Experimental Section[7]

Ethyl 2-Phthalimido-2-[2-(1,3-dithiolano)]acetate (6).—To a stirred solution of ethyl α-phthalimidomalonaldehydate (**5**)[4] (0.02 mole) in 160 ml of dry $CHCl_3$ was added ethanedithiol (23.5 g, 0.25 mole); the solution was saturated with dry HCl and stirred at 25° for 12 hr. It was neutralized with 10% Na_2CO_3 solution, washed (H_2O), dried ($MgSO_4$), and filtered and most of the solvent was removed at 100° under N_2. The oily yellow residue was dissolved in EtOAc and treated with 5% NaOH solution. The aqueous portion was extracted again with EtOAc and the combined EtOAc solutions were washed (H_2O), dried, and evaporated to give a thick red syrup. An orange solid which was produced by standing overnight at 25° was recrystallized from EtOH to yield 40.6 g (60%) of **6**. An analytical sample recrystallized several times from C_6H_6 and from EtOH melted at 118°. The nmr spectra were as expected. *Anal.* ($C_{15}H_{15}NO_4S_2$) C, H, N, S.

Ethyl 2-Amino-2-[2-(1,3-dithiolano)]acetate (7).—Compound **6** (20.0 g, 0.066 mole) was dissolved in 500 ml of EtOH, 5.4 ml of 85% $(H_2N)_2 \cdot H_2O$ (0.09 mole) was added, and the solution was heated under reflux for 2.5 hr. The reaction mixture was cooled and the solid was removed by filtration. EtOH was removed, and the remaining liquid was dissolved in $CHCl_3$ and MeOH. This was chromatographed on 130 g of silica gel using hexane–$CHCl_3$ (1:1) as the eluent followed by $CHCl_3$ to give 8.0 g (59%) of the liquid amino ester **7**.

2-Amino-2-[2-(1,3-dithiolano)]acetic Acid (1).—The ester **7** (8.50 g, 0.041 mole) was added to a solution of 3.10 g (0.055 mole) of KOH in 100 ml of H_2O. Dioxane (15 ml) was added to effect partial solution and this mixture was refluxed for 2.5 hr. The solvent was removed under reduced pressure leaving an orange solid which was dissolved (H_2O), filtered, and neutralized by passing through an ion-exchange column of 12 g of Amberlite IRC-50 (H^+ form). The H_2O in the eluate was evaporated with a stream of air to leave 4.64 g (63%) of amino acid **1**, which was heated with activated charcoal and recrystallized from H_2O and EtOH to yield white crystals, mp 209° dec. *Anal.* ($C_5H_9NO_2S_2 \cdot 0.5H_2O$) C, H, N.

1,1,6,6-Tetracarbethoxy-1,6-diacetamido-3-hexene (9).[5]—NaOEt [from 2.3 g (0.1 g-atom) of Na in dry EtOH (225 ml)] was mixed with 21.7 g (0.1 mole) of diethyl acetamidomalonate and the stirred solution was heated to reflux for 30 min. A solution of 10.70 g (0.05 mole) of 1,4-dibromo-2-butene in 50 ml of dry EtOH was added dropwise over 30 min. The solution was refluxed for 6 hr, the NaBr was removed by filtration, and the EtOH was evaporated *in vacuo*. The residue was partitioned between $CHCl_3$ and H_2O, and the $CHCl_3$ extract was dried ($MgSO_4$) and evaporated *in vacuo* to yield 24.7 g (0.05 mole) of crude **9** (quantitative yield). Recrystallization from C_6H_6–C_6H_{14} produced white crystals, mp 118–119° (lit.[5] mp 112–114°). *Anal.* ($C_{22}H_{34}N_2O_{10}$) C, H, N.

3,3-Dicarbethoxy-3-acetamidopropionaldehyde (10).—Compound **9** (2.43 g, 0.005 mole) was treated with O_3 for 1 hr (60 mg/min) in 25 ml of EtOAc at −80°. The solution was warmed to 25° and N_2 was passed through for 30 min. EtOAc (75 ml) and 0.25 g of 5% Pd–C were added; the mixture was hydrogenated at 2 atm for 1.5 hr. The catalyst was removed by filtration and the EtOAc solution was stored at 4° for 12 hr. The solvent was removed giving **10** as a thick liquid which was not purified.

