144–146°. An analytical sample, recrystallized twice from PhMe, had mp 147–148°.

(b) Compound **24** (5 g) was added to a solution of 0.4 g of Na in 10 g of N,N-diethylethylenediamine. The mixture was heated at 125–130° for 7 hr. A little H_2O was added and most of the amine was distilled under reduced pressure. The residue was taken up in 10% AcOH. After filtering, the filtrate was alkalinized with NH_4OH and extracted with $CHCl_3$. The extracts were washed (H_2O), dried (Na_2SO_4), and evaporated; the residue was triturated with Et_2O and crystallized (PhMe) giving **26**, mp 142–143°. This was identical with the compound obtained by decarboxylation (mixture melting point, ir).

N,N-Dimethylaminoethyl 8,9-Dimethoxy-5,6-dihydro-2-methylpyrrolo[2,1-*a*]isoquinoline-3-carboxylate (21) (Method F).—A solution of 15.7 g (0.05 mole) of ethyl 8,9-dimethoxy-5,6-dihydro-2-methylpyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**19**)[5c] and 7 g (0.078 mole) of dimethylaminoethanol in 230 ml of PhMe was placed in the flask at the bottom of a Fenske-Todd column and made anhydrous by distilling until the boiling point reached 110°. Then 7.8 mmoles of NaOEt (4 ml of a 13% solution in anhydrous EtOH) was added and the solution was refluxed while distilling the EtOH (4 hr). The solution was cooled, washed (H_2O), and extracted with 10% AcOH. The acid extracts were alkalinized with NH_4OH and extracted with $CHCl_3$, and the extracts were dried and evaporated. The residue was crystallized from petroleum ether (bp 80–120°) giving 12.6 g (70%) of **21**, mp 98–99°. The hydrochloride had mp 252–255° (EtOH–Et_2O). *Anal.* ($C_{20}H_{26}N_2O_4 \cdot HCl$) Cl, N.

Ethyl 1-Morpholinomethyl-2-methyl-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (27) (Method G).—A solution of 6.3 g (0.02 mole) of **19**[5c] and 1.9 g (0.022 mole) of a 30% (w/v) solution of formaldehyde in 125 ml of AcOH was kept at 60° for 3 hr, then cooled, diluted (H_2O) to 600 ml, filtered, made basic with NH_4OH, and extracted with Et_2O. The extracts were dried (Na_2SO_4) and evaporated; the residue was crystallized from petroleum ether (bp 80–120°) giving 3.8 g (45%) of **27**: mp 154–155°; nmr, τ 1.79, 3.17, 7.62; **19**: nmr, τ 2.90, 3.21, 3.64, 7.59.

Acknowledgments.—The authors are indebted to Dr. G. V. Marchetti for the preliminary hemodynamic data, and to Dr. G. Severini Ricca for determination and valuable help in interpretation of the nmr and mass spectra.

Urinary Metabolites of 7-Chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one Dihydrochloride

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Metabolites of the title compound (Ia) extracted from human and dog urine were characterized by a combination of tlc and high-resolution mass spectrometry and were compared with authentic compounds prepared as described in the immediately following publication.[1] Only one metabolite, 7-chloro-1-(2-hydroxyethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (IV), was detected as a glucosuronic acid and/or sulfate conjugate in urine of two human subjects given 60 mg of Ia orally. It was estimated that one subject excreted roughly 25% of the administered drug in the first day as conjugated IV. Chronic oral administration of 40 mg/kg of Ia to a dog resulted in the urinary excretion of nonconjugated I, 7-chloro-1,3-dihydro-1-(2-ethylaminoethyl)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (II), and 1-(2-aminoethyl)-7-chloro-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (III), and the excretion of conjugated II–IV, 7-chloro-5-(2-fluorophenyl)-3-hydroxy-1,3-dihydro-2H-1,4-benzodiazepin-2-one (VI), and a phenolic derivative of 7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one whose structure was not definitively established. In addition, 8-chloro-6-(2-fluorophenyl)-1,2-dihydro-4H-imidazo[1,2-*a*][1,4]benzodiazepine (VII) was shown to be an artifact resulting from tlc of III.

