Anthelmintic Agents. 1,2-Dihydro-*s*-Triazines[1]

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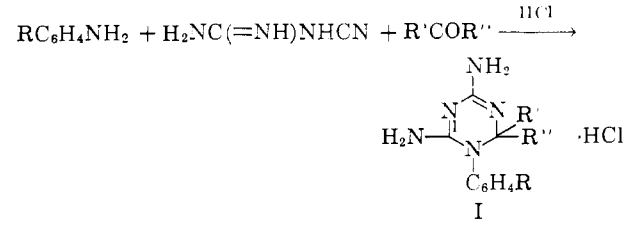
A series of 1-aryl-4,6-diamino-1,2-dihydro-*s*-triazines which contain *ortho*-substituents in the benzene ring, or bulky groups in the 2-position of the dihydrotriazine ring, is described. Such compounds have been found to have high anthelmintic activity against intestinal parasites and negligible microbiological activity. This is in contrast to the related compounds without the sterically hindering substituents, which have been found by various groups in the past to be potent antimicrobial agents.

In the course of some chemical studies with a series of 2,6-diamino-5-(*ortho*-substituted phenyl)-4,5-dihydropyrimidines,[2] it became of interest to prepare some of the corresponding dihydrotriazines for comparative purposes. Carrington, Crowther, and co-workers[3-5] and Modest and co-workers[6-8] have prepared a large number of 1-aryl-4,6-diamino-1,2-dihydro-*s*-triazines by the condensation of biguanides with ketones or aldehydes, or by a one step reaction in which aromatic amines are heated with dicyandiamide in the presence of ketones or aldehydes. 1-(*p*-Chlorophenyl)-4,6-diamino-1,2-dihydro-2,2-dimethyl-*s*-triazine (I, R = *p*-Cl, R′ and R″ = CH_3) was found by the investigators at the Imperial Chemical Industries, Ltd., to be the active metabolite of the antimalarial drug chlorguanide (N^1-(*p*-chlorophenyl)-N^5-isopropylbiguanide).[3,9] A considerable number of compounds of this type have been demonstrated to possess activity against experimental avian and rodent malaria,[5,10] activity against coccidiosis in chicks,[11,12] anti-folic acid activity in microbiological systems,[6,13-15] antibacterial activity against certain pathogenic bacteria,[16,17] antitumor activity against certain experimental tumors,[18,19] and activity against experimental murine toxoplasmosis.[20] In all of these studies the compounds which were particularly active contained *meta* or *para* substitution in the benzene ring; those containing *ortho* substitution, particularly di-*ortho* substitution, were almost completely inactive. The more active compounds also had small alkyl groups, such as dimethyl, or one longer unbranched alkyl group in the 2-position of the triazine ring, while bulky groups, such as pentamethylene, usually led to low activity.



I

The two compounds which were initially chosen for our laboratory study of *ortho*-substituted dihydrotriazines were of the formula I where R = *o*-ethyl or *o,o*′-dimethyl, and R′ and R″ = methyl in each case. These compounds were subjected to routine pharmacological screening. As expected, they showed no activity in the microbiological assay with *Lactobacillus casei*, nor in the adenocarcinoma 755 tumor screen. However, in determining the acute toxicity, the observation was made that the oral LD_{50} was greater than 10 times the LD_{50} by the parenteral route. This prompted the suggestion that since the compounds were evidently not well absorbed from the intestinal tract, they might possibly have some utility against intestinal parasites. Accordingly, they were screened against *Syphacia obvelata* infestations in mice, and it was found that at oral dosages of 300 mg./kg./day for 3 days, over 90% of the worms were cleared, with no apparent adverse effects on the mice. Foley[15] had demonstrated that there was a direct relation between increasing steric hindrance and decrease in activity as microbiological inhibitors. It became of interest then to see whether this pattern was followed with regard to intestinal parasites. Accordingly, the chlorguanide metabolite was screened against *Syphacia obvelata*, and surprisingly, it was found to be practically devoid of activity. These results led to the synthesis of a series of *ortho*-substituted phenyldihydrotriazines. A number of *meta*- and *para*-substituted derivatives were prepared for comparison. The substituents in the 2-position of the triazine ring were varied also to include some of a bulky nature. All compounds were screened routinely for microbiological activity against *Lactobacillus casei*, as well as against intestinal parasites.

Initially all compounds were screened *vs. Syphacia*

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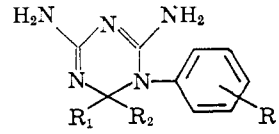
TABLE I

