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ACKNOWLEDGMENTS

Supported by a grant from the Natural, Applied and Health Sciences, University of British Columbia.

The authors thank Ayerst Pharmaceuticals, Montreal, Canada, for their gift of equine estrogens, and Dr. B. Lodge, Health Protection Branch, Ottawa, Canada, for a reference sample of equol. The authors are grateful to Mr. R. Burton for the mass spectral analysis.

Thiourea and Thiosemicarbazide Derivatives Structurally Related to Hexestrol: Synthesis and Anticancer and Other Pharmacological Properties

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Received May 16, 1980, from the **Department of Pharmaceutical Chemistry and the* ‡*Department of Pharmacology, Faculty of Pharmacy, University of Alexandria, Alexandria, Egypt.* Accepted for publication November 24, 1980.

Abstract □ Two novel series of thio compounds bearing internal structural modifications of hexestrol were synthesized as potential anticancer agents. The first contains several *N*-substituted thiourea functions, and the second contains various N^4-substituted-3-thiosemicarbazide moieties in place of one α-ethyl group of hexestrol dimethyl ether. The products showed no antileukemic activity in the P-388 lymphocytic leukemia system and did not exhibit any anticonvulsant or estrogenic properties.

Keyphrases □ Hexestrol—structurally related thiourea and thiosemicarbazide derivatives as anticancer agents □ Anticancer drugs, potential—compounds related to hexestrol, screened against P-388 lymphocytic leukemia □ Thioureas—synthesis, hexestrol derivatives, evaluation of anticonvulsant and anticancer activities □ Thiosemicarbazide—synthesis of hexestrol derivatives, evaluation of anticonvulsant and anticancer activities

Concurrent with ongoing studies of the cyclodesulfurization of thio compounds into various heterocyclic derivatives (1), related studies have been concerned with the synthesis of thio compounds derived from menadione (2), phthiocol (2), steroids (3), diethylstilbestrol (4), and theophylline (5), the biologically active nuclei, for various pharmacological purposes. Extending these studies to compounds containing thio functions as internal modifications of hexestrol, the thio derivatives IV–XI and XIV–XVIII (Scheme I) were prepared and tested for anticancer, estrogenic, and anticonvulsant activities.

RESULTS AND DISCUSSION

Chemistry—1,2-Bis(*p*-methoxyphenyl)butylamine (II), required as the starting material, was prepared through conversion of α-ethyldesoxyanision (I) into the corresponding oxime (6), using hydroxylamine hydrochloride and potassium acetate in ethanol, followed by reduction of the product with aluminum amalgam in aqueous ethanol (7). The amine (II) was reacted with the equivalent amount of alkyl-, aryl-, or aralkylisothiocyanates (III) in refluxing ethanol to give *N*-[1,2-bis(*p*-methoxyphenyl)butyl]-*N'*-substituted thioureas (IV–XI) in high yields (Table I).

The treatment of the amine (II) with ethyl bromoacetate and sodium carbonate in anhydrous acetone gave the glycinate ester (XII), which was heated with excess hydrazine hydrate to yield the N^{α}-[1,2-bis(*p*-methoxyphenyl)butyl]-α-aminoacetohydrazide (XIII). Heating equimolar amounts of this acid hydrazide and the selected isothiocyanate derivatives (III) in refluxing ethanol gave the required 4-substituted-1-{N^{α}-[1,2-bis(*p*-methoxyphenyl)butyl]-α-aminoacetyl}-3-thiosemicarbazides (XIV–XVIII) (Scheme I and Table I). The products were identified by the appearance of four bands at 1550–1525, 1345, 1320–1305, and 945–910 cm^{-1}, characteristic for the –N–C=S amides of I, II, III, and IV, respectively, in the IR spectra (5, 8).

The PMR spectra of representative examples of the thiourea derivatives IV, VIII, and IX and the thiosemicarbazides XIV, XV, and XVII showed the common protons resonating at various shifts (Table II). In addition to these signals, the other NH proton of the thiourea part was identified at various shifts depending on the substituent present. It appeared as a triplet at δ 5.90 ppm for the allyl derivative (IV), as a singlet at δ 8.11 ppm for the *m*-tolyl derivative (VIII), and as a multiplet at δ 6.11 ppm for the benzyl thiourea (XI). Likewise, the N^4-H proton of the thiosemicarbazides appeared as a broad multiplet at δ 6.59 and 6.54 ppm for XIV and XV, respectively, and as a singlet at δ 8.57 ppm for XVII.