2-(2,2-Dicarbethoxy-2-acetamidoethyl)-1,3-dithiolane (11).—The yellow oil **10** (0.01 mole) was dissolved in 25 ml of AcOH and 3.0 g (0.03 mole) of ethanedithiol and 5 ml of freshly distilled $BF_3 \cdot Et_2O$ was added. This solution was stirred for 12 hr, neutralized with 16.6 g of aqueous NaOH, and extracted ($CHCl_3$). The extract was dried ($MgSO_4$), filtered, and evaporated *in vacuo* to produce a solid which was recrystallized from H_2O–EtOH to yield 1.16 g of **11** (0.0037 mole, 37% from **9**). An analytical sample, mp 112°, was prepared by sublimation at 95–100° (0.3 mm). *Anal.* ($C_{13}H_{21}NO_5S_2$) H, N, S; C: calcd, 46.53; found, 46.99.

2-Amino-3-[2-(1,3-dithiolane)]propionic Acid (2).—A solution of 0.5 g (1.5 mmoles) of **11** in 1.3 ml of EtOH and 0.53 g of Na_2CO_3 in 3.75 ml of H_2O was refluxed for 20 hr. The solution was cooled and partitioned between EtOAc and the basic aqueous solution. The aqueous extract was acidified with dilute HCl to pH 3 and extracted with three 75-ml portions of EtOAc. The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to yield 0.27 g (1.15 mmoles, 78%) of the intermediate amido acid, mp 189.5–190.5°. The 2-acetamido-3-[2-(1,3-dithiolano)]-propionic acid (0.27 g, 1.15 mmoles) was refluxed in 5 ml of 1 *M* H_2SO_4 for 4.5 hr. The reaction mixture was cooled and neutralized by stirring with 40 g of Dowex 3 (OH^- form) ion-exchange resin in 50 ml of H_2O. The H_2O solution was filtered off and the resin was washed with 50 ml of H_2O. The obtained extracts were combined and the H_2O was evaporated with a stream of air to yield 0.17 g (0.9 mmole, 78%) of relatively pure amino acid **2**, which was recrystallized from H_2O–EtOH, mp 246°. *Anal.* ($C_6H_{11}NO_2S_2$) C, H.

2-(3,3-Dicarbethoxy-3-acetamidopropyl)-1,3-dithiolane (13).—The crude yellow syrup (0.50 mole) of **12**[6] was dissolved in $CHCl_3$ (200 ml) and 47.0 g (42.7 ml, 0.50 mole) of $(HSCH_2)_2$ was added. The solution was saturated with dry HCl, and the flask was stoppered and stirred for 12 hr. The $CHCl_3$ solution was washed to neutrality (H_2O), the solution was dried (Na_2SO_4), and most of the solvent was removed at 100° with N_2. The slightly viscous solution yielded 121 g (76%) of **13**. Recrystallization (Et_2O, aqueous EtOH) produced a white solid, mp 92–93°. *Anal.* ($C_{14}H_{23}NO_5S_2$) C, H, N, S.