1-ARYLDIHYDROTRIAZINES

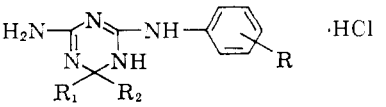


Compd. No.	2,2-Substituents(R_1R_2)	Benzene substituents(R) 2	3	4	5	6	Empirical formula	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
I	H, CH_3	C_2H_5					$C_{12}H_{17}N_5 \cdot HCl$	277–279	53.82	54.17	6.77	6.89		
II	$(CH_3)_2$	C_2H_5					$C_{13}H_{19}N_5 \cdot HCl$	209–211	55.41	55.26	7.15	7.04	24.86	24.70
III	$(CH_3)_2$	C_3H_7-*n*					$C_{14}H_{21}N_5 \cdot HCl$	210	56.85	57.04	7.50	7.36	23.68	23.45
IV	$(CH_3)_2$	C_4H_9-*n*					$C_{15}H_{23}N_5 \cdot HCl$	191	58.14	57.95	7.81	7.70		
V	$(CH_3)_2$	OCH_3					$C_{12}H_{17}N_5O$	226–229	58.28	58.38	6.93	7.18	28.32	28.27
VI	$(CH_3)_2$		CH_3				$C_{12}H_{17}N_5 \cdot HCl$	212	53.82	53.81	6.77	6.65		
VII	$(CH_3)_2$	CH_3	CH_3				$C_{13}H_{19}N_5 \cdot HCl$	220	55.41	55.34	7.15	7.19		
VIII	$(CH_3)_2$	CH_3	Cl				$C_{12}H_{16}ClN_5 \cdot HCl$	218–220	47.69	48.13	5.67	5.59	23.18	22.92
IX	$(CH_3)_2$	CH_3		CH_3			$C_{13}H_{19}N_5 \cdot HCl$	211–212	55.41	55.22	7.15	7.10		
X	$(CH_3)_2$	CH_3		Cl			$C_{12}H_{16}ClN_5 \cdot HCl$	219–220	47.69	47.97	.67	5.78		
XI	$(CH_3)_2$	OCH_3		NO_2			$C_{12}H_{16}N_6O_3 \cdot HCl$	220–222	43.84	44.22	5.21	5.35	25.56	25.29
XII	$(CH_3)_2$	CH_3			CH_3		$C_{13}H_{19}N_5 \cdot HCl$	228	55.41	55.89	7.15	7.12	24.85	24.42
XIII	$(CH_3)_2$	CH_3			Cl		$C_{12}H_{16}ClN_5 \cdot HCl$	220–223	47.69	48.04	5.67	5.61	23.18	23.58
XIV	$(CH_3)_2$	CH_3			C_3H_7-*i*		$C_{15}H_{23}N_5 \cdot HCl$	211	58.14	58.23	7.81	7.79		
XV	$(CH_3)_2$	OCH_3			Cl		$C_{12}H_{16}ClN_5O \cdot HCl$	218–220	45.29	45.14	5.39	4.83	22.01	21.99
XVI	$(CH_3)_2$	CH_3				CH_3	$C_{13}H_{19}N_5 \cdot HCl$	220	55.41	55.55	7.15	7.20	24.86	24.71
XVII	$(CH_3)_2$		CH_3		CH_3		$C_{13}H_{19}N_5 \cdot HCl$	212	55.41	55.13	7.15	6.84		
XVIII	$(CH_3)_2$	CH_3		CH_3	CH_3		$C_{14}H_{21}N_5 \cdot HCl$	223	56.85	57.28	7.50	7.43	23.68	23.32
XIX	CH_3, C_2H_5	C_2H_5					$C_{14}H_{21}N_5 \cdot HCl$	195–196	56.85	56.54	7.50	6.83		
XX	CH_3, C_2H_5	CH_3				CH_3	$C_{14}H_{21}N_5 \cdot HCl$	210	56.85	56.74	7.50	7.39		
XXI	CH_3, C_3H_7-*n*	C_2H_5					$C_{15}H_{23}N_5 \cdot HCl$	200–201	58.14	58.55	7.80	7.84		
XXII	H, C_6H_{13}-*n*	C_2H_5					$C_{17}H_{27}N_5 \cdot HCl$	222	60.41	60.21	8.36	8.16	20.72	20.31
XXIII	H, C_9H_{19}	C_2H_5					$C_{20}H_{33}N_5 \cdot HCl$	243–244	63.15	63.30	9.11	9.15		
XXIV	$-(CH_2)_4-$	C_2H_5					$C_{15}H_{21}N_5 \cdot HCl$	224	58.52	58.82	7.20	6.77		
XXV	$-(CH_2)_5-$	C_2H_5					$C_{16}H_{23}N_5 \cdot HCl$	224	59.70	59.50	7.51	7.30		
XXVI	$-(CH_2)_5-$	Br					$C_{14}H_{18}BrN_5 \cdot HCl$	235	45.11	45.39	5.14	4.98	18.79	18.38
XXVII	$-(CH_2)_5-$	CH_3				CH_3	$C_{16}H_{23}N_5 \cdot HCl$	295	59.70	59.50	7.51	6.67	21.76	21.63
XXVIII	$-CH_2CH(CH_2)_3-$ (CH$_3$ on CH)	Br					$C_{15}H_{20}BrN_5 \cdot HCl$	199	46.58	46.90	5.47	5.76	18.11	17.92
XXIX	$-CH_2CH(CH_2)_3-$ (CH$_3$ on CH)			Cl			$C_{15}H_{20}ClN_5 \cdot HCl$	210					20.46	20.42
XXX	$-CH_2CH_2CHCH_2CH_2-$ (CH$_3$ on CH)						$C_{15}H_{21}N_5 \cdot HCl$	229	58.52	58.46	7.21	7.26		
XXXI	$-CH_2CH_2CHCH_2CH_2-$ (CH$_3$ on CH)	CH_3					$C_{16}H_{23}N_5 \cdot HCl$	217–218	59.70	59.50	7.51	6.67	21.76	21.63
XXXII	$-CH_2CH_2CHCH_2CH_2-$ (CH$_3$ on CH)	C_2H_5					$C_{17}H_{25}N_5 \cdot HCl$	217	60.78	61.24	8.00	7.87	20.85	20.54
XXXIII	$-CH_2CH_2CHCH_2CH_2-$ (CH$_3$ on CH)	Br					$C_{15}H_{20}BrN_5 \cdot HCl$	226	46.58	46.50	5.47	5.28	18.11	18.17
XXXIV	$-CH_2CH_2CHCH_2CH_2-$ (CH$_2$ on CH)	Cl					$C_{15}H_{20}ClN_5 \cdot HCl$	209	52.63	52.60	6.18	5.88	20.46	19.81
XXXV	$-CH_2CH_2CHCH_2CH_2-$ (CH$_3$ on CH)			CH_3			$C_{16}H_{23}N_5 \cdot HCl$	215	59.70	59.44	7.51	7.42	21.76	21.36
XXXVI	$-CH_2CH_2CHCH_2CH_2-$ (CH$_3$ on CH)			Cl			$C_{15}H_{20}ClN_5 \cdot HCl$	229	52.63	52.55	6.18	6.07		
XXXVII	$-CH_2CH_2CHCH_2CH_2-$ (CH$_3$ on CH)			Br			$C_{15}H_{20}BrN_5 \cdot HCl$	210	46.58	46.66	5.47	5.10	18.11	18.28
XXXVIII	$-CH_2CH_2CHCH_2CH_2-$ (CH$_3$ on CH)	CH_3				CH_3	$C_{17}H_{25}N_5 \cdot HCl$	222–224	60.78	60.55	8.00	7.43	20.85	20.62
XXXIX	$-CH_2CH_2CHCH_2CH_2-$ (CH$_3$ on CH)	Cl			Cl		$C_{15}H_{19}Cl_2N_5 \cdot HCl$	200	47.82	47.52	5.35	5.41		
XL	$-CH_2CH_2CHCH_2CH_2-$ (CH$_3$ on CH)		Cl	Cl			$C_{15}H_{19}Cl_2N_5 \cdot HCl$	186–187	47.82	48.24	5.35	4.97	18.59	18.52

obvelata in a 3-day test, starting at a dosage of 300 mg./kg. The results of this test are shown in Table VI, in which the compounds are listed roughly in decreasing order of activity. It will be seen at a glance that in almost every instance the compounds with the greatest anthelmintic activity are those with bulky substituents in the 2-position of the dihydrotriazine ring, or else bulky *ortho*-substituents in the benzene ring. Conversely, Table IX, which lists microbiological inhibition in increasing order of activity, shows that *ortho*-substituted phenyl derivatives, and the derivatives with bulky 2-substituents, have the least inhibitory