The mass spectrum of *N*-[1,2-bis(*p*-methoxyphenyl)butyl]-*N'*-benzylthiourea (XI) did not show the molecular ion peak at *m/z* 434. However, it indicated that the compound had undergone fragmentation through two pathways (Scheme II). The first pathway produced ions A and B at *m/z* 284 and 150, while the second pathway gave ions C and D at *m/z* 269 and 165, respectively. These four ions, on further fragmentation, produced various daughter ions (Scheme II), of which the tropylium ion at *m/z* 91 was almost as intense as the base peak at *m/z* 78. The mass spectrum of the thiosemicarbazide (XVII) did not show the molecular ion peak at *m/z* 506, but it showed the base peak at *m/z* 208 (see *Experimental*).

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Table I—*N*-1,2-Bis(*p*-methoxyphenyl)butyl-*N'*-substituted Thioureas (IV–XI), Thiosemicarbazide Derivatives (XIV–XVII), and Results of Their Screening for Anticonvulsant Activity

Compound	Yield, %	Melting Point	Molecular Formula	Analysis, %	Calc.	Found	Anticonvulsant[a] Protection, %	Anticonvulsant[a] Mortality, %
IV	85	151–152°	$C_{22}H_{28}N_2O_2S$	C	68.71	68.50	10	60
				H	7.34	7.20		
				N	7.29	7.30		
				S	8.34	8.60		
V	82	114–116°	$C_{23}H_{32}N_2O_2S$	C	68.96	68.70	—[b]	—[b]
				H	8.05	7.80		
				N	7.00	7.00		
				S	8.00	7.90		
VI	70	122–123°	$C_{25}H_{28}N_2O_2S$	C	71.39	71.30	—[b]	—[b]
				H	6.71	6.80		
				N	6.66	6.20		
				S	7.62	7.80		
VII	84	142–144°	$C_{26}H_{30}N_2O_2S$	C	71.85	71.85	20	50
				H	6.96	6.80		
				N	6.45	6.80		
				S	7.38	7.30		
VIII	81	127–128°	$C_{26}H_{30}N_2O_2S$	C	71.85	71.90	0	80
				H	6.96	7.00		
				N	6.45	6.10		
				S	7.38	7.50		
IX	76	147–149°	$C_{25}H_{27}ClN_2O_2S$	C	65.99	65.70	40	50
				H	5.98	5.80		
				Cl	7.79	7.70		
				N	6.16	5.70		
				S	7.05	7.20		
X	68	175–176°	$C_{25}H_{27}BrN_2O_2S$	C	60.12	60.10	20	70
				H	5.45	5.80		
				Br	16.00	16.00		
				N	5.61	5.30		
				S	6.42	6.50		
XI	90	119–120°	$C_{26}H_{30}N_2O_2S$	C	71.85	71.60	0	90
				H	6.96	6.80		
				N	6.45	6.10		
				S	7.38	7.10		
XIV	90	110–111°	$C_{24}H_{32}N_4O_3S$	C	63.13	62.80	0	90
				H	7.06	6.60		
				N	12.27	11.80		
				S	7.02	7.50		
XV	76	134–135°	$C_{25}H_{36}N_4O_3S$	C	63.53	63.60	10	30
				H	7.68	7.50		
				N	11.86	12.00		
				S	6.76	6.60		
XVI	87	148–150°	$C_{27}H_{32}N_4O_3S$	C	65.82	65.80	—[b]	—[b]
				H	6.55	6.60		
				N	11.38	11.40		
				S	6.57	7.10		
XVII	85	139–141°	$C_{28}H_{34}N_4O_3S$	C	66.37	66.10	50	40
				H	6.76	6.10		
				N	11.06	11.30		
				S	6.33	6.00		
XVIII	70	151–152°	$C_{28}H_{34}N_4O_3S$	C	66.37	65.95	10	60
				H	6.76	6.60		
				N	11.06	10.90		
				S	6.33	7.00		

[a] The compounds, in doses equivalent to 100 mg of meprobamate/kg, were suspended in gum acacia and orally given to albino mice (seven to 11 mice for each compound). The percent protection and percent mortality were determined as previously reported (5). [b] Not tested.