2-Amino-4-[2-(1,3-dithiolano)]butyric Acid (3).—Compound **13** (17.1 g, 0.05 mole) was dissolved in 45 ml of EtOH. A solution of 125 ml of 1.25 *M* Na_2CO_3 was added and refluxed for 20 hr. The solution was cooled and extracted with two 75-ml portions of EtOAc. The aqueous solution was separated and the EtOAc extract was evaporated *in vacuo*. This residue again was treated with 25 ml of EtOH and 50 ml of 1.25 *M* Na_2CO_3 and refluxed for 24 hr. The combined aqueous solutions were acidified to pH 3, extracted with two 75-ml portions of EtOAc, dried (Na_2SO_4), and evaporated *in vacuo*. The residue, a brown liquid, was chromatographed on a silicic acid column and eluted with 2% MeOH in $CHCl_3$ to yield 7.25 g (0.035 mole, 70%) of 2-acetamido-4-[2-(1,3-dithiolano)]butyric acid. Recrystallization from $CHCl_3$ produced a white solid, mp 156.5–157°. The intermediate, 2-acetamido acid (7.25 g, 0.035 mole), and 100 ml of 1 *M* H_2SO_4 were refluxed for 5 hr. The orange solution was extracted with two portions of $CHCl_3$. The aqueous solution was neutralized to pH 6 with $Ba(OH)_2$ solution, $BaSO_4$ was removed by filtration, and the aqueous solution was concentrated *in vacuo* to 150 ml, which yielded 2.5 g of crude amino acid **3** upon standing. The mother liquor was evaporated to dryness and the residue was dissolved in a small amount of H_2O to yield an additional 1.52 g of **3**. The total yield of **3** was 0.019 mole (56%) which was dissolved in boiling H_2O, heated with activated charcoal, and filtered to give **3**, mp 262–263° dec. *Anal.* ($C_7H_{13}NO_2S_2$) C, H, N, S.

Acknowledgment.—The authors wish to acknowledge the assistance of Professor R. A. Wiley, University of Kansas.

(7) All melting points were taken on a calibrated Thomas–Hoover capillary melting point apparatus. Analyses were performed by Drs. G. Weiler and F. B. Strauss, Oxford, England, by Midwest Microlab, Inc., Indianapolis, Ind., and on an F & M Model 185, University of Kansas. Spectral data were obtained using Beckman IR-8, IR-10, Varian A-60, and A-60A spectrometers. The latter used Me_4Si as an internal standard except in D_2O where 3-trimethylpropanesulfonic acid sodium salt was employed. The nmr spectra were as expected. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements are within 0.4% of the theoretical values.

Antimicrobial Activity of a Series of Aminoalkyl Esters of Benzyldithiocarbamic Acids

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In continuation of our previous work[1] on the preparation of water-soluble antimicrobial agents, we have prepared a number of 2-aminoethyl esters of N-benzyldithiocarbamic acids, in an effort to combine water solubility with the known activity of benzyl

(1) R. C. Tweit, R. D. Muir, S. Mizuba, and W. R. Crowley, Jr., *J. Med. Chem.*, **8**, 374 (1965).