TABLE II

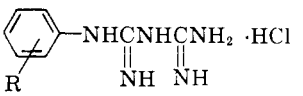
6-ARYLAMINODIHYDROTRIAZINES



Compd. no.	2,2-Substituents(R_1, R_2)	Benzene substituents(R) 2	3	4	5	6	Empirical formula	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
XLI	—$CH_2CH_2CHCH_2CH_2$—						$C_{13}H_{21}N_5 \cdot HCl$	230	58.52	58.44	7.21	7.02	22.75	22.58
	CH_3													
XLII	—$CH_2CH_2CHCH_2CH_2$—	C_2H_5					$C_{17}H_{26}N_5 \cdot HCl$	246–247	60.78	60.76	8.00	7.94		
	CH_3													
XLIII	—$CH_2CH_2CHCH_2CH_2$—	Br					$C_{16}H_{25}BrN_5 \cdot HCl$	226	46.58	46.71	5.47	5.50	18.11	17.76
	CH_3													
XLIV	—$CH_2CH_2CHCH_2CH_2$—			Cl			$C_{15}H_{24}ClN_5 \cdot HCl$	262	52.63	52.87	6.18	6.18	20.46	19.99
	CH_3													
XLV	—$CH_2CH_2CHCH_2CH_2$	CH_3				CH_3	$C_{17}H_{28}N_5 \cdot HCl$	266	60.78	60.31	8.00	7.69		
	CH_3													

TABLE III

N¹-ARYLBIGUANIDES



Compd. No.	Benzene substituents(R)	Empirical formula	M.p., °C.	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
XLVI	2-C_2H_5	$C_{10}H_{15}N_5 \cdot HCl$	204	49.73	49.60	6.67	6.55
XLVII	2,6-$(CH_3)_2$	$C_{10}H_{15}N_5 \cdot HCl$	218–219	49.73	49.72	6.67	6.43
XLVIII	2,4,5-$(CH_3)_3$	$C_{11}H_{17}N_5 \cdot HCl$	228	51.65	51.77	7.09	6.81

activity, in confirmation of the earlier data of Foley[15] and the I.C.I. group. Thus, from a biological point of view, the anthelmintic dihydrotriazines may be considered to form a different class of compounds from the antimalarial dihydrotriazines. This difference is qualitative in character, and can probably be explained best by increasing steric hindrance associated with more bulky *ortho* substitution. This would gradually impose a nearly perpendicular and increasingly rigid arrangement of the two rings about their common axis. Such a change in conformation might well block the action at enzyme sites which normally causes the antifolic activity, and by the same token might create some new type of interference associated with the anthelmintic action.

The mechanism by which the dihydrotriazines exert their effect against the pinworms is not known. However, these compounds have the advantage over some other anthelmintic agents that they are active against immature, as well as mature, forms of the parasite. Detailed studies which illustrate this effect were carried out on one of the more active derivatives (XXXVI), and are described by Burrows and Hunt.[21]

In seeking the more active compounds of this series, it was considered advisable to determine whether the dihydrotriazines would be useful in a single dose treatment. The activity against immature forms of the parasite indicated that this might well be the case. Table V lists the results of these tests, which show that several members of this series of compounds are indeed sufficiently active to clear all parasites in a single dose. It was difficult to choose among these closely related compounds on the basis of the anthelmintic screen alone. However, an investigation of the acute toxicities of these compounds left no doubt as to which was the compound of choice. Selected toxicity data are shown in Table X. Although the toxicities obtained by parenteral administration are quite similar, this is not true of oral administration. One compound [XXXVI, 1-(*p*-chlorophenyl)-4,6-diamino-1,2-dihydro-2,2-(3-methylpentamethylene)-*s*-triazine hydrochloride] stands out as being unique in its lack of toxicity. It was found physically impossible to administer sufficient drug to mice to kill them (except by suffocation). This substance has a solubility of approximately 0.2% in water at room temperature, so, although it is less soluble than some of the other derivatives, it is unlikely that insolubility is an adequate explanation of its lack of toxicity.

The dihydrotriazines were screened against a wide variety of intestinal parasites in addition to *Syphacia obvelata*. Although they were found active against the related pinworm *Aspiculuris tetraptera* in mice, they were relatively inactive against hookworms (*Ancylostoma caninum*), ascarids (*Ascaris lumbricoides*, *Toxocara cati*, *Toxascaris leonina*), whipworms (*Trichuris vulpis*), trichostrongyles (*Nippostrongylus muris*, *Nematospiroides dubius*), and nodular worms (*Oesophagostomum sp.*), and were inactive against four species of tapeworms.

Carrington[4] and Modest[7] have described the irreversible rearrangement of the aryldihydrotriazines in alkali to yield arylaminodihydrotriazines. The products were found devoid of microbiological activity. We were interested in preparing the anilino isomers of a few of the more active derivatives described here, to determine whether anthelmintic activity might be

(21) R. B. Burrows and G. R. Hunt, *J. Parasitol.*, **46**, 873 (1960).

