig for spectral data.

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In Vitro Metabolism of a New 4-Hydroxycoumarin Anticoagulant. Structure of an Unusual Metabolite

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Received July 12, 1976

The metabolism of clocoumarol, 3-[1-[*p*-(2-chloroethyl)phenyl]butyl]-4-hydroxycoumarin, by rat liver microsomes was investigated. The chemical structure of the main metabolite is 6-[1-hydroxy-2-oxo-3-[*p*-(2-chloroethyl)-phenyl]hexylidene]-2,4-cyclohexadien-1-one; such a structure has not been previously reported for metabolites from anticoagulants of the 4-hydroxycoumarin group.

Clocoumarol [3-[1-[*p*-(2-chloroethyl)phenyl]butyl]-4-hydroxycoumarin (**1**)], a new synthetic vitamin K antagonist, exhibits strong anticoagulant properties in both rat and rabbit.[1,2] Related compounds, such as warfarin and phenprocoumon, are extensively metabolized in vivo by man and animals.[3-5] This paper presents our results on the in vitro biotransformation of clocoumarol by liver microsomes, as well as the identification of the main