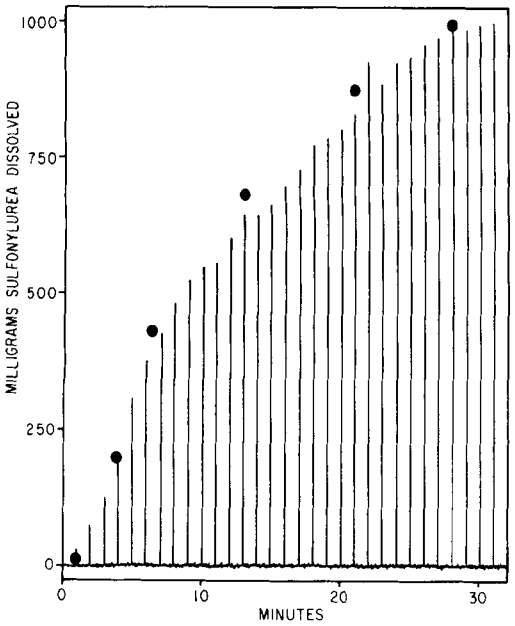

Fig. 8.—Dissolution profile of two sulfonylurea tablets in 750 ml. pH 7.2 THAM buffer at 37.5° using U.S.P. disintegration apparatus without disks. Vertical solid lines redrawn from curve obtained using automated procedure with dilution device. Theoretical drug content of two test tablets taken as 1000 mg. Solid circles represent values obtained by simultaneous, independent assays of dissolution fluid.

CONCLUSIONS

Automated dissolution rate studies of solid dosage forms serve as an extremely useful method for controlling the quality of these products. The method is applicable to the evaluation of virtually all tablets, capsules, and granules containing drugs soluble in about 1 L. of dissolution fluid. The total dissolution profile expressed as per cent drug in solution as a function of time may be obtained for these products. However, dosage forms containing drugs not wholly soluble in the dissolution medium may also be evaluated; results are expressed in terms of absolute initial rate of dissolution.

Savings in laboratory man-hours can be enormous if the automated procedure is used regularly to control the quality of solid dosage forms. One investigator working with the automated device can perform the same number of dissolution studies as four technicians working with conventional, manual procedures. Also, the automated procedure uses a modified Beckman DU spectrophotometer in place of a Cary recording spectrophotometer for measuring absorption changes in the solution. This frees the more expensive recording spectrophotometer for other more versatile analytical jobs. The automated device also serves as a useful and versatile analytical tool for automatically re-recording the progress of chemical kinetic reactions which involve changes in absorption of monochromatic light.

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Synthesis and Antifungal Evaluation of Some Derivatives of Dialkoxybenzoic and Dialkoxycinnamic Acids

By A. K. KAPADIA† and GAIL A. WIESE

A number of dialkylaminoalkyl esters of dialkoxybenzoic and dialkoxycinnamic acids and their halogenated analogs were prepared. The compounds, in the form of their hydrochloride salts, together with the parent acids were tested *in vitro* against three pathogenic fungi using undecylenic acid and griseofulvin as controls. In general, the results of the tests indicated that most of the compounds had little or no antifungal activity *in vitro*.

IT HAS BEEN shown that fungal diseases in man are a growing health hazard (1). The search for antifungal agents has been in progress for several decades. In reviewing the literature it was noted that there have been few investigations directed toward the study of antifungal activity of the derivatives of dialkoxybenzoic and dialkoxycinnamic acids and their halogenated analogs.

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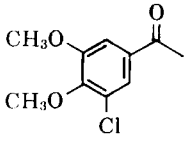
TABLE 1.—COMPOUNDS SYNTHESIZED AND/OR TESTED