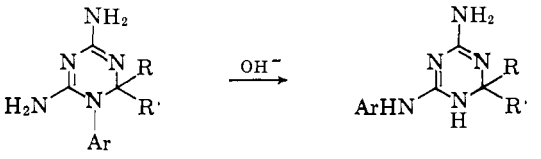
TABLE IV

ULTRAVIOLET ABSORPTION SPECTRA OF SOME 1-ARYLDIHYDROTRIAZINES AND THEIR 6-ARYLAMINO ISOMERS[a]

Compd. no.	Dihydrotriazine substituents 1	2,2	6	Solvent or pH	Ultraviolet absorption spectra λ_{max}, mμ	$\epsilon \times 10^{-3}$	λ_{min}, mμ	$\epsilon \times 10^{-3}$
XXX	C_6H_5	$-CH_2CH_2CHCH_2CH_2-$ (CH₃)	NH_2	7.02[b]	242	9.41	229	7.55
XLI	H	$-CH_2CH_2CHCH_2CH_2-$ (CH₃)	C_6H_5NH-	7.02	256	15.3	229	7.84
XXXIII	2-Br-C_6H_4	$-CH_2CH_2CHCH_2CH_2-$ (CH₃)	NH_2	7.02	240	9.75	235	9.70
XLIII	H	$-CH_2CH_2CHCH_2CH_2-$ (CH₃)	2-Br-C_6H_4NH-	7.02	246.5	12.9	233	11.3
XXXII	2-C_2H_5-C_6H_4	$-CH_2CH_2CHCH_2CH_2-$ (CH₃)	NH_2	7.02	241	9.70	229	8.23
XLII	H	$-CH_2CH_2CHCH_2CH_2-$ (CH₃)	2-C_2H_5-C_6H_4NH-	7.02	245	13.1	229	10.4
XXXVIII	2,6-(CH₃)₂-C_6H_3	$-CH_2CH_2CHCH_2CH_2-$ (CH₃)	NH_2	7.02	236	12.0	230	11.7
XLV	H	$-CH_2CH_2CHCH_2CH_2-$ (CH₃)	2,6-(CH₃)₂-C_6H_3NH-	7.02	241	12.3	230	11.0
XXXVI	4-Cl-C_6H_4	$-CH_2CH_2CHCH_2CH_2-$ (CH₃)	NH_2	0.1 *N* HCl	Sh 242	7.25		
				7.02	241	11.2	234	10.8
				0.1 *N* NaOH	[c]			
XLIV	H	$-CH_2CH_2CHCH_2CH_2-$ (CH₃)	4-Cl-C_6H_4NH-	0.1 *N* HCl	259	15.0	230	8.38
				7.02	261	17.5	229	7.95
				0.1 *N* NaOH	222.5	8.74	230	8.38
					261	17.8		
Ref. 7	4-Cl-C_6H_4	$(CH_3)_2$	NH_2	7.02	241	13.4	232	12.3
Ref. 7	H	$(CH_3)_2$	4-Cl-C_6H_4NH-	7.02	256	18.2	227	9.36

[a] Spectra were determined at a concentration of 10 mg./l., with a Beckman DU spectrophotometer. [b] Sørensen phosphate buffer. [c] Slow isomerization at room temperature; initial reading (30°) shows no maximum; sloping curve has slight shoulder with mid-point 250 mμ ($\epsilon \times 10^{-3} = 5.7$).

retained on isomerization, and also to determine whether or not there might be a difference in ease of isomerization between the different types of derivatives. The new compounds which were characterized are described in Table II. Table VII lists their anthelmintic activities, which were found to be negligible.



Thus, the 4,6-diamino configuration appears to be required for both microbiological and anthelmintic activity. A few of the intermediate biguanides (Table III) were also tested for anthelmintic activity and found lacking in interest (Table VIII).

Carrington[4] and Modest[7] also described the change in ultraviolet absorption spectra which occurs on isomerization of the dihydrotriazines, using 1-(*p*-chlorophenyl)-4,6-diamino-1,2-dihydro-2,2-dimethyl-*s*-triazine as an example. In this case, λ_{max} changes from 241 to 256 mμ at pH 7, and the molecular extinction coefficient is also markedly increased (see Table IV), so that it is easy to follow the course of the isomerization. It was found that when bulky groups were introduced into the 2-position of the dihydrotriazine ring, as with XXXVI, the change in spectrum was even more marked; λ_{max} shifted from 241 to 261 mμ, with a correspondingly large hyperchromic shift. Compound XXXVI was also found to isomerize at almost 3 times the rate of the 2,2-dimethyl analog, reflecting decreased stability of the original diamino configuration when the bulky groups are present.

When the diaminodihydrotriazines contained *ortho* substituents in the benzene ring, the change in spectrum upon treatment with alkali was found to be much less marked. The shift in λ_{max} was only about 5 mμ, and the increase in extinction coefficient was correspondingly lessened. The data of Table IV illustrate these changes. Whereas practically all of the diaminodihydrotriazines with *meta* or *para* substitution had λ_{max} = 241–242 mμ, some of the *ortho*-substituted compounds had only slight maxima or shoulders at about 235 mμ. After treatment of the compounds with alkali, the maxima shifted only to about 241 mμ, so that an

TABLE V

ANTHELMINTIC ACTIVITY OF 1-ARYLDIHYDROTRIAZINES *vs. Syphacia Obvelata* IN MICE. SINGLE DOSE TESTS

Compd. No. or ref.	2,2-Substituents	Benzene substituents	Dose,[a] mg./kg.	Cured/treated	Av. % eliminated
XXXVI	—(CH$_2$)$_2$CH(CH$_2$)$_2$— | CH$_3$	4-Cl	1000	3/3	100
			750	3/3	100
			600	23/30	97
			500	19/24	99
			400	23/30	89
			300	17/30	83
			200	7/25	49
			100	2/26	27
Ref. 7	—(CH$_2$)$_5$—	4-Cl	600	6/6	100
			500	5/6	98
			400	6/6	100
			300	5/6	99+
			200	3/6	90
XXXVIII	—(CH$_2$)$_2$CH(CH$_2$)$_2$— | CH$_3$	2,6-(CH$_3$)$_2$	600	6/6	100
			500	6/6	100
			400	8/9	93
			300	4/6	93
			200	2/6	67
XXIX	—CH$_2$CH(CH$_2$)$_3$— | CH$_3$	4-Cl	500	1/5	96
			400	1/6	79
			300	1/3	66
XL	—(CH$_2$)$_2$CH(CH$_2$)$_2$— | CH$_2$	3,4-Cl$_2$	400	6/6	100
			300	1/6	68
			200	0/6	35
			100	0/6	13
XXXIII	—(CH$_2$)$_2$CH(CH$_2$)$_2$— | CH$_3$	2-Br	400	2/3	99
XXVIII	—CH$_2$CH(CH$_2$)$_3$— | CH$_3$	2-Br	400	5/6	90
			300	1/3	40
XXXV	—(CH$_2$)$_2$CH(CH$_2$)$_2$— | CH$_3$	4-CH$_3$	400	2/3	93
XXXII	—(CH$_2$)$_2$CH(CH$_2$)$_2$— | CH$_3$	2-C$_2$H$_5$	500	0/3	98
			400	0/3	63
			300	2/5	82
Ref. 5, and 7	—(CH$_2$)$_4$—	4-Cl	500	2/5	71
			400	1/6	78
			300	0/6	55
XXXIX	—(CH$_2$)$_2$CH(CH$_2$)$_2$— | CH$_3$	2,5-Cl$_2$	400	0/6	73
			300	2/6	82
XXXI	—(CH$_2$)$_2$CH(CH$_2$)$_2$— | CH$_3$	2-CH$_3$	500	1/3	67
			400	2/3	82
			300	0/6	36
XXX	(CH$_2$)$_2$CH(CH$_2$)$_2$— | CH$_3$	—	400	2/6	66
			300	1/6	70
XXXVII	—(CH$_2$)$_2$CH(CH$_2$)$_2$— | CH$_3$	4-Br	400	0/6	39
			300	1/6	38
XXVI	—(CH$_2$)$_5$—	2-Br	400	0/6	19
			300	0/6	15
XXXIV	—(CH$_2$)$_2$CH(CH$_2$)$_2$— | CH$_3$	2-Cl	400	3/6	63
			300	0/6	29
Ref. 7	(CH$_3$)$_2$	2-Br	400	0/3	13