The synthesis and a comparison of the pharmacology of 7-chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one dihydrochloride (Ia) with that of other 1,4-benzodiazepines has been reported[2] as well as the clinical use of this compound as a hypnotic.[3]

The combination of thin layer chromatography (tlc) for metabolite isolation and purification and high-resolution mass spectrometry for characterization has been used to identify the metabolites in the rat of ^{3}H-labeled diazepam[4] and ^{14}C-labeled chlordiazepoxide.[5] In the present study these combined techniques were utilized to identify one metabolite of unlabeled Ia in human urine and five metabolites in dog urine.

Experimental Section

Urine Specimens.—The human urine was obtained from two female subjects who each received a 60-mg oral dose of Ia. Two collections were made: one consisted of the 24-hr urine excreted prior to drug administration (control urine) and the other was the urine excreted during the first day after dosing.

The dog urine was obtained from one animal which had received an oral dose of 40 mg/kg of Ia (in a gelatin capsule) daily for 6 months and from another which had not received the drug. Both of these samples were approximately 100 ml.

Isolation Procedures.—Each urine sample was first fractionated by solvent extraction. The urine adjusted to pH 9.0 with 1 *N* NaOH was extracted twice with equal volumes of ether. The combined ether extract which contained any I present plus neutral and basic nonpolar metabolites was concentrated to an oil and brought to 1 ml with EtOH. The aqueous phase was then adjusted to pH 7.0 with 1 *N* HCl and extracted twice with equal volumes of EtOAc to remove neutral but more polar metabolites. The combined EtOAc extract was dried (Na_2SO_4) and after evaporation of the solvent was brought to 1 ml with EtOH and designated "EtAc B.G." Now the aqueous phase was adjusted to pH 5.5, incubated for 3 hr at 37° with Glusulase[6]

(1) J. V. Earley, R. I. Fryer, D. Winter, and L. H. Sternbach, *J. Med. Chem.*, **11**, 774 (1968).

(2) (a) L. H. Sternbach, G. A. Archer, J. V. Earley, R. I. Fryer, E. Reeder, N. Wasyliw, L. O. Randall, and R. Banziger, *ibid.*, **8**, 815 (1965), designated as **12**. (b) See G. Zbinden and L. O. Randall, *Advan. Pharmacol.*, **5**, 254, 258 (1967), for animal pharmacology and clinical pharmacology of this compound which is designated Ro 5-6901.

(3) H. Jick, *Curr. Therap. Res.*, **9**, 355 (1967). Compound is referred to as Ro 5-6901.

(4) M. A. Schwartz, P. Bommer, and F. M. Vane, *Arch. Biochem. Biophys.*, **121**, 508 (1967).

(5) M. A. Schwartz, F. M. Vane, and E. Postma, *Biochem. Pharmacol.*, in press.

(6) Product of Endo Labs Inc., Garden City, N. Y., which contains 100,000 units of β-glucuronidase and 50,000 units of sulfatase/ml.

(at a final concentration of 1% v/v), then readjusted to pH 7.0, and reextracted with two equal volumes of EtOAc. This EtOAc extract (treated as above and brought to 1 ml with EtOH) was designated "EtAc A.G." and contained those metabolites which were originally present in the urine as glucosuronic acid and/or sulfate conjugates.