No.	Name	Yield, %	M.p.,[a] °C. Observed	M.p.,[a] °C. Reported	Ref.
I	Benzoic acid[b]	...	...	...	...
II	Vanillic acid	74.0	210–211	210–211	8
III	Veratric acid[b]	56.6	180–181	180–181	9
IV	5-Chlorovanillin	83.5	165–166	165–166	10
V	5-Chlorovanillic acid	80.0	242	242	11
VI	5-Chloroveratric acid[b]	70.0	189–190	189–190	12
VII	5-Bromovanillin	95.5	164	164	13
VIII	5-Bromovanillic acid	72.5	231–232	231–232	14
IX	5-Bromoveratric acid[b]	100.0	192–193	192–193	15
X	5-Iodovanillin	78.6	179–180	179–180	16
XI	5-Iodoveratraldehyde	77.2	72–73	72–73	12
XII	5-Iodoveratric acid[b]	80.4	184–185	184–185	12
XIII	5-Chloro-4-hydroxy-3-ethoxybenzaldehyde	80.0	149–150	...	[c]
XIV	5-Chloro-4-hydroxy-3-ethoxybenzoic acid	100.0	199–200	...	[d]
XV	5-Chloro-4-methoxy-3-ethoxybenzoic acid[b]	58.7	167–168	...	[e]
XVI	3-Ethoxy-4-hydroxybenzoic acid	66.0	164–165	164–165	17
XVII	5-Bromo-4-hydroxy-3-ethoxybenzoic acid	79.0	207	207	17
XVIII	5-Bromo-4-methoxy-3-ethoxybenzoic acid[b]	79.0	183–184	183–184	17
XIX	Cinnamic acid[b]	...	...	...	...
XX	3-Ethoxy-4-acetoxycinnamic acid	45.2	176–177	...	...
XXI	5-Chloroferulic acid	83.0	251	251	18
XXII	5-Chloro-3,4-dimethoxycinnamic acid[b]	80.2	126–127	126–127	19
XXIII	5-Bromoferulic acid	100.0	257–258	257–258	20
XXIV	5-Bromo-3,4-dimethoxycinnamic acid[b]	88.0	138–139	138–139	21

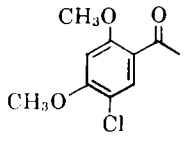
[a] Melting points are uncorrected and were taken on Fisher-Johns melting point apparatus. [b] Tested for antifungal activity. [c] *Anal.*—Calcd. for $C_9H_9ClO_3$: Cl, 17.7. Found: Cl, 17.55. [d] *Anal.*—Calcd. for $C_9H_9ClO_4$: Cl, 16.4. Found: Cl, 16.34. [e] *Anal.*—Calcd. for $C_{10}H_{11}ClO_4$: Cl, 15.4. Found: Cl, 15.42.

It is interesting to note that the structural fragment I included in this investigation is a



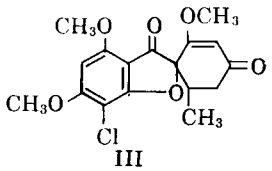
I

position isomer of the structure II present in the



II

griseofulvin molecule III.

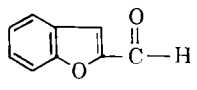


III

MacMillan has shown that the aromatic chlorine substituent in the griseofulvin molecule enhances the antifungal activity of griseofulvin (2).

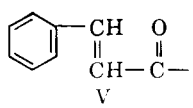
Woodward, *et al.* (3), have studied the fungicidal properties of various halogens and alkyl substituents on the aromatic ring of phenol *in vitro*. They found that in going from chlorine to bromine to iodine, there was a four to tenfold increase in antifungal activity. Taking these facts into consideration, it was decided that the effect of removal of halogen from the aromatic ring and the interchange of chlorine for bromine and iodine should be studied.

Pan and Wiese (4) found that benzofuran-2-carboxaldehyde (IV) had



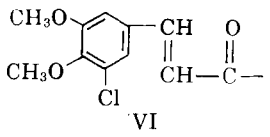
IV

significant antifungal activity as compared to undecylenic acid *in vitro*. The cinnamoyl group (V) is present in benzofuran-2-carboxaldehyde (IV).



V

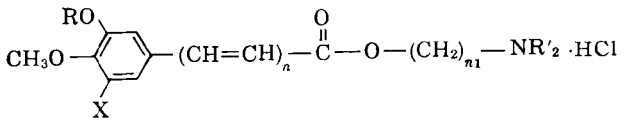
The structural fragment VI was included in this investigation. This is a vinylog of I.



VI

Since dialkylaminoalkyl esters of other acids have shown useful properties (5–8), the dialkylaminoalkyl esters were of interest in this investigation. These alkamine esters were water insoluble, therefore they were converted into the hydrochloride salts. The compounds prepared in this investigation are summarized in Tables I and II.