[a] As hydrochloride salt.

arylamino derivative could easily be mistaken for a diaminodihydrotriazine. All the *ortho* substituted derivatives were therefore examined for identity by heating in 0.1 *N* sodium hydroxide on the steam bath and observing whether or not a spectral shift occurred. In a few instances of doubt, biological activity was also used as a criterion for structure. This was useful with XXVII, for example, where even the melting point did not change on isomerization, and the spectrum changed from a slight indistinct peak at 236 mμ to another slight indistinct peak at 241 mμ (ε changed from 9700 to 13,200). In this case the alkali-treated material was completely inactive against pinworms, whereas the original material was quite active.

TABLE VI

ANTHELMINTIC ACTIVITY OF 1-ARYLDIHYDROTRIAZINES *vs. Syphacia obvelata* IN MICE. THREE DOSE TESTS

Compd. no. or ref.	2,2-Substituents	Benzene substituents	Dose,[a] mg./kg./day	Cured/ treated	Av. % eliminated
XXXVI	—$(CH_2)_2CH(CH_2)_2$— | CH_3	4-Cl	300	2/2	100
XXIX	—$CH_2CH(CH_2)_3$— | CH_3	4-Cl	500	6/6	100[b]
			400	12/12	100
			300	4/6	99
XXXII	—$(CH_2)_2CH(CH_2)_2$— | CH_3	2-C_2H_5	500	2/3	98
			400	2/3	97
			300	3/5	97
XXV	—$(CH_2)_5$—	2-C_2H_5	300	4/4	100
			200	1/4	95
			100	1/10	73
XXIV	—$(CH_2)_4$—	2-C_2H_5	300	2/4	83
			200	2/4	84
			100	0/4	76
Ref. 7	—$(CH_2)_5$—	4-Cl	300	2/4	97
			200	0/2	95
			100	0/2	58
XXVII	—$(CH_2)_5$—	2,6-$(CH_3)_2$	300	1/6	66
			200	1/2	97
			100	1/2	98
XXI	CH_3, C_3H_7-*n*	2-C_2H_5	300	2/2	100
			200	2/2	100
			100	0/2	21
IV	$(CH_3)_2$	2-C_4H_9-*n*	300	2/4	99
			200	1/6	66
			100	0/6	41
XX	CH_3, C_2H_5	2,6-$(CH_3)_2$	300	0/2	98
			200	0/4	25
			100	0/2	52
XXXI	—$(CH_2)_2CH(CH_2)_2$— | CH_3	2-CH_3	500	3/3	100
			400	3/3	100
			300	3/9	81
II	$(CH_3)_2$	2-C_2H_5	300	2/6	90
			200	0/4	71
			100	0/6	61
XVI	$(CH_3)_2$	2,6-$(CH_3)_2$	300	0/4	93
			200	0/2	97
			100	0/2	19
XIX	CH_3, C_2H_5	2-C_2H_5	300	2/4	90
			200	0/2	45
			100	0/2	17
XXII	H, C_6H_{13}-*n*	2-C_2H_5	300	0/2	93
			200	0/2	46
VII	$(CH_3)_2$	2,3-$(CH_3)_2$	300	0/2	80
XIV	$(CH_3)_2$	2-CH_3-5-C_3H_7-iso	300	1/4	78
			200	0/2	20
			100	0/2	4
XXIII	H, C_9H_{19}	2-C_2H_5	300	0/2	78
Ref. 7	$(CH_3)_2$	2-Cl	300	0/2	77
XXVII	$(CH_3)_2$	3,5-$(CH_3)_2$	300	0/2	75[c]
Ref. 5, 7	—$(CH_2)_4$—	4-Cl	500	10/10	100
			400	9/9	100
			300	3/9	61
XVIII	$(CH_3)_2$	2,4,5-$(CH_3)_3$	300	0/4	73[d]
VIII	$(CH_3)_2$	2-CH_3-3-Cl	300	2/4	67
Ref. 8	H, C_6H_{13}-*n*	4-Cl	300	0/2	70
IX	$(CH_3)_2$	2,4-$(CH_3)_2$	300	0/2	67
XV	$(CH_3)_2$	2-OCH_3-5-Cl	300	0/2	66
			200	1/2	66
Ref. 7	$(CH_3)_2$	2,4-Cl_2	300	0/4	65
			200	0/2	34
VI	$(CH_3)_2$	3-CH_3	300	0/2	62[e]
V	$(CH_3)_2$	2-OCH_3	300	0/2	61
			200	0/2	54
XIII	$(CH_3)_2$	2-CH_3-5-Cl	300	0/4	52

TABLE VI (*Continued*)