The extracted metabolites were separated by tlc on a fluorescent silica gel (Camag Kieselgel DF-5). The following solvent systems were used: 1, EtOAc–EtOH–concentrated NH_3 (90:10:0.3); 2, heptane–$CHCl_3$–EtOH–concentrated NH_3 (50:50:25:1); 2a, heptane–$CHCl_3$–EtOH–concentrated NH_3 (50:50:20:1); 3, *i*-PrOH–concentrated NH_3 (100:1); 4, Me_2CO–$CHCl_3$–concentrated NH_3 (50:50:1); 5, EtOAc–EtOH–concentrated NH_3 (90:10:1); 6, heptane–Me_2CO–EtOH–concentrated NH_3 (50:50:25:1); 7, $CHCl_3$–Me_2CO–concentrated NH_3 (80:60:1); and 8, C_6H_6–EtOAc–EtOH–concentrated NH_3 (80:20:20:2).

Solvent system 1 was the initial system used to separate the metabolites. The migration of I and of related compounds is shown in Table I. Detection of I and metabolites was accomplished by spraying the plate with a modified Dragendorff reagent[7] which was prepared by mixing equal volumes of a solution of 1.7% (w/v) bismuth nitrate in 20% AcOH with 40% (w/v) aqueous solution of KI and diluting the mixture with 4 vol of 10% H_2SO_4. For isolation purposes, greater aliquots were streaked across large 20 × 20 cm chromatoplates and after development in system 1 a narrow vertical channel on each plate was sprayed with the Dragendorff reagent. Those bands seen under short-wave uv light which were Dragendorff positive were scraped off, eluted with EtOH (5–10 ml twice), and concentrated. The tlc (in different solvent systems) and elution of Dragendorff-positive bands was then repeated twice with each concentrate.

Mass Spectrometry.—The preparation of samples for introduction into the Consolidated Electrodynamics Corp. 21-110 mass spectrometer and a brief description of how the high-resolution mass spectral data were obtained have been reported.[4]

Results and Discussion

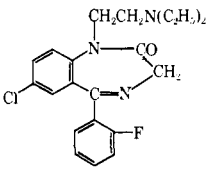
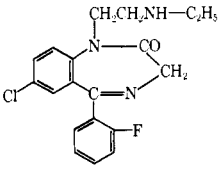
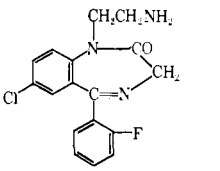
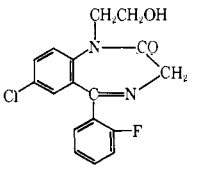
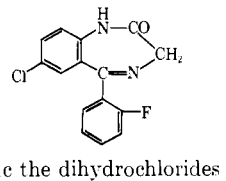
Human Urinary Metabolite.—Tlc in system 1 of the ether, EtAc B.G., and EtAc A.G. extracts of pre- and posttreatment urine gave one clear-cut indication of a metabolite: the presence of IV in the EtAc A.G. extracts of both subjects. This ethyl acetate extract of the posttreatment urine of subject B was used for isolation and further identification of this metabolite. Tlc systems 2, 4, and 5 were used serially for the purification of Dragendorff-positive metabolite which in each system migrated as authentic IV. High-resolution mass spectral analysis of this metabolite (Table IV, see last column labeled Human) yielded a molecular composition ($C_{17}H_{14}FClN_2O_2$) which differed from that of I by $-C_4H_9N + O$ and indicated that the diethylamino group in the side chain had been replaced by a hydroxyl group; the loss of CH_2OH to form the *m/e* 301 fragment and loss of C_2H_4O to form *m/e* 288 supported this conclusion. Finally, the mass spectrum of this metabolite was identical with that obtained with IV and on two-dimensional tlc (system 6 followed by system 3); the metabolite and IV did not separate but migrated as one compound. It was therefore concluded that Ia was metabolized to IV which was excreted as a glucosuronic acid and/or sulfate conjugate.

An aliquot of EtAc A.G. extract of subject A posttreatment urine was chromatographed in system 1 alongside graded amounts of IV. Visual comparison of the intensity of the Dragendorff reaction of metabolite and standards led to the estimation that roughly 25% of the 60-mg dose of Ia was excreted during the first day as conjugated IV.