Biological—Compounds IV, V, VII, IX–XI, and XIV–XVIII did not exhibit any anticancer activity when tested in the P-388 lymphocytic leukemia system (9). In addition, the testing of representative examples of the products for other pharmacological properties revealed that they lacked estrogenic (Table III) and anticonvulsant (Table I) activities.

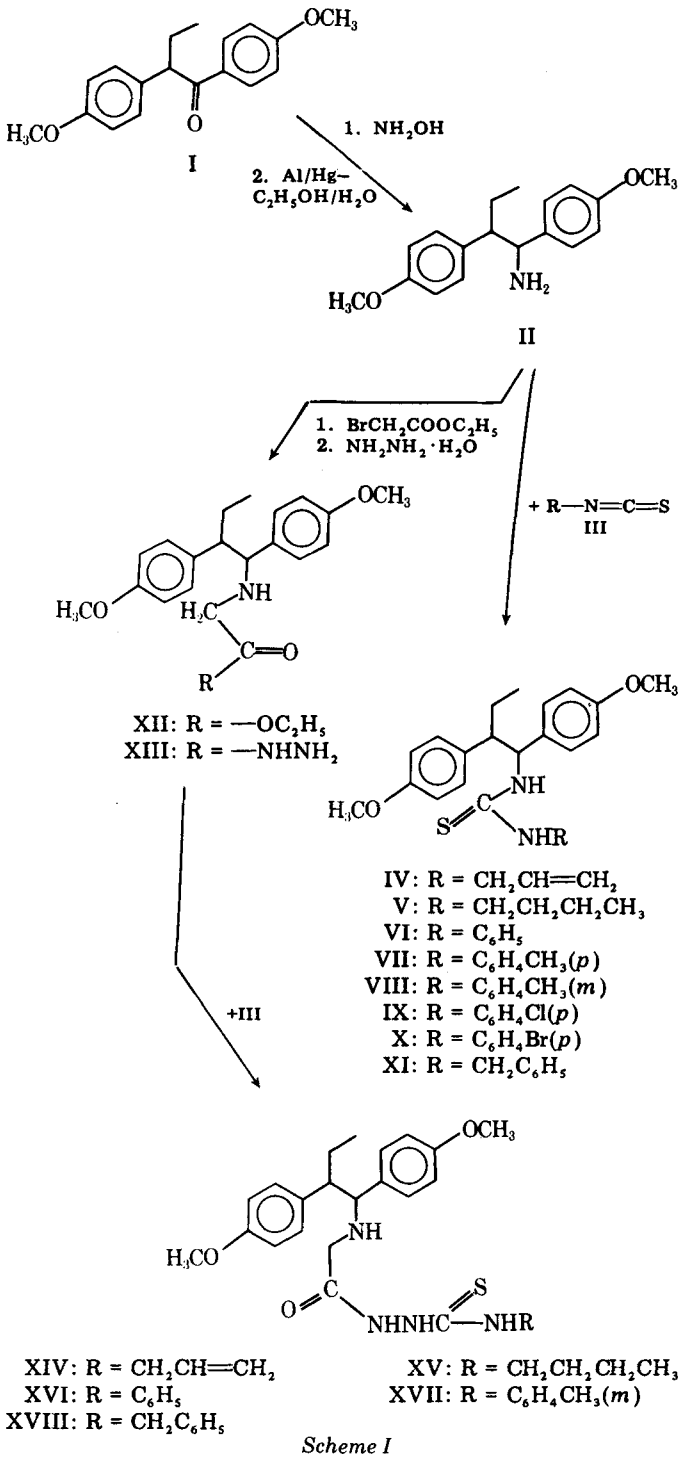
As revealed in the literature, various compounds possessing anticancer (10) and other pharmacological properties can be produced through chemical modifications involving the replacement of the one or two α-ethyl groups of hexestrol by ethylidenyl (10–12), cyclopropyl (13), aryl (14, 15), or substituted amide (16, 17) moieties. As a supplementary modification of hexestrol, the designed compounds contained the thiourea and the thiosemicarbazide functions. The thiosemicarbazide compounds are known to produce anticancer activity when attached to certain heterocyclic compounds (18–21).