Compd. no. or ref.	2,2-Substituents	Benzene substituents	Dose,[a] mg./kg./day	Cured/treated	Av. % eliminated
Ref. 5	$(CH_3)_2$	4-OCH_3	300	0/2	45
Ref. 7	$(CH_3)_2$	2,5-Cl_2	300	0/2	41
III	$(CH_3)_2$	2-C_3H_7-*n*	300	0/2	40
Ref. 5, 7	$(CH_3)_2$	4-CH_3	300	0/2	40
XI	$(CH_3)_2$	2-OCH_3-4-NO_2	300	0/2	22
			200	0/2	54
Ref. 7	$(CH_3)_2$	2-CH_3	300	0/2	34
XII	$(CH_3)_2$	2,5-$(CH_3)_2$	300	0/2	29
I	H, CH_3	2-C_2H_5	300	0/2	26
Ref. 3, 4, 5, 7	$(CH_3)_2$	4-Cl	300	0/2	21
X	$(CH_3)_2$	2-CH_3-4-Cl	300	0/2	19
Ref. 5, 7	$(CH_3)_2$	3-Cl	300	—	—[e]
Ref. 5	$(CH_3)_2$	3,4-$(CH_3)_2$	300	—	—[f]
Ref. 3, 5, 7	$(CH_3)_2$	3,4-Cl_2	300	—	—[g]

[a] As hydrochloride salt. [b] One death. [c] Weight loss. [d] Many worms disintegrated. [e] Diarrhea. [f] Weight loss, diarrhea, 1 death. [g] Weight loss, diarrhea.

TABLE VII

ANTHELMINTIC ACTIVITY OF 6-ARYLAMINODIHYDROTRIAZINES *vs. Syphacia Obvelata* IN MICE. SINGLE DOSE TESTS.

Compd. no.	2,2-Substituents	Benzene substituents	Dose, mg./kg.[a]	Cured/treated	Av. % eliminated
XLI	—$CH_2CH_2CHCH_2CH_2$— (CH$_3$)	——	400	0/6	34
			300	0/6	20
XLII	—$CH_2CH_2CHCH_2CH_2$— (CH$_3$)	2-C_2H_5	400	0/6	32
			300	0/6	44
XLIII	—$CH_2CH_2CHCH_2CH_2$— (CH$_3$)	2-Br	400	0/3	3
XLIV	—$CH_2CH_2CHCH_2CH_2$— (CH$_3$)	4-Cl	400	0/3	3
XLV	—$CH_2CH_2CHCH_2CH_2$— (CH$_3$)	2,6-$(CH_3)_2$	400	1/6	57
			300	0/6	3

[a] As hydrochloride salt.

Compound XXXVI has been subjected to extensive anthelmintic and pharmacological investigation. It has been found active against the pinworm of man, *Enterobius vermicularis*, and has undergone extensive clinical testing. The results of these tests will be published elsewhere.

Experimental[22]

1-Aryl-2,2-dialkyl-4,6-diamino-1,2-dihydrotriazines.—These compounds were prepared by the method of Modest[7] from the corresponding anilines, plus a ketone or aldehyde, and dicyandiamide, in the presence of slightly more than one equivalent of HCl. New derivatives are characterized in Table I. Results followed the pattern of Modest's description very closely. The products normally precipitated from the reaction mixture in 30 to 90% yields in the form of their hydrochloride salts. When no precipitate was formed, ether was added to precipitate the product. No attempts was made to determine absolute yields by investigation of the mother liquors. Products were normally recrystallized from ethanol, water, or mixtures of the two solvents. In a number of instances, the reactions were unsuccessful with hindered ketones or amines under a variety of conditions. This was the case, for example, with 2-methylcyclohexanone when reacted with dicyandiamide and *p*-chloroaniline. Other ketones which did not react satisfactorily, either in the 3 component synthesis or with the intermediate biguanide, included diethyl ketone with *o*-ethylaniline or 2,6-dimethylaniline, heptaldehyde with 2,6-dimethylaniline, undecylaldehyde with *o*-ethylaniline, methyl propyl ketone with 2,6-dimethylaniline, ethyl butyl ketone and methyl hexyl ketone with *p*-chloroaniline, and 3-methylcyclopentanone (identity not verified) with several anilines. 2,6-Diethylaniline proved to be too hindered to form a dihydrotriazine using acetone as the ketone.

The decomposition points of the dihydrotriazine hydrochlorides were normally in the vicinity of 200–220°. In two or three instances, the melting points were abnormally high, suggesting that the compounds might actually be the isomeric 6-anilinodihydrotriazines. However, an investigation of the ultraviolet spectra indicated that this was not the case; treatment with warm 0.1 *N* sodium hydroxide resulted in the bathochromic and hyperchromic shift which is characteristic of this type of isomerization.[7] The spectrum of an anilinodihydrotriazine would not be expected to undergo a change with such relatively mild treatment.

In most cases the anilines used as the starting materials were commercially available. ***o*-Propylaniline** was prepared by the nitration of propiophenone,[23] followed by separation of the *ortho* isomer. The nitro group was reduced with Raney nickel in methanol, and the ketone reduced by the Wolff–Kishner method, following directions of Baker[24] for *m*-propylaniline. The *o*-propylaniline boiled at 114–116° (15 mm.).[25] ***o*-Butylaniline** was prepared by the method of Read and Mullin,[26] which involves nitration of butylbenzene, followed by careful fractional distillation and catalytic reduction with platinum.

(22) Melting points are corrected, but represent decomposition points and are not always completely reproducible. See ref. 7.

(23) B. L. Zenitz and W. H. Hartung, *J. Org. Chem.*, **11**, 444 (1946).

(24) B. R. Baker, R. E. Schaub, J. P. Joseph, F. J. McEvoy, and J. H. Williams, *ibid.*, **17**, 164 (1952).

(25) J. von Braun and M. Rawicz, *Ber.*, **49**, 799 (1916).

(26) R. R. Read and D. B. Mullin, *J. Am. Chem. Soc.*, **50**, 1763 (1928).

TABLE VIII

ANTHELMINTIC ACTIVITY OF N^1-ARYLBIGUANIDES *vs.* *Syphacia Obvelata* IN MICE

Compd. no.	Benzene substituents	Days treated	Dose, mg./kg.[a]	Cured/ treated	Av. % eliminated
XLVI	2-C_2H_5	3	300	0/2	38
XLVII	2,6-$(CH_3)_2$	2	300	0/2	12
XLVIII	2,4,5-$(CH_3)_2$	3	300	0/2	61
[b]	2-CH_3-5-(C_3H_7)-*i*	3	300	0/2	29

[a] As hydrochloride salt. [b] S. L. Shapiro, V. A. Parrino, E. Rogow, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3725 (1959).