(7) This reagent, developed by R. Colarusso, E. Heylweil, and B. Z. Senkowski, Analytical Research Laboratory, Hoffmann-La Roche Inc., becomes more sensitive as it ages. After 3–4 weeks it detected 1–2 μg of I and analogs as rust red spots on a light yellow background.

TABLE I

TLC MIGRATION OF I AND RELATED COMPOUNDS IN SYSTEM 1

Compound[a]	Structure	R_f
7-Chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (I)		0.50
7-Chloro-1,3-dihydro-1-(2-ethylaminoethyl)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (II)		0.09
1-(2-Aminoethyl)-7-chloro-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (III)		0.09
7-Chloro-1-(2-(hydroxyethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (IV)		0.71
7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (V)		0.88

[a] As reference compounds for tlc the dihydrochlorides of I, II, and III and the monohydrochloride of IV were used. Ia represents the dihydrochloride of I.

Urinary Metabolites of the Chronically Treated Dog.—Aliquots of the ether, EtAc B.G., and EtAc A.G. extracts prepared from 50 ml of urine from a control dog and one treated for 6 months with Ia were chromatographed in system 1. As seen in Table II there were four definite metabolite bands, two in the ether extract and two in the EtAc A.G. extract.

Band 3 and band 4 components of the EtAc A.G. extract were each separated into a number of Dragendorff-positive components (Table III). Band 3 yielded 3A, 3B, and 3C; and 3C migrated as IV. Band 4 yielded $4A_1$ (which migrated as III), $4A_2$, 4B (which migrated as II), and 4C.

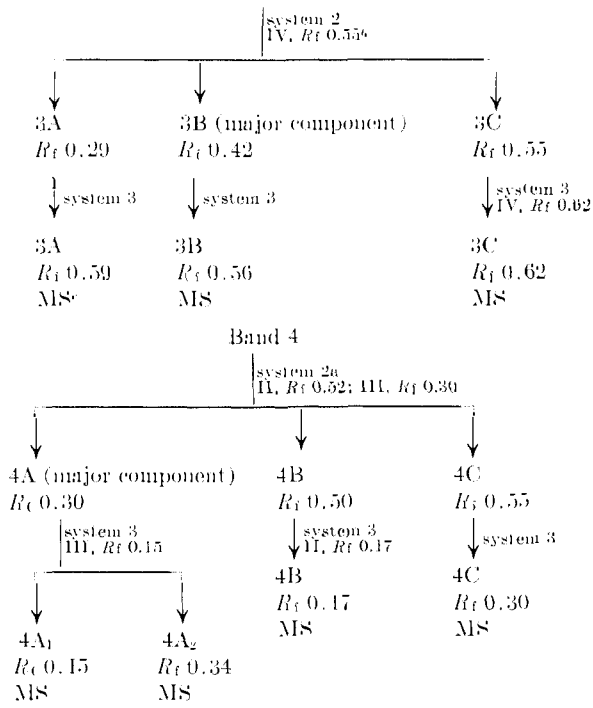
TABLE II

DRAGENDORFF-POSITIVE SUBSTANCES IN EXTRACTS OF URINE FROM A DOG CHRONICALLY TREATED WITH Ia WHICH WERE ABSENT FROM CONTROL DOG URINE EXTRACTS

Urine extract[a]	Dragendorff-positive bands on tlc in system 1 Designation	R_f
Ether	Band 1	0.51
	Band 2	0.15
EtAc B.G.	None	
EtAc A.G.	Band 3	0.76
	Band 4	0.16

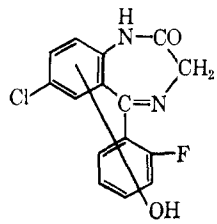
[a] Preparation of extracts is described in the Experimental Section.