The inactivity of the products in the P-388 lymphocytic leukemia system has provided another example (9) of the inability of these thio functions, due to the variation of structures, to form the tridentate ligands (22) necessary for blocking DNA synthesis in tumor cells. The thio groups were too bulky relative to the α-ethyl groups in hexestrol to allow IV and XIV to bind to the receptors; hence, they did not exhibit estrogenic activity (3). The results of anticonvulsant screening for XVII (5), which indicated 50% protection, confirmed the failure of related types of these compounds to fulfill the structural requirement for a proper anticonvulsant agent.

EXPERIMENTAL[1]

1,2-Bis(*p*-methoxyphenyl)butylamine (II)—Aluminum amalgam, prepared from aluminum (22 g) and mercuric chloride (17.5 g) as reported (7), was treated with the solution of the oxime (12 g, 0.04 mole) in ethanol (220 ml) and distilled water (220 ml). The reaction mixture was stirred for 48 hr and filtered, and the residue was washed with ethanol (2 × 200 ml). Ethanol was distilled off from the combined filtrate and washings, and the residue was extracted with ether (4 × 100 ml). The ether extracts

[1] All melting points are uncorrected. IR spectra were measured as Nujol mulls on a Beckman 4210 IR spectrophotometer. NMR and mass spectra were measured on a Perkin-Elmer R 32 and a AEI-MS-50, respectively.

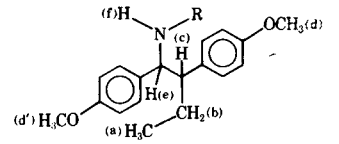


Scheme I

were dried (anhydrous sodium sulfate) and evaporated to leave an oil, which soon solidified. Crystallization from light petroleum (bp 60–80°) gave 8.6 g (75% yield) of white needles, mp 94–95° [lit. (23) mp 94–95.5°].

***N*-[1,2-Bis(*p*-methoxyphenyl)butyl]-*N'*-substituted Thioureas (IV–XI)**—A solution of II and the equivalent amount of the appropriate alkyl-, aryl-, or aralkylisothiocyanate (III) in ethanol was heated under reflux for 30 min. The solvent was evaporated, and the residue was scratched with drops of light petroleum (bp 40–60°) or an ether–light petroleum mixture to deposit into a solid. The products were crystallized from a benzene–light petroleum mixture and identified by elemental analysis, IR, PMR (Table II), and mass spectra; IR (mineral oil): 3400–3330 and 3310–3220 (NH), 1610, 1585, and 1510 (C=C aromatic), and 1550–1525, 1345, 1320–1305, and 945–910 cm^{-1} (–N–C=S, amide I, II, III, and IV bands, respectively). Yields and physical constants of the products are recorded in Table I. The mass spectrum of XI showed

Table II—Signals of the Common Protons in the PMR Spectra of the Thioureas IV, VIII, and XI and the Thiosemicarbazide Derivatives XIV, XV, and XVII



Compound	Chemical Shift[a], δ ppm ($CDCl_3$)						
	H(a)	H(b)	H(c)	H(d)	H(d')	H(e)	H(f)
IV	0.70 t	1.54 q	2.77 q	3.80 s	3.80 s	5.00 m	6.34 d
VIII	0.70 t	1.56 m	2.76 m	3.75 s[b]	3.78 s	5.69 t	6.30 d
XI	0.75 t	1.55 m	2.77 m	3.75 s[b]	3.87 s	5.00 m	6.70 m
XIV	0.60 t	1.36 m	2.72 m	3.88 s	3.88 s	3.58 m	—[c]
XV	0.60 t	—	2.74 m	3.84 s	3.84 s	3.53 m	—[c]
XVII	0.58 t	1.33 m	2.70 m	3.72 s[b]	3.75 s	3.54 m	—[c]

[a] s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. [b] The difference in the chemical shift between the (d) and (d') group protons is due to the presence of the protons of the methoxyl group (d) in the positive shielding area caused by the anisotropic effect of the aryl substituents in the thio chains of these compounds. [c] H(f) in the thiosemicarbazides appeared between 0.90 and 1.82 ppm mixed with the methylenic protons.

m/z (relative abundance %) $M^{\cdot}$ at 434 absent, 284 (2), 269 (46), 240 (6), 165 (6), 150 (8), 149 (42), 136 (42), 135 (9), 134 (9), 133 (5), 121 (31), 107 (9), 106 (16), 91 (99), and 78 (100).

