Central Nervous System Depressants. 14. *as*-Triazino-1,4-benzodiazepines (1)

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Seven series of *as*-triazino[4,3-*a*][1,4]benzodiazepines were prepared which differed in the degree of unsaturation or the nature and position of oxygen function on the triazino ring. These were prepared by closing the triazino ring of appropriately substituted hydrazones from 2-hydrazinobenzodiazepines or by condensing substituted hydrazines with 2-thiobenzodiazepines. Most of these represent new ring systems. They were tested in a battery of tests designed to uncover central nervous system activities. Most of the activity was found in tests thought to be indicative of anxiolytic, hypnotic or sedative potential. Five of the series contained members more active than the standard, diazepam, and a few of the compounds were among the most potent benzodiazepines known. Some of the intermediate benzodiazepine hydrazones were also active.

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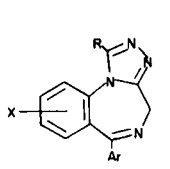
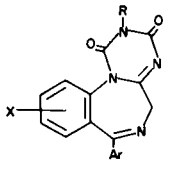
Certain *s*-triazolo (I) (3) and *s*-triazino (II) (4) benzodiazepines have been reported from these laboratories to have very high anxiolytic activity in animals.

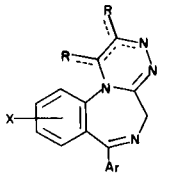


I



II

We have now found that some *as*-triazino (III) benzodiazepines also show very high activity.



A very large number of such *as*-triazino compounds would be possible differing only in the oxidation state of the triazine ring. We are reporting here examples of seven such series (Series A-G).

Series A-E were made from 2-hydrazino-benzodiazepines by condensation with various two carbon moieties as shown in Scheme I. The open chain intermediates were usually isolated.

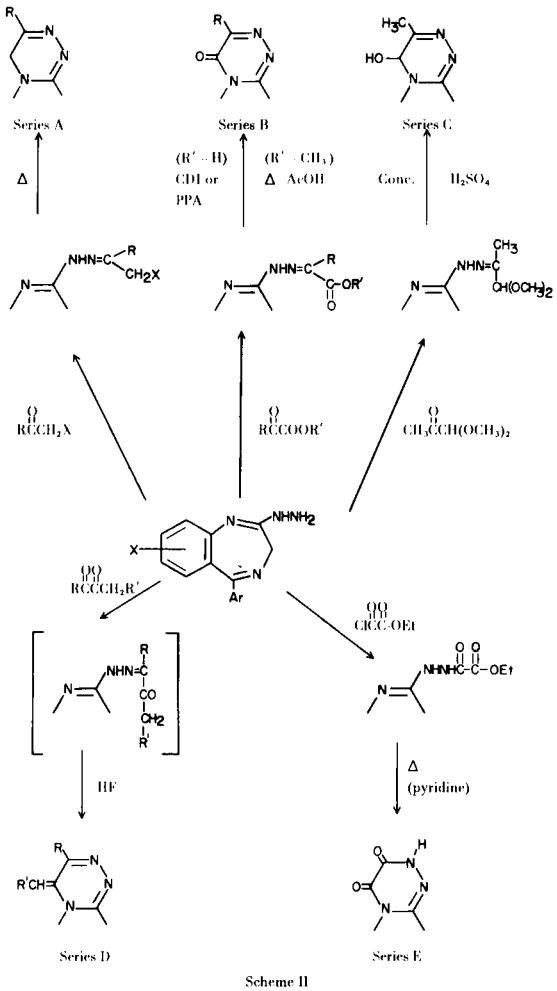
Series F was made as shown in Scheme II.

Examples of Series G have been reported from these laboratories by Szmuszkovicz (5). We have extended the series by the addition of two new side chains as shown in Scheme III. Likewise various side chains were introduced in series A, C, and E by modification of the first formed *as*-triazino compound. The specific compounds prepared are listed in Tables I and II.

Pharmacology.