4-Amino-6-arylamino-2,2-dialkyl-1,2-dihydrotriazines.—A few of the 1-aryldihydrotriazines were isomerized by the method of Modest.[7] New derivatives are characterized in Table II. The relative rates of isomerization of 1-(*p*-chlorophenyl)-4,6-diamino-1,2-dihydro-2,2-(3-methylpentamethylene)-*s*-triazine (XXXVI) and the corresponding 2,2-dimethyl derivative (chloroguanide metabolite)[3,4] were determined in 0.1 *N* sodium hydroxide in sealed ampoules at concentrations of 100 mg./liter. Solutions were diluted tenfold into acid buffers for spectral determinations. At 70.0–70.1°, the isomerization of the first substance was half-completed in 8 min., whereas the second required 21 min. Details of this and further kinetic experiments will be published elsewhere.

N^1-Arylbiguanides.—These were prepared by heating equimolar mixtures of the aniline hydrochloride and dicyandiamide in ethanol, propanol, or water for 18 hr.[7] Upon chilling, the hydrochloride salts of the products normally precipitated, and were recrystallized from ethanol. New derivatives are found in Table III.

Procedure for Screening Compounds *vs. Syphacia obvelata* **Infestations in Mice.**—The mice used in these experiments were kept in individual cages. Each cage contained a feeding rack, designed to prevent food particles from falling through the wire mesh bottom of the cage, and a water bottle. Beneath each cage was a pan of water to collect the feces and worms passed by the mouse.

The weighed amount of compound was placed in a mortar, 1 to 3 drops of Tween 80 added to the mortar and the two ground together. Then water was added, a little at a time, while grinding, until the desired concentration was obtained. The resulting emulsion was used for dosing the mice. Each mouse was weighed, the required amount of the emulsion drawn up into a 1 ml. syringe, graduated in hundredths, the blunt needle inserted into the stomach through the mouth, and the contents discharged into the stomach. Then the mouse was placed in its individual cage.

Mice dosed for 3 successive days were autopsied 72 hr. after the initial dose, whereas those given a single dose were autopsied at the end of 48 hr. After 24 hr. the pan of water was removed from under the cage and a new pan of water put in its place. This procedure was repeated every 24 hr. for the duration of the experiment. The contents of a pan were poured, a little at a time, into a petri dish under a dissecting microscope and all worms counted. At the end of the experiment the mouse was killed in a chloroform jar, the cecum and large intestine removed and opened. The worms remaining were counted. Then the worms from the last 24-hr. pan were counted. For each mouse the percentage of elimination of worms was determined by dividing the number of worms passed by the total number of worms harbored. The average percentage of elimination for a group (all animals given the same dosage level of the same compound) was obtained by adding all the percentages and dividing by the number of mice in the group.

Mice were not checked for infection prior to treatment, as the majority are generally positive. Occasionally a mouse passed no worms after treatment and none was found at autopsy. These mice were not considered in the tabulations, which dealt only with mice positive for *Syphacia*. A normal worm burden found in the mice is roughly 75 to 100 pinworms. As untreated mice may pass from 0 to 28% of *Syphacia* during a 48 to 72-hr. period, these percentages are considered as normal elimination. A compound causing about 50% loss of worms would be slightly active. However, only those compounds which resulted in over 75% elimination of mouse pinworms at a dose of 300 mg./kg. were considered for further investigation. The intermediate range percentages are not at all absolute, particularly in small groups,

TABLE IX

GROWTH INHIBITORY ACTIVITY OF 1-ARYLDIHYDROTRIAZINES *vs. L. casei*

Compd. no. or ref.	2,2-Substituents	Benzene substituents	Concentration, γ/ml.[a]	% Growth inhibition in *L. casei*[b]
Ref. 7	$(CH_3)_2$	2-Cl	100	0
Ref. 7	$(CH_3)_2$	2,5-Cl_2	100	0
IX	$(CH_3)_2$	2,4-$(CH_3)_2$	100	0
XII	$(CH_3)_2$	2,5-$(CH_3)_2$	100	0
XVI	$(CH_3)_2$	2,6-$(CH_3)_2$	100	0
XVIII	$(CH_3)_2$	2,4,5-$(CH_3)_3$	100	0
XIV	$(CH_3)_2$	2-CH_3-5-Pr-*i*	100	0
XX	CH_3, C_2H_5	2,6-$(CH_3)_2$	100	0
XXIV	—$(CH_2)_4$—	2-C_2H_5	100	0
XXV	—$(CH_2)_5$—	2-C_2H_5	100	0
XXVII	—$(CH_2)_5$—	2,6-$(CH_3)_2$	100	0
XXXI	—$(CH_2)_2CH(CH_3)(CH_2)_2$—	2-CH_3	100	−11
			5	0
XIII	$(CH_3)_2$	2-CH_3-5-Cl	100	−13
			5	0
X	$(CH_3)_2$	2-CH_3-4-Cl	100	−19
			5	0
V	$(CH_3)_2$	2-OCH_3	100	−15
			5	−16
XV	$(CH_3)_2$	2-OCH_3-5-Cl	100	−18
			5	−10
I	H, CH_3	2-C_2H_5	100	−21
			5	−11
XXXVIII	—$(CH_2)_2CH(CH_3)(CH_2)_2$—	2,6-$(CH_3)_2$	100	−22
			5	0
VIII	$(CH_3)_2$	2-CH_3-3-Cl	100	−31
			5	0
XI	$(CH_3)_2$	2-OCH_3-4-NO_2	100	−32
			5	0
Ref. 7	$(CH_3)_2$	2-CH_3	100	−34
			5	0
Ref. 7	$(CH_3)_2$	2,4-Cl_2	100	−39
			5	0
II	$(CH_3)_2$	2-C_2H_5	100	−44
			5	0
XIX	CH_3, C_2H_5	2-C_2H_5	100	−51
			5	−16
IV	$(CH_3)_2$	2-C_4H_9-*n*	100	−53
			5	−20
XXI	CH_3, C_3H_7-*n*	2-C_2H_5	100	−57
			5	−19
VII	$(CH_3)_2$	2,3-$(CH_3)_2$	100	−72
			5	−12
XXII	H, C_6H_{13}-*n*	2-C_2H_5	100	−87
			5	0
Ref. 7	—$(CH_2)_5$—	4-Cl	100	−95
			5	0
XXXII	—$(CH_2)_2CH(CH_3)(CH_2)_2$—	2-C_2H_5	100	−95
			5	0
XXIX	—$CH_2CH(CH_3)(CH_2)_3$—	4-Cl	100	−96
			5	0
Ref. 5,7	—$(CH_2)_4$—	4-Cl	100	−94
			5	−14
XXXVI	—$(CH_2)_2CH(CH_3)(CH_2)_2$—	4-Cl	100	−96
			5	−20
Ref. 5, 7	$(CH_3)_2$	4-CH_3	100	−88
			5	−64
Ref. 5	$(CH_3)_2$	3,4-$(CH_3)_2$	100	−93
			5	−72
Ref. 3, 4, 5, 7	$(CH_3)_2$	4-Cl	100	−90
			5	−79
Ref. 8	H, C_6H_{13}-*n*	4-Cl	100	−93
			5	−78
			1	−20
			0.1	0
III	$(CH_3)_2$	2-C_3H_7-*n*	100	−91
			5	−79
VI	$(CH_3)_2$	3-CH_3	100	−90
			5	−85
XXIII	H, C_9H_{19}	2-C_2H_5	100	−96
			5	−96
			1	+25
			0.1	0
Ref. 5	$(CH_3)_2$	4-OCH_3	100	−94