TABLE I

PHYSICAL CONSTANTS AND ANTIMICROBIAL ACTIVITIES OF AMINOALKYL ESTERS OF BENZYLDITHIOCARBAMATES

Compd	R	R′	HX	Formula	Analyses	Mp, °C	Ref to isothiocyanate	Lowest level of inhib, μg/ml *T. foetus*	*T. aceti*	*C. albicans*
1	H	H	HCl	$C_{10}H_{14}N_2S_2 \cdot HCl$	Cl, S	174.5–177	*a*	100	1	20
2	H	CH_3	HCl	$C_{12}H_{18}N_2S_2 \cdot HCl$	Cl, S	172.5–174	*a*	100	1	20
3	H	CH_3		$C_{12}H_{18}N_2S_2$	C, H	86.5–89	*a*	100	10	100
4	H	C_2H_5	HCl	$C_{14}H_{22}N_2S_2 \cdot HCl$	N, Cl	152–153	*a*	10	1,000	10
5	H[b]	CH_3	HCl	$C_{13}H_{20}N_2S_2 \cdot HCl$	C, H	164–166.5	*c*	10	1,000	1,000
6	H	$CH_3(CH_2)_6$, H	HCl	$C_{20}H_{34}N_2S_2 \cdot HCl$	C, H	146.5–148.5	*a*	100	1	1,000
7	H[d]	CH_3	HCl	$C_{14}H_{22}N_2S_2 \cdot HCl$	C, H	155–156.5	*e*		100	20
8	H	CH_3	HBr[f]	$C_{14}H_{22}N_2S_2 \cdot HBr$	Br, N	128.5–137.5	*a*	1,000	1,000	10,000
9	H	CH_3	*f*	$C_{14}H_{22}N_2S_2$	N, S	Oil	*a*			
10	4-CH_3	CH_3	HCl	$C_{13}H_{20}N_2S_2 \cdot HCl$	Cl, S	169.5–171	*c*	10	1	10
11	4-CH_3	C_2H_5	HCl	$C_{15}H_{24}N_2S_2 \cdot HCl$	C, H	146–148.5	*c*	10	100	20
12	4-CH_3	C_2H_5	Pamoic acid[g]	$C_{30}H_{48}N_4S_4 \cdot C_{23}H_{16}O_6$	C, H	Glass	*c*	10,000	1	1
13	4-$(CH_3)_3C$	CH_3	HCl	$C_{16}H_{26}N_2S_2 \cdot HCl$	N, S	203.5–206.5	New	100	1	1,000
14	2,5-$(CH_3)_2$	CH_3	HCl	$C_{14}H_{22}N_2S_2 \cdot HCl$	C, H	173.5–176	*c*	10	10	1,000
15	2,5-$(CH_3)_2$	C_2H_5	HCl	$C_{16}H_{26}N_2S_2 \cdot HCl$	C, H	109.5–112.5	*e*	10	1,000	>1,000
16	2,5-$(CH_3)_2$	C_2H_5		$C_{16}H_{26}N_2S_2$	C, H	73.5–75.5	*e*	100	1	1,000
17	2,5-$(CH_3)_2$	C_2H_5	CH_3Br	$C_{17}H_{29}BrN_2S_2$	C, H	129.5–132.5	*e*	1,000	1,000	100
18	2,4-$(CH_3)_2$, 5-$COCH_3$	CH_3	HCl	$C_{16}H_{24}N_2OS_2 \cdot HCl$	C, H	157–160	New	10	10,000	100
19	2-CH_3, 5-NO_2	CH_3		$C_{13}H_{19}N_3O_2S_2 \cdot 0.25C_3H_6O$[h]	C, H	110.5–114.5	New	100	1	1,000
20	3-NO_2	CH_3	HCl	$C_{12}H_{17}N_3O_2S_2 \cdot HCl$	C, H	158–160	*i*	1,000	1,000	1,000
21	4-F	CH_3	HCl	$C_{12}H_{17}FN_2S_2 \cdot HCl$	C, H	174.5–177.5	*j*	10	100	10
22	3-CF_3	CH_3	HCl	$C_{13}H_{17}F_3N_2S_2 \cdot HCl$	N	136–139	*j*	100	1	100
23	2-Cl	CH_3	HCl	$C_{12}H_{17}ClN_2S_2 \cdot HCl$	C, H	152.5–153.5	*k*	10	1	1,000
24	2-Cl	CH_3	HCl[f]	$C_{14}H_{21}ClN_2S_2 \cdot HCl$	S	146.5–150.5	*k*		1	1,000
25	3-Cl	CH_3	HCl	$C_{12}H_{17}ClN_2S_2 \cdot HCl$	C, H	166.5–168.5	*k*	100	10	13
26	4-Cl	CH_3	HCl	$C_{12}H_{17}ClN_2S_2 \cdot HCl$	C, H	191–193	*k*	100	1	20
27	4-Cl	CH_3		$C_{12}H_{17}ClN_2S_2$	C, H	82–85	*k*	100	100	10
28	4-Cl		2-Maleic acid	$C_{15}H_{22}ClN_3S_2 \cdot 2C_4H_4O_4$	C, H	140–143	*k*	10,000	10	1,000
29	2,6-Cl_2	CH_3	HCl	$C_{12}H_{16}Cl_2N_2S_2 \cdot HCl$	C, H	192–194	New	10	1,000	10
30	3,4-Cl_2	CH_3	HCl	$C_{12}H_{16}Cl_2N_2S_2 \cdot HCl$	Cl, S	183.5–187	*l*	1,000	1	10
31	3,4-Cl_2		Citric acid	$C_{16}H_{22}Cl_2N_2S_2 \cdot C_6H_8O_7$	N, S	103–107	*l*	1	1	100
32	4-Br	CH_3	HCl	$C_{12}H_{17}BrN_2S_2 \cdot HCl$	Br, Cl, S	185–188.5	*k*	1,000	1	13
33	4-OCH_3	CH_3	HCl	$C_{13}H_{20}N_2OS_2 \cdot HCl$	N, S	180.5–185.5	*e*	10	10	100
34	4-Ph	CH_3	HCl	$C_{18}H_{22}N_2S_2 \cdot HCl$	C, H	172.5–174.5	New	100	1	100