TABLE II.—HYDROCHLORIDES OF DIALKYLAMINOALKYL ESTERS SYNTHESIZED AND TESTED



No.	R	X	n	m	R′	Yield, %	M.P.,[a] °C.	Formula[b]	Analysis, % N[c] Calcd.	N[c] Found	Halogen Calcd.	Halogen Found
XXV	CH_3	H	0	2	CH_3	10.0	165–166	$C_{13}H_{20}ClNO_4$	4.84	4.86	12.26	12.10
XXVI	CH_3	H	0	2	C_2H_5	37.8	145–146	$C_{15}H_{24}ClNO_4$	4.41	4.34	11.18	11.39
XXVII	CH_3	Cl	0	2	CH_3	73.7	152–153	$C_{13}H_{19}Cl_2NO_4$	4.32	4.35	21.92	22.20
XXVIII	CH_3	Cl	0	[d]	CH_3	44.8	132–133	$C_{14}H_{21}Cl_2NO_4$	4.14	4.19	21.00	20.93
XXIX	CH_3	Cl	0	2	C_2H_5	32.0	154–155	$C_{15}H_{23}Cl_2NO_4$	3.98	3.98	20.18	20.18
XXX	CH_3	Cl	0	3	CH_3	51.9	135–136	$C_{14}H_{21}Cl_2NO_4$	4.14	4.10	21.00	21.05
XXXI	CH_3	Cl	0	3	C_2H_5	49.7	140–141	$C_{16}H_{25}Cl_2NO_4$	3.83	3.86	19.40	19.20
XXXII	CH_3	Br	0	2	CH_3	63.7	161–162	$C_{13}H_{19}BrClNO_4$	3.80	3.75	31.34	31.00
XXXIII	CH_3	Br	0	2	C_2H_5	48.7	164–165	$C_{15}H_{23}BrClNO_4$	3.53	3.60	29.14	28.70
XXXIV	CH_3	I	0	2	C_2H_5	60.4	166–167	$C_{15}H_{23}ClINO_4$	3.16	3.20	36.64	37.20
XXXV	C_2H_5	Cl	0	2	CH_3	35.6	112–113	$C_{14}H_{21}Cl_2NO_4$	4.16	4.22	20.77	21.00
XXXVI	C_2H_5	Cl	0	2	C_2H_5	39.1	133–134	$C_{16}H_{25}Cl_2NO_4$	3.84	3.88	19.18	19.22
XXXVII	C_2H_5	Br	0	2	CH_3	28.7	109–110	$C_{14}H_{21}BrClNO_4$	3.66	3.70	30.19	30.24
XXXVIII	C_2H_5	Br	0	2	C_2H_5	28.1	130–131	$C_{16}H_{25}BrClNO_4$	3.41	3.45	28.14	28.30
XXXIX[e]	C_2H_5	H	1	2	CH_3	26.2	151–152	$C_{17}H_{23}ClNO_5$	3.92	3.85	9.93	9.85
XL[e]	C_2H_5	H	1	2	C_2H_5	39.7	175–176	$C_{19}H_{28}ClNO_5$	3.62	3.57	9.20	9.12
XLI	CH_3	Cl	1	2	CH_3	25.6	140–141	$C_{15}H_{21}Cl_2NO_4$	4.00	4.10	20.29	19.95
XLII	CH_3	Cl	1	2	C_2H_5	28.9	148–149	$C_{17}H_{25}Cl_2NO_4$	3.70	3.69	18.78	19.00
XLIII	CH_3	Br	1	2	C_2H_5	30.6	149–150	$C_{17}H_{25}BrClNO_4$	3.32	3.26	27.34	27.00

[a] Melting points are uncorrected and were taken on Fisher-Johns melting point apparatus. [b] All the compounds were recrystallized from an absolute alcohol-anhydrous ether mixture. [c] Nitrogen analysis by a semimicro Kjeldahl method. [d] $-(CH_2)-$ is equal to $-\underset{\displaystyle CH_3}{\overset{|}{CH}}-CH_2-$. [e] $p-OCH_3$ is replaced by $p-OCOCH_3$.

TABLE III.—MINIMUM WIDTH OF ZONES OF INHIBITION[a]