***N*$^{\alpha}$-[1,2-Bis(*p*-methoxyphenyl)butyl] -α- aminoacetohydrazide (XIII)**—A solution of ethyl bromoacetate (2.24 g, 0.0134 mole) in dry acetone (10 ml) was added dropwise (during 30 min) onto a well-stirred mixture of II (3.45 g, 0.012 mole) and anhydrous sodium carbonate in dry acetone (40 ml). The mixture was heated under reflux while stirring for 8 hr, allowed to cool, and then filtered. The filtrate was evaporated to leave an oily residue, which was dissolved in benzene (50 ml). The benzene solution was washed successively with 10% aqueous HCl (2 × 25 ml), sodium carbonate solution, and water. Benzene was evaporated to leave 3.78 g (84%) of a viscous oil, which was homogeneous on TLC and used directly in the subsequent experiments: IR (mineral oil): 3340 (NH), 1740 (C=O), 1610, 1585, and 1510 (C=C, aromatic), 1300 (δ NH), and 1250, 1175, and 1040 (C–O–C) cm^{-1}.

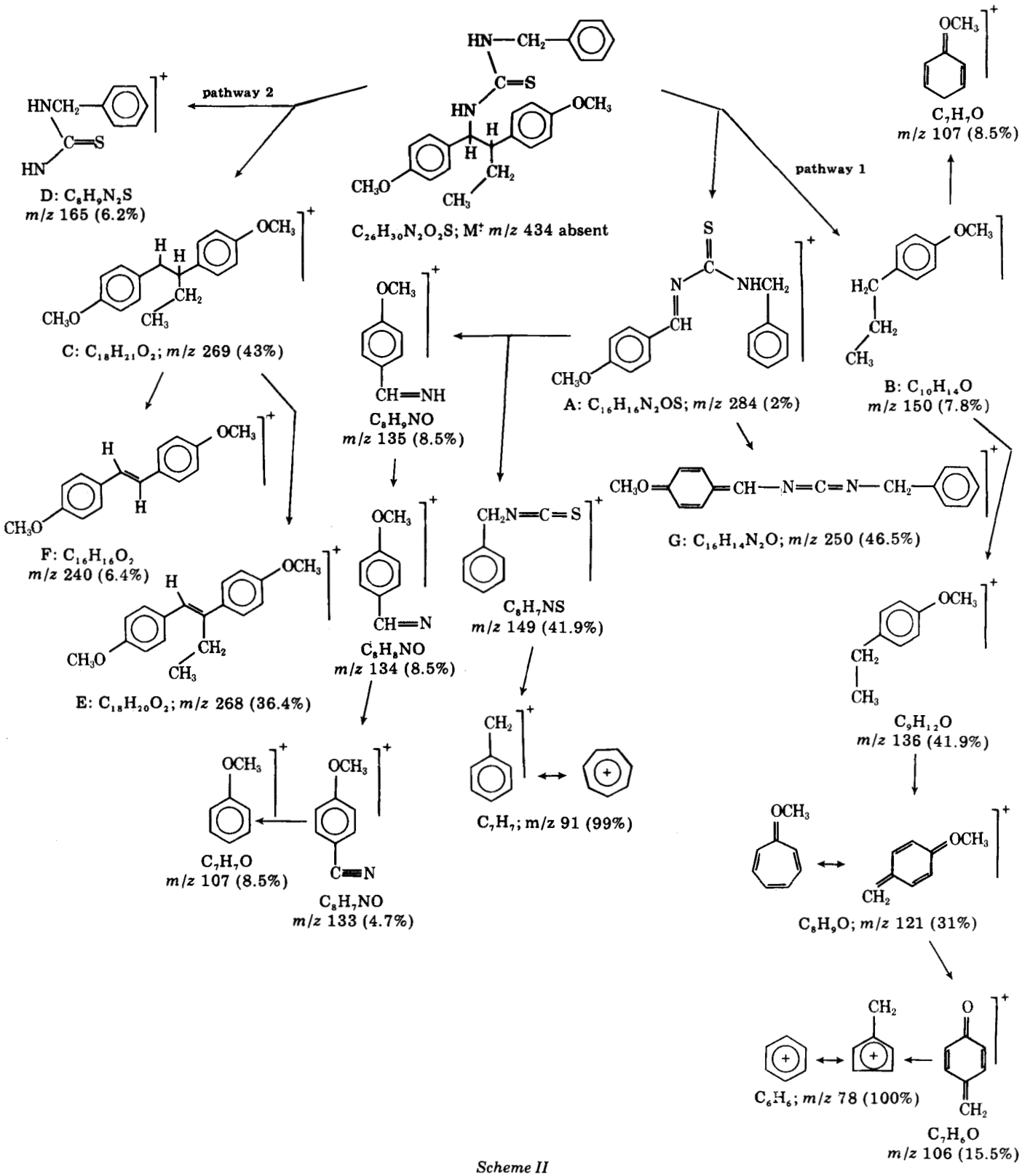
The mixture of ester XII (3 g, 0.0081 mole) and hydrazine hydrate (15 ml) was heated for 3 hr at 90–110° (external temperature). The mixture was poured onto excess water to separate the oil, which was extracted with benzene (2 × 50 ml). The benzene extract was washed with water, dried (anhydrous sodium sulfate), and evaporated. The oil left (2.57 g, 89%) was homogeneous on TLC and used directly for preparation of the thiosemicarbazides; IR (liquid film): 3350 (NH), 1670 (C=O), 1615, 1585, and 1510 (C=C aromatic), 1305 (δ NH), and 1250, 1180, and 1040 (C–O–C) cm^{-1}.