[a] Commercial product. [b] $CHCH_3$ instead of CH_2. [c] J. P. Trivedi and J. J. Trivedi, *J. Indian Chem. Soc.*, **35**, 657 (1958). [d] $(CH_2)_8$ instead of CH_2. [e] J. V. Braun and H. Deutsch, *Ber.*, **45**, 2188 (1912). [f] $CH_2CH(CH_3)CH_2$ instead of CH_2CH_2. [g] 4,4′-Methylenebis-(3-hydroxy-2-naphthoic acid). [h] 0.25 mole of acetone. [i] Reference 6. [j] Reference 5. [k] J. H. Shah, J. P. Trivedi, and J. J. Trivedi, *J. Indian Chem. Soc.*, **33**, 423 (1956). [l] Reference 2.

isothiocyanates and dithiocarbamate esters.[2] Other workers have reported the preparation of similar aminoethyl esters of N-phenylthiol-[3] and -dithiolcarbamic acids,[4,5] but no mention was made of antimicrobial activities. Most of the compounds in Table I were prepared by the triethylamine-catalyzed reaction of the appropriate benzyl isothiocyanate with 2-aminoethanethiols. Since almost all of the compounds prepared were made from dialkylaminoethanethiols, there was no possibility of reaction at other than the sulfur atom. In the case of 2-aminoethanethiol, the use of the hydrochloride salt prevents reaction at the amino group, even though as Ferris and Schutz[4] have shown, the thiourea is the more stable product.

Where the aminothiol or the isothiocyanate is not available, the substances can be prepared from dithiocarbamate salts and aminoalkyl halides, although the yields were poorer by this method.

Some aspects of the nmr spectra of the salts run in DMSO-d_6 are of interest. The benzyl hydrogens appear as a doublet (J = 5–6 cps) in the dialkylamino compounds and a singlet where a proton is present on the amino nitrogen. When the benzene ring is unsubstituted the doublet is centered at δ 4.88. A paramagnetic shift is caused by aromatic ring substituents, such as 2,6-dichloro, 3-trifluoromethyl, and 3-nitro in order of increasing magnitude. Diamagnetic shifts are caused by 4-bromo, 2,4-dimethyl-5-acetyl, 4-methyl, 4-*t*-butyl, and 4-methoxy. The shifts range from δ +0.11 for 3-NO_2 to −0.09 for 4-methoxy. The ring protons appeared as a singlet at δ 2.67 in the unsubstituted compounds, 2.69 in the *p*-*t*-butyl, and 2.81 in the *p*-methyl. From these values the 3-hydrogen in the 2,4-dimethyl-5-acetyl compound could be assigned a singlet at δ 2.89 and the 6-hydrogen to the peak at δ

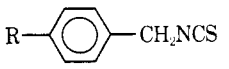
(2) A. F. McKay, D. L. Garmaise, R. Gaudry, H. A. Baker, G. Y. Paris, R. W. Kay, G. E. Just, and R. Schwartz, *J. Amer. Chem. Soc.*, **81**, 4328 (1959).

(3) K. H. Risse and G. Haberland, British Patent 920,755 (1963); *Chem. Abstr.*, **59**, 8762*b* (1963).

(4) A. F. Ferris and B. A. Schutz, *J. Org. Chem.*, **28**, 3140 (1963).

(5) E. Cherbuliez, A. Buchs, J. Marszalek, and J. Rabinowitz, *Helv. Chim. Acta*, **48**, 1414 (1965).