Compound No.[b]	*T. mentagrophytes*, mm. Concn. % w/v 0.5	1.0	2.0	*T. rubrum*, mm. Concn. % w/v 0.5	1.0	2.0	*M. gypseum*, mm. Concn. % w/v 0.5	1.0	2.0
I	3	3	3	3	5	6	0	0	2
III	0	1	2	1	2	4	0	0	0
VI	0	1	3	1	2	2	0	0	0
IX	0	0	0	1	4	4	0	0	0
XV	0	0	0	1	2	3	0	0	0
XIX	4	5	10	5	11	13	2	4	5
XXI	4	4	4	2	3	5	0	0	0
XXIV	2	2	2	2	2	3	0	0	0
XXX	0	1	2	1	2	3	0	1	2
XXXI	2	2	3	2	2	2	1	2	2
XXXVI	2	2	3	2	2	2	0	1	2
XLI	2	2	3	1	1	2	0	2	3
XLIII	2	4	10	1	2	2	1	2	2
Undecylenic acid[c]	10	10	11	9	9	9	3	5	5
Ethyl vanillate[c]	0	8	19	2	4	16	2	8	13
Ethanol 95%[d]	0	0	0	0	0	0	0	0	0
Griseofulvin[e]		14			1			7	

[a] Average of two measurements. [b] Numbers according to Tables I and II. [c] Controls. [d] Solvent. [e] Saturated solution.

ANTIFUNGAL EVALUATION

The compounds were tested *in vitro* against *Trichophyton mentagrophytes*, *Trichophyton rubrum*, and *Microsporum gypseum*. The testing procedure was similar to that described by Waters (22), with the exceptions that ethanolic solutions of the compounds and a 7-day incubation period were employed. At the end of the incubation period, the minimum zone of inhibition was measured. The zone of inhibition was the distance between the periphery of the paper disk and the colony growth. Undecylenic acid and griseofulvin were used as controls. Ethyl vanillate and 95% ethanol were also included in this study. The results of this antifungal study are given in Table III. Each value in this table represents an average of two zones of inhibition. Only those compounds which had a zone of inhibition 3 mm. and greater are reported in Table III.

DISCUSSION

The dialkylaminoalcohols used in these studies are readily available. The required acids were synthesized according to the procedures described in the literature with certain modifications.

Raiford and co-workers (12, 14, 15) have reported the synthesis of a number of dialkoxybenzoic acids. Vanillin was first alkylated and subsequently oxidized to the acid with potassium permanganate. We found that oxidizing vanillin to the corresponding vanillic acid and then alkylating it was a more efficient process and gave better yields.

The method of Pearl (8) for preparing vanillic acid (II) from vanillin using silver oxide in an alkaline medium was preferred for the preparation of 5-chlorovanillic acid (V), 5-bromovanillic acid (VIII), and 5-chloro-4-hydroxy-3-ethoxybenzoic acid (XIV).

Veratric acid (III) was synthesized from vanillic acid (II) according to the method used by Fosdick and Starke (23) for preparing 3,4-dimethoxycinnamic acid from ferulic acid. The same procedures were used for preparing 5-chloroveratric acid (VI), 5-bromoveratric acid (IX), and 5-chloro-4-methoxy-3-ethoxybenzoic acid (XV) from their respective aldehydes. Attempts to prepare 5-iodoveratric acid (XII) in this way were unsuccessful. Therefore, the following method was employed: the aldehyde, 5-iodovanillin was first methylated to give 5-iodoveratraldehyde (XI) which was subsequently oxidized to 5-iodoveratric acid (XII) with potassium permanganate. In the case of 5-bromo-4-methoxy-3-ethoxybenzoic acid (XVIII), 3-ethoxy-4-hydroxybenzaldehyde was first oxidized to 3-ethoxy-4-hydroxybenzoic acid (XVI). This compound was brominated yielding 5-bromo-4-hydroxy-3-ethoxybenzoic acid (XVII). Subsequent methylation gave rise to 5-bromo-4-methoxy-3-ethoxybenzoic acid (XVIII).

The compounds, 5-chloro-3,4-dimethoxycinnamic acid (XXI) and 5-bromo-3,4-dimethoxycinnamic acid (XXIV) were synthesized according to the methods of Pearl and Beyer (18) and Fosdick and Starke (23).

The aldehydes, 5-chlorovanillin (IV) and 5-chloro-4-hydroxy-3-ethoxybenzaldehyde (XIII), were obtained by a modification of the method of Menke and Bentley (10). Because of solubility problems, carbon tetrachloride was employed as a solvent instead of chloroform. The compounds, 5-bromovanillin (VII) and 5-iodovanillin (X) were obtained by the methods of McIvor and Pepper (24) and Erdtman (16), respectively.

The alkamine esters were prepared by refluxing the dialkylaminoalcohol in dry benzene with the appropriate acid chloride. The alkamine esters that formed precipitated as the hydrochloride salts.

The results of the antifungal studies, as shown in Table III, indicate that none of the compounds had an antifungal activity comparable to that of the compounds used as controls.

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