4-Substituted -1- {*N*$^{\alpha}$-[1,2-bis(*p*-methoxy)butyl] -α- aminoacetyl}-3-thiosemicarbazides (XIV–XVIII)—The mixture of the acid hydrazide XIII (0.71 g, 0.002 mole) and an equimolar amount of the appropriate alkyl-, aryl-, or aralkylisothiocyanate (III) in dry benzene (20 ml) was heated under reflux for 2.5 hr. The solvent was removed, and the residue was boiled in light petroleum while being scratched to deposit into solid. Crystallization from benzene–light petroleum gave the required thiosemicarbazides (XIV–XVIII) (Table I). The products were identified by microanalysis and IR, PMR (Table II), and mass spectra. The mass spectrum for the *m*-tolylthiosemicarbazide (XVII) showed *m/z* (relative abundance %) $M^{\cdot}$ at 506 absent, 325 (3), 296 (2), 269 (12), 268 (6), 208

Table III—Results of Estrogenic Activities

Compound	Doses, μmoles/kg	Number of Animals	Uterine Weight, mg/100 g of body weight ± *SE*	*p* Value[a]
Ovariectomized control	0	5	56.4 ± 6.1	—
Hexestrol	2	4	123.5 ± 9.5	<0.001
	8	4	155.0 ± 19.4	<0.01
IV	2	4	46.1 ± 7.5	NS
	8	4	45.8 ± 2.9	NS
	32	4	48.6 ± 3.4	NS
XIV	2	4	49.9 ± 7.2	NS
	8	4	53.8 ± 3.2	NS
	32	4	98.6 ± 15.5	<0.02

[a] NS = not significant.



Scheme II

(100), 193 (20), 150 (35), 149 (99), 148 (64), 136 (46), 135 (9), 134 (8), 133 (4), 121 (61), 117 (22), 116 (16), 107 (36), 106 (34), 91 (99), 85 (28), 83 (44), and 78 (12).

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ACKNOWLEDGMENTS

Supported in part by Pharco Pharmaceuticals, Cairo, Egypt.

The authors thank the members of the Drug Research and Development Division of Cancer Research, National Cancer Institute, for screening the compounds and the members of the Microanalytical Unit, Faculty of Science, University of Cairo, for microanalytical data.