TABLE III
SEPARATION BY SERIAL TLC OF THE METABOLITES IN BANDS 3 AND 4 ELUTED FROM CHROMATOPLATES DEVELOPED IN SYSTEM 1[a]



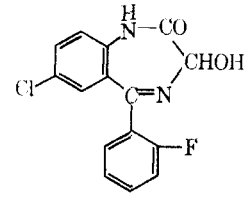
[a] Solvent systems below are designated by number (see Experimental Section). The metabolites were detected with the Dragendorff spray. [b] R_f values of those reference compounds run with the metabolite fractions. [c] MS indicates that these components were analyzed by high-resolution mass spectrometry.

The essential data obtained from high-resolution mass spectral analysis of these isolated fractions are presented in Table IV. 3A and 3B had the same molecular composition (at *m/e* 304) which indicated that the entire N-1 side chain of I had been replaced by a hydrogen and one oxygen had been added to the remainder of the molecule. However, the fragmentation patterns of 3A and 3B differed. With respect to 3A, the presence of the *m/e* 248 fragment (see footnote *c* of Table IV) and the M − CH_2N fragment (which indicates the retention of both hydrogens at C-3 of 1,4-benzodiazepines[4,5]) together with the absence of M − H_2O strongly suggested a phenolic structure.



A more definite structure was obtained for 3B because the presence of the *m/e* 232 and M − H_2O fragments indicated the oxygen was added at C-3. This compound, 7-chloro-5-(2-fluorophenyl)-3-hydroxyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (VI), was subsequently synthesized[1] and the mass spectra of 3B and VI were identical.

The last component, 3C, exhibited a molecular ion and fragmentation pattern identical with that of the



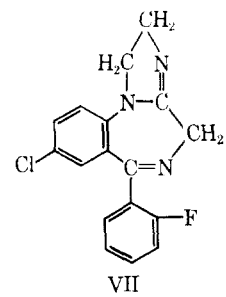
VI (metabolite 3B)

human metabolite and, as was suggested by its tlc migration, it was identical with IV.

The high-resolution mass spectra of the band 4 components (Table IV) also yielded metabolite structures. The molecular composition of 4B ($C_{19}H_{19}N_3OClF$) indicated that one ethyl group on the side-chain nitrogen of I had been replaced by a hydrogen (the molecular composition of 4B differed from that of I by $-C_2H_4$). Furthermore, the mass spectrum of 4B was identical with that of II, the N-desethyl analog of I.

The mass spectra of component $4A_1$ and reference compound III were identical and showed strong fragment ions at *m/e* 313 (M − H_2O) and 302 (M − CH_2NH_2) but no molecular ion at *m/e* 331 ($C_{17}H_{15}N_3OClF$). Therefore the mass spectral analysis confirmed the identifications of 4B as II and $4A_1$ as III which had been suggested by the tlc data.

Identical mass spectra were obtained for components $4A_2$ and 4C; both spectra differed from that of $4A_1$ only in that they showed a weaker *m/e* 302. These results could be explained by assuming that the highest observed mass, *m/e* 313, was the molecular ion and that *m/e* 302 was due to contamination (see footnote *b* of Table IV). On the basis of these assumptions the structure of both $4A_2$ and 4C would be that of a dehydrated III. Such a compound, 8-chloro-6-(2-fluorophenyl)-1,2-dihydro-4H-imidazo-[1,2-*a*][1,4]benzodiazepine (VII), had been synthesized[1] and its mass spectrum, except for the absence of *m/e* 302, was identical with those of $4A_2$ and 4C. In addition, on two-dimensional tlc (system 7 followed by system 8) there was no separation of either $4A_2$ or 4C from VII when each isolated compound was spotted at the origin with authentic compound.