TABLE IX (*Continued*)

Compd. no. or ref.	2,2-Substituents	Benzene substituents	Concentration, γ/ml.[a]	% Growth inhibition in *L. casei*[b]
			5	−86
			1	−55
			0.1	0
Ref. 5, 7	$(CH_3)_2$	3-Cl	100	−93
			5	−90
Ref. 3, 5, 7	$(CH_3)_2$	3,4-Cl_2	100	−99
			5	−90
			1	−51
			0.1	0
XVII	$(CH_3)_2$	3,5-$(CH_3)_2$	100	−95
			5	−94
			1	−66
			0.1	0

[a] As hydrochloride salt. [b] In OFA medium which contains 0.046 mμg. of folic acid per ml.[27] A negative sign indicates growth inhibition, whereas a + sign indicates that the substance promotes growth.

and are only useful in showing a trend, when considered over the range of a large number of compounds.

Testing results are shown in Tables V–VIII.

The *L. casei* Screen.—Details of this screening procedure, which was designed for the preliminary screening of substances for activity as antagonists of nucleic acid synthesis, are described by Hitchings and co-workers.[27] Results are shown in Table IX.

TABLE X

ACUTE TOXICITY OF SELECTED ARYLDIHYDROTRIAZINES

Compound no.	2,2-Substituents	Benzene substituents	LD_{50}, mg./kg.[a] I.P.	P.O.
XXXVI	$-CH_2CH_2CHCH_2CH_2-$ (CH$_3$ at CHCH$_2$CH$_2$)	4-Cl	320	>20,000
XXXIII	$-CH_2CH_2CHCH_2CH_2-$ (CH$_3$ at CHCH$_2$CH$_2$)	2-Br	70	5,000
XXXVII	$-CH_2CH_2CHCH_2CH_2-$ (CH$_3$ at CHCH$_2$CH$_2$)	4-Br	ca. 95	>1,000
XXX	$-CH_2CH_2CHCH_2CH_2-$ (CH$_3$ at CHCH$_2$CH$_2$)	—	66	ca. 4,000
XXV	$-(CH_2)_5-$	2-C_2H_5	47	1,500
XVIII	$(CH_3)_2$	2,4,5-$(CH_3)_3$	90	1,370
XXXVIII	$-CH_2CH_2CHCH_2CH_2-$ (CH$_3$ at CHCH$_2$CH$_2$)	2,6-$(CH_3)_2$	56	1,180
XXIX	$-CH_2CHCH_2CH_2CH_2-$ (CH$_3$ at CHCH$_2$)	4-Cl	48	1,100
Ref. 7	$-(CH_2)_5-$ (CH$_3$ at CH$_2$)	4-Cl	56	1,058
XXXII	$-CH_2CH_2CHCH_2CH_2-$ (CH$_3$ at CHCH$_2$)	2-C_2H_5	—	ca. 1,000
Ref. 5,7	$-(CH_2)_5-$ (CH$_3$ at CH$_2$)	4-Cl	—	870
IV	$(CH_3)_2$	2-C_4H_9-*n*	72	809
XXI	CH_3, C_3H_7-*n*	2-C_2H_5	78	701
XXVII	$-(CH_2)_5-$	2,6-$(CH_3)_2$	35	612
XXIV	$-(CH_2)_5-$	2-C_2H_5	43	436

[a] As hydrochloride salt.

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The Synthesis and Pharmacological Activity of Some Chloro-α-alkyltryptamines[1]

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The synthesis of eight new monochloro analogs of α-methyl- and α-ethyltryptamines are described. These compounds were prepared by condensations of 4-, 5-, 6-, and 7-chloroindole-3-aldehydes with either nitroethane or nitropropane and subsequent reduction of the condensation products with lithium aluminum hydride. The tryptamines have been found to possess stimulant and anticonvulsant properties in rodents and to produce behavioral changes in cats.

Included in a program of work,[2] which involved the synthesis of a series of tryptamine derivatives related to the physiologically active substance 5-hydroxytryptamine and their examination for biological activity on the cardiovascular and central nervous systems, were the two compounds, α-methyl- and α-ethyltryptamine. Earlier, Govier, *et al.*,[3] had shown that α-ethyltryptamine was an inhibitor of tyramine oxidation and its activity as an inhibitor of the enzyme monoamine-oxidase was confirmed in our Laboratories. α-Methyltryptamine was also found to be a more potent monoamine oxidase inhibitor than the α-ethyl homolog. Both compounds caused reversal of reserpine ptosis in mice but α-methyltryptamine evoked a striking change in the behavior of the animals.[4] An account of the pharmacology of these tryptamines has been given by Greig, *et al.*,[5] and the efficacy of α-ethyltryptamine as an antidepressant drug in man has been

(1) U. K. Patent Application, 2017/61.

(2) E. H. P. Young, *J. Chem. Soc.*, 3493 (1958).

(3) W. M. Govier, B. G. Howes, and A. J. Gibbons, *Science*, **118**, 596 (1953).

(4) Personal communication from Dr. A. Spinks of these Laboratories who is thanked for permission to quote unpublished results.

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