NOTES

Pharmacokinetic Linearity of Desipramine Hydrochloride

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Received July 10, 1980, from the *Merrell Dow Pharmaceuticals Inc., Subsidiary of the Dow Chemical Company, Cincinnati, OH 45215.* Accepted for publication February 2, 1981. *Present address: A. H. Robins Co., Richmond, VA 23220.

Abstract □ The pharmacokinetic linearity of two single oral doses of desipramine hydrochloride was examined in a parallel study involving 30 subjects. Fourteen subjects received 75 mg (3 × 25 mg) of desipramine hydrochloride, and 16 subjects received 150 mg (1 × 150 mg). An open one-compartment model with a lag time to the start of absorption was used to examine the pharmacokinetic linearity. The results of the study suggest that the kinetics are linear in the dose range studied.

Keyphrases □ Desipramine hydrochloride—pharmacokinetic linearity, bioavailability, comparison of two tablet dose levels, humans □ Pharmacokinetic linearity—desipramine hydrochloride, humans □ Tricyclic antidepressants—desipramine hydrochloride, pharmacokinetic linearity, bioavailability, comparison of two tablet dose levels, humans

Tricyclic antidepressants are widely used in the treatment of depression. Recent studies (1–9) showed a relationship between steady-state plasma tricyclic levels and therapeutic response. Several investigations (10–14) were undertaken to find a means of predicting steady-state plasma tricyclic antidepressant concentrations based on plasma levels obtained after a single dose, thus avoiding time-consuming dosage titration to therapeutic plasma levels. These studies indicated that steady-state plasma levels can be predicted accurately by the area under the plasma concentration curve (*AUC*) following a single dose or by a single plasma level obtained 24, 48, or 72 hr after dosing.

This study determined the pharmacokinetic linearity of two single doses of desipramine hydrochloride[1], providing additional evidence that the steady-state predictions are reasonable.

EXPERIMENTAL

Subjects—Thirty healthy male volunteers were randomized into two parallel treatment groups; 14 received 75 mg (three 25-mg tablets) of desipramine hydrochloride and 16 received one 150-mg tablet. The subjects were 19–40 years of age and 47–78 kg. All subjects were within 10% of their ideal weight.

Protocol—Each subject received the prescribed dose at 8:00 am. A 15-ml blood sample (vacuum blood-drawing tubes[2] containing lithium heparin as anticoagulant) was drawn just prior to dosing (time zero) and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, 24, 36, 48, and 72 hr postdosing. No solid food was permitted from 8:00 pm of the preceding day until 12:00 noon of the dose day, at which time a standard lunch was served. A low-fat dinner was served at 6:00 pm; after collection of the 24-hr sample, the subject resumed eating *ad libitum*. A parallel design was employed instead of a crossover design since the elimination half-life for desipramine can be long and variable (15).

Analytical Method—The separated plasma was kept frozen until it was assayed. Desipramine was measured using a GLC–mass spectrometric technique adapted from Pantarotto *et al.* (16). The method involved the addition of the internal standard (nortriptyline) and extraction of the alkalinized plasma with *n*-hexane. The extract was reacted with acetic anhydride and pyridine without prior evaporation. The acetylated extract then was evaporated to dryness, and the residue was dissolved in ethanol. An aliquot was injected into the apparatus with selected-ion monitoring at *m/z* 305 and 308.

Calculations—Pharmacokinetic parameters were computed for each dosage level corresponding to an open one-compartment model with a lag time (17) using:

$$C(t) = \frac{FD}{V}\frac{K_a}{(K_a - K_e)}\left[e^{-K_e(t-L)} - e^{-K_a(t-L)}\right] \qquad \text{(Eq. 1)}$$

where D is the administered oral dose, F is the fraction of the dose absorbed, V is the apparent volume of distribution, K_a is the apparent first-order absorption rate constant, K_e is the first-order elimination rate constant, L is the lag time to the start of absorption, and t is the time

[1] Norpramin, Merrell Dow Pharmaceuticals.

[2] Kimble-Terumo Venoject tubes.

0022-3549/81/0900-1079$01.00/0