VII

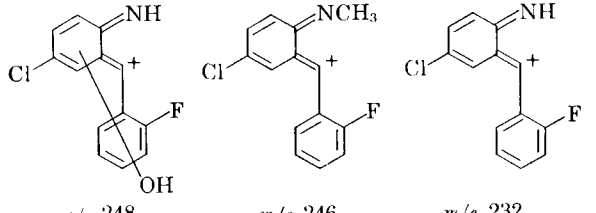
From Table III it is evident that $4A_2$ was isolated from 4A, the major component, which in system 2a not only migrated as III but was clearly separated from 4C. This suggested that VII might be formed during the tlc purification by dehydration of III. This speculation was supported by further tlc experiments; III as the free base, and to a much lesser extent as the dihydrochloride salt which was used as reference compound (Table I), yielded readily detectable amounts of VII on tlc in the solvent systems used for purification of band 4. Therefore, VII is much more likely to have been an artifact produced from III than a metabolite originally present in band 4.

TABLE IV

HIGH-RESOLUTION MASS SPECTRAL DATA[a] ON METABOLITES AND REFERENCE COMPOUNDS

Mass,	Formula						Metabolites (and reference compounds)						
							1	2A1, 4A1	2A2, 2C 4A2, 4C	2B, 4B		3B	Human 3C
m/e	C	H	N	O	Cl	F	(I)	(III)	(VII)	(II)	3A	(VI)	(IV)
387	21	23	3	1	1	1	M	...	...	...	...	...	...
359	19	19	3	1	1	1	...	...	...	M	...	...	...
341	19	17	3	...	1	1	...	...	...	M − H_2O	...	...	...
332	17	14	2	2	1	1	...	...	...	...	...	...	M
315	17	13	2	1	1	1	M − $(C_2H_5)_2N$	...	...	M − C_2H_5NH	...	...	...
313	17	13	3	...	1	1	...	M − H_2O	M	...	...	...	...
304	15	10	2	2	1	1	...	...	...	...	M	M	...
304	16	12	1	2	1	1	...	...	...	...	...	...	M − CH_2N
302	16	12	2	1	1	1	...	M − CH_2NH_2	*b*	M − $C_2H_5NCH_2$	...	...	...
301	16	11	2	1	1	1	...	...	...	...	...	...	M − CHOH
288	15	10	2	1	1	1	...	...	...	...	...	...	M − C_2H_4O
286	15	8	2	1	1	1	...	...	...	...	...	M − H_2O	...
285	16	11	2	...	1	1	...	M − H_2O, CH_2N	M − CH_2N	...	...	...	...
276	14	8	1	2	1	1	...	...	...	...	M − CH_2N	...	...
275	14	9	2	1	1	1	...	...	...	...	M − CHO	M − CHO	...
274	15	12	2	...	1	1	...	...	...	M − $C_2H_5NCH_2$, CO	...	...	...
273	15	11	2	...	1	1	M − $C_6H_{12}NO$	M − CH_2NH_2, CO	M − C_2H_2N	...	...	...	M − CH_2OH, CO
273	15	9	1	1	1	1	...	...	...	...	...	...	M − CH_2OH, CH_2N
248[c]	13	8	1	1	1	1	...	...	...	...	M − C_2H_2NO	...	...
246[c]	14	10	1	...	1	1	M − $C_7H_{15}N_2O$	M − $C_3H_5N_2O$	M − $C_3H_3N_2$	M − $C_5H_{13}N_2O$	...	...	M − $C_3H_4NO_2$
232[c]	13	8	1	...	1	1	...	...	...	...	...	M − $C_2H_2NO_2$	M − $C_4H_6NO_2$

[a] Only the pertinent strong mass spectral peaks are presented. The data were obtained from high-resolution spectra, but only the nominal masses are presented in the table. The elemental compositions of the observed masses are presented (error ≤3 millimass units). [b] A weak *m/e* 302 peak observed in $4A_2$ and 4C but not in $2A_2$ and 2C was probably due to the formation of a small amount of III during the elution and sample preparation procedures. [c] These fragment ions consist of the two benzene ring systems. The postulated structures are shown below.