TABLE II



R	Mp, °C	Analyses
$(CH_3)_3C$	42–45 (not analyzed)	
2,4-$(CH_3)_2$, 5-$COCH_3$	46–53	N
2-CH_3, 5-NO_2	Used as an undistilled oil, 80% pure	
2,6-Cl_2	53.5–55	S
4-Ph	55–60 (only about 93% pure)	

2.23. In the compounds examined as free bases, the benzyl hydrogens appeared as a singlet.

Biology.—The compounds were tested quantitatively against the two fungi *Trichophyton mentagrophytes* and *Candida albicans*, the protozoan *Tritrichomonas foetus*, and the helminth *Turbatrix aceti*. In the testing against *T. mentagrophytes*, all the compounds tested except **6**, **8**, and **12** had lowest levels of inhibition ranging between 1 and 40 μg/ml. Compound **6** was active at 100 μg/ml and **8** and **12** had minimal activity at best. These results were not included in Table I since the range of activity was so small.

The most satisfying structure–activity relationship was found in the *T. aceti* assay. Here, the parent compound **1** was active at 1 μg/ml, *in vitro*. Changing the amino group to dimethylamino (*i.e.*, **2**), *n*-decylamino (**6**), or N′-methylpiperazino (**31**) had essentially no effect on the activity, but changing to diethylamino (**4**, **11**, **15**) reduced the activity by a factor of 100–1000. The free bases were less active than the hydrohalide salts by a factor of 10–100. This may be due to lower water solubility which may also explain the inactivity of the pamoate salt (**12**). Lengthening the chain between the S and N atoms from ethylene to 2-methylpropylene reduced the activity by at least a factor of 1000.

At the benzyl end of the molecule, adding a methyl on the benzylmethylene or lengthening this chain to three carbons reduced the activity by factors of 1000 and 100, respectively. Placing a strongly electronegative group such as nitro, acetyl, or fluoro on the phenyl ring also lowered activity by factors of 100–1000. Even two chlorines on the ring did not adversely affect the activity, except in the case of the 2,6-dichloro compound. Here the cause may be steric.

The activities against the last two organisms do not follow such a neat pattern. In the *Candida albicans* assay, the best compounds were active in the 10–40-μg/ml range, had no substituent or only small *meta* or *para* substituents on the benzene ring, had an unbranched alkyl chain connecting this ring to the amide nitrogen, had an ethylene chain between the N and S atoms, and had an amino, dimethylamino, or diethylamino group at the other end of the molecule. In the *T. foetus* assay, still fewer clear-cut effects are apparent. An N′-methylpiperazino group lowers the activity by a factor of 100 and a 2-methylpropylene linkage between N and S is also detrimental.

The compounds were also tested qualitatively for antibiotic activity against the bacteria, *Bacillus subtilis*, *Escherichia coli*, and *Diplococcus pneumoniae*; the alga, *Chlorella vulgaris*; and the protozoan, *Tetrahymena geleii*, as described in our previous paper.[1] Against the alga, 30 of the compounds were active, 31 killed the protozoan, and 28 prevented growth of *D. pneumoniae*. A few of the compounds were tested quantitatively against the other two bacteria. Compounds **21** and **25**, the most active of these, inhibited growth at 6 μg/ml.

A number of the compounds were found ineffective in mice intraperitoneally infected with *C. albicans* when injected at the 0.5-mg dose level in aqueous 50% propylene glycol; at higher doses some of the animals died.

Experimental Section[6]

The corrected melting points, taken in a bath, of the dithiocarbamates are listed in Table I. Most of them were prepared as described for the hydrochloride of the 2-dimethylaminoethyl ester of 4-chlorobenzyldithiocarbamic acid (**25**). Commercial samples of dialkylaminoethanethiol hydrochlorides should be recrystallized from $CHCl_3$ to remove the corresponding disulfides which are difficult to separate from the desired dithiocarbamates. Most of them were obtained in yields of 50–80% and many were analytically pure without recrystallization. Others were recrystallized from MeOH or $CHCl_3$–EtCOMe.