m/e 248 *m/e* 246 *m/e* 232

The ether-extractable Dragendorff-positive components, bands 1 and 2 (Table II), were characterized with little difficulty. Band 1 which migrated as intact I (compare R_f with that of I in Table I) was found to be identical with I by further tlc and by high-resolution mass spectrometry (Table IV). Band 2, on purification by tlc, yielded a pattern of metabolites (and artifact) which was almost an exact duplicate of that obtained with band 4. Components $2A_1$, $2A_2$, 2B, and 2C analogous to the band 4 components (Table III) were obtained and each component was found by high-resolution mass spectrometry (Table IV) to be identical with the analogous band 4 component. Furthermore, components $2A_2$ and 2C were more readily identified as VII because they did not contain the extraneous *m/e* 302 fragment. It is evident from the above that nonconjugated II, III, and intact drug (I) were excreted in the urine.

The hydroxyl-bearing compounds IV, VI, and metabolite 3A (phenolic analog of V) would be expected to be excreted as glucosuronic acid and/or sulfate conjugates and were found as such. However, II and III were also found in the ethyl acetate extracts after treatment of the urine with Glusulase which suggests that these compounds were either conjugated in the enolate form with sulfate and/or glucuronate or were present in some other chemical form susceptible to modification upon treatment with Glusulase. Further work is required to clarify this unexpected finding.

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Quinazolines and 1,4-Benzodiazepines. XL.[1] The Synthesis of Metabolites of 7-Chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one

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The synthesis of a number of compounds related to the hypnotic, 7-chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**2**), is reported. These compounds were prepared as potential metabolites and many were found to be identical with the metabolites isolated and discussed in the preceding paper.[2]

In connection with the metabolic studies of the hypnotic, 7-chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**2**)[3] discussed in the preceding paper,[2] we have synthesized a number of related compounds designed as possible *in vivo* and/or *in vitro* metabolites. By means of direct comparison or by a comparison of mass spectra and the use of tlc techniques, many of these derivatives were shown by Schwartz, Vane, and Postma[2] to be identical with the metabolites of **2**.

Some of these compounds were synthesized after their initial tentative identification by an interpretation of mass spectral data while others were prepared based on our knowledge of the metabolism of other 1,4-benzodiazepines (*e.g.*, diazepam is known to yield a 3-hydroxy derivative[4]).

The synthesis of the monoethylamino derivative (**4**) was carried out by a von Braun degradation of the side chain of **2**. Thus treatment of **2** with cyanogen bromide gave the cyanamide **3** which on reaction with sulfuric acid gave the desired secondary amine **4** (Scheme I). By treating the cyanamide with base and with H_2O_2, the urea **5** could be obtained. The hydrolysis of **3** in concentrated H_2SO_4 under milder conditions than those used for the synthesis of **4** also gave the intermediate urea **5**. From both of these reactions, we also isolated the hydroxyethyl derivative **6**. This compound was synthesized in much better yield from **1** either by treatment with sodium methoxide and 2-bromoethanol, or by a direct condensation with ethylene oxide.

Another compound synthesized as a possible metabolite was the aminoethyl derivative **8**. Again the unalkylated compound **1** was used as the starting material and was treated first with sodium methoxide and then with carbobenzoxybromoethylamine to give **7**. Compound **7** was then treated with a solution of HBr in glacial acetic acid to give the free amino derivative **8**. The dehydration product **16** formed by heating **8** under reflux in ethanol[1] was found as an artifact of **8** in the metabolic studies carried out by Schwartz and Postma.[2]

The 3-hydroxy compound (**12**) was prepared in the conventional manner from **10** by a Polonovski rearrangement of the N-oxide to give **11** which was subsequently hydrolyzed to **12**. Compound **10** was synthesized from **1** in two steps. In the first step, **1** was oxidized with peracetic acid to give the nitrone **9**, and in the second step **9** was alkylated *via* the sodio

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