2-Dimethylaminoethyl 4-Chlorobenzyldithiocarbamate Hydrochloride (25).—Triethylamine (6 drops) was added to a mixture of 18.4 g (0.1 mole) of *p*-chlorobenzyl isothiocyanate, 14.2 g (0.1 mole) of 2-dimethylaminoethanethiol hydrochloride, and 25 ml of MeOH. The temperature rose, the solid dissolved, and a new solid formed which was separated by filtration, 24.1 g, mp 188–190°.

The substituted-benzyl isothiocyanates can be prepared from the corresponding halides by the easy method of Tarlton and McKay.[7] The halides are commercially available or were prepared by chloromethylation.[8] The new isothiocyanates are listed in Table II. N-(2-Mercaptoethyl)-N′-methylpiperazine was prepared as described by Risse and Haberland.[3] Compounds **8** and **23** were prepared by the method below since the necessary aminothiol was not available.

2-Dimethylamino-2-methylpropyl Benzyldithiocarbamate Hydrobromide (8).—A slurry of 56.8 g (0.2 mole) of the NEt_3 salt of benzyldithiocarbamic acid[2] in 150 ml of *i*-PrOH was stirred while a solution of 34.4 g (0.2 mole) of 3-dimethylamino-2-methylpropyl chloride hydrochloride in 50 ml of MeOH and 150 ml of *i*-PrOH was added over 20 min. The mixture was stirred until all the solid was gone and then concentrated under vacuum. The residue was dissolved in CH_2Cl_2–H_2O. The aqueous layer was separated, washed once with CH_2Cl_2, and made basic. The oil which formed was separated and the aqueous layer was extracted two times with CH_2Cl_2. The combined organic layers were dried and evaporated. The residue was triturated with ether and 0.18 mole of *i*-PrOH–HBr. The solid which formed was recrystallized (hot H_2O) to yield 11.9 g of **8**, mp 128.5–137.5°.

The free bases can be prepared as illustrated for **16**. **2-Diethylaminoethyl 2,5-Dimethylbenzyldithiocarbamate (16).**—The corresponding HCl salt (**15**) (20.2 g) was added to 100 ml of 3% aqueous NaOH and 50 ml of CH_2Cl_2. The mixture was agitated and then filtered. The CH_2Cl_2 solution was separated, washed (H_2O), dried, and concentrated. When pentane and Et_2O were added to the residue and the solution was cooled, a solid formed, 16.7 g.

2-Diethylaminoethyl 2,5-Dimethylbenzyldithiocarbamate Methobromide (17).—Compound **16** (9.3 g) was dissolved in 100 ml of 2-butanone in a citrate bottle. The solution was cooled while 21 g of MeBr was bubbled in. The resulting solution was held at 0° for 5 days. A solid formed, was separated by filtration, and recrystallized from $CHCl_3$–MeCOEt to yield 8.2 g of **17**.

Testing.—Quantitative tests against *Tritrichomonas foetus* were run in a modification of Diamond medium containing 20% serum and inoculated with 1% of a 48- or 72-hr culture of the organism. Serial dilutions of the compounds were prepared

(6) Where analyses are indicated only by the symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(7) E. J. Tarlton and A. F. McKay, U. S. Patent 3,111,536 (1963); *Chem. Abstr.*, **60**, 2825*g* (1961).

(8) R. C. Fuson and C. H. McKeever, *Org. Reactions*, **1**, 63 (1942).

in the inoculated medium and incubated at 37° for 48 hr. The resulting cultures were examined microscopically for the presence or absence of motile organisms.

Anthelmintic activity against *Turbatrix aceti* was determined by preparing series of dilutions of the compounds in washed suspensions of the nematodes in distilled H_2O. These preparations were incubated at room temperature for 48 hr and examined for the presence or absence of motile worms.

The quantitative tests with *C. albicans* and *T. mentagrophytes* were run in Sabouraud dextrose agar. The test compounds were dissolved in the hot agar and then diluted serially in test tubes. These were permitted to cool in a vertical position and the test organisms were inoculated onto the surface of the agar. Following a suitable incubation period, the presence or absence of growth was determined by visual inspection.

Quantitative antibacterial tests with *Bacillus subtilis* and *Escherichia coli* were run in nutrient broth. The test compounds were dissolved and diluted serially in preinoculated medium. The preparations were incubated for 24 hr at 37° and then observed grossly for the presence or absence of growth.

New Compounds

Some 3-Alkoxyestra-1,3,5(10)-trien-17β-ols

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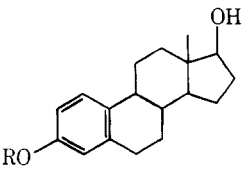
As part of a program[1] directed toward the development of an irreversibly acting analog of 17β-estradiol we have prepared the new 3-alkoxyestra-1,3,5(10)-trien-17β-ols listed in Table I. These compounds possess weak estrogenic activities (at least 0.0001 times as active as 17β-estradiol); however, a number of them inhibit the uptake (*in vitro*) of ^{3}H-17β-estradiol by mouse uteri. Pharmacological results were supplied by M. May and C. Liarokos and will be published in detail elsewhere.

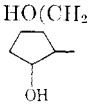
Experimental Section

The compounds described in Table I were prepared, by standard procedures,[2] from 17β-estradiol and the appropriate alkyl halide.

TABLE I

3-ALKOXYESTRA-1,3,5(10)-TRIEN-17β-OLS. PHYSICAL DATA



R	Yield, %	Mp, °C[b]	Crystn[a] solvent	Formula	Analyses[b]
CH_3CH_2	61	124–125[c]	2	$C_{20}H_{28}O_2$	C, H
$CH_3(CH_2)_2$	50	105–106	2	$C_{21}H_{30}O_2$	C, H
$CH_3(CH_2)_3$	31	55–57	1	$C_{22}H_{32}O_2$	C, H
$CH_3(CH_2)_5$	50	76–78	4	$C_{24}H_{36}O_2$	CH
$CH_3(CH_2)_6$	43	68–70	1	$C_{25}H_{38}O_2$	C, H
$(CH_3)_2CH(CH_2)_2$	45	99–100	4	$C_{23}H_{34}O_2$	CH
$HO(CH_2)_3$	25	166–168	6	$C_{21}H_{30}O_3$	C, H
$HO(CH_2)_4$	50	232–233	5	$C_{22}H_{32}O_3$	C, H
$HO(CH_2)_5$	50	150–152	5	$C_{23}H_{34}O_3$	C, H
	42	154–156	4	$C_{23}H_{32}O_3$	C, H
$(CH_3CH_2)_2N(CH_2)_3$	70	222–224	6	$C_{25}H_{39}NO_2 \cdot HCl$	C, H, N
$(CH_3CH_2)_2N(CH_2)_4$	54	211–213	6	$C_{26}H_{41}NO_2 \cdot HCl \cdot H_2O$	C, H, N
$(CH_3CH_2)_2N(CH_2)_5$	25	215–217	7	$C_{27}H_{43}NO_2 \cdot HCl$	C, H, N
$Br(CH_2)_5$	40	79–81	3	$C_{23}H_{39}BrO_2$	C, H, Br

[a] 1, petroleum ether (bp 40–60°); 2, petroleum ether (bp 60–80°); 3, petroleum ether (bp 80–100°); 4, C_6H_{14}; 5, C_6H_6; 6, *i*-PrOH; 7, MeCN. [b] Melting points were recorded on a Thomas–Kofler hot stage and are corrected. Analyses are by Dr. A. E. Bernhardt, Mülheim, Germany. Where analyses are indicated only by symbols of the elements, the analytical results obtained for those elements are within ±0.4% of the theoretical values. [c] R. Courier, L. Velluz, J. J. Alloiteau, and G. Rousseau, *Compt. Rend.*, **139**, 128 (1945), report mp 115° for this compound.

(1) The rationale of our approach is discussed in a previous publication: M. May, B. J. Johnson, D. J. Triggle, J. F. Danielli, and S. S. H. Gilani, *Life Sci.*, **4**, 705 (1965).

(2) (a) N. P. Buu-Hoi, *Bull. Soc. Chim. France*, **12**, 866 (1945); (b) W. J. Hikinbottom, "Reactions of Organic Compounds," Longmans, Green and Co., London, 1957, p 112.