The compounds listed in Table III were all evaluated in a battery of tests for various CNS activities. Although

Scheme I



Scheme II

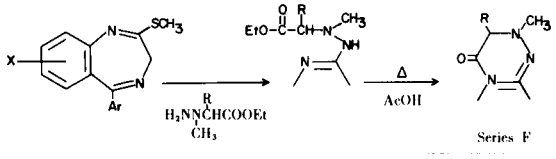
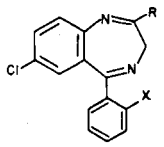


Table I

Intermediates



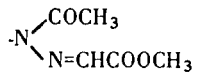
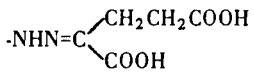
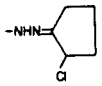
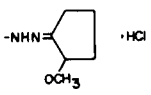
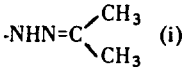
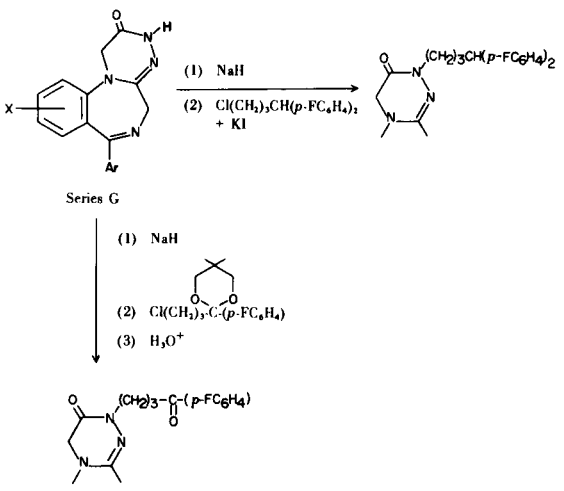
No.	R	X	Formula (a)	Analysis (b) C	H	Cl	N
1	-NHN=C(CH_3)CH_2Cl (c)	H	$C_{18}H_{16}Cl_2N_4$	59.92 (60.18)	4.53 (4.49)	19.81 (19.74)	15.49 (15.60)
2	-HNH=C(CH_3)CH_2Cl	Cl	$C_{18}H_{15}Cl_3N_4$	54.62 (54.91)	4.13 (3.84)	27.35 (27.01)	14.23 (14.23)
3	-NHN=C(CH_2Cl)$_2$	H	$C_{18}H_{15}Cl_3N_4$	54.66 (54.91)	3.90 (3.84)	27.07 (27.01)	14.33 (14.23)
4	-NHN=C(CH_3)CH(OCH_3)$_2$	H	$C_{20}H_{21}ClN_4O_2$	62.62 (62.41)	5.55 (5.50)	9.16 (9.21)	14.72 (14.56)
5	-NHN=C(CH_3)CH(OCH_3)$_2$	Cl	$C_{20}H_{20}Cl_2N_4O_2$	57.55 (57.28)	4.95 (4.81)	16.95 (16.91)	13.20 (13.36)
6	-NHN=CHCOOH	H	$C_{17}H_{13}ClN_4O_2$ (d)	57.41 (57.24)	4.81 (4.88)	9.43 (9.16)	14.80 (14.48)
7	-NHN=CHCOOCH_3	H	$C_{18}H_{15}ClN_4O_2$	60.75 (60.93)	4.52 (4.26)	10.21 (9.99)	15.45 (15.79)
8		H	$C_{20}H_{17}ClN_4O_3$	60.58 (60.53)	4.36 (4.32)	8.95 (8.94)	14.07 (14.12)
9	-NHN=C(CH_3)COOH	H	$C_{18}H_{15}ClN_4O_2$	60.99 (60.94)	4.26 (4.26)	9.95 (9.99)	15.78 (15.79)
10	-NHN=C(CH_3)COOCH_3	H	$C_{19}H_{17}ClN_4O_2$ (e)	60.91 (60.88)	4.48 (4.57)	10.69 (11.12)	15.09 (14.90)
11	-NHN=C(CH_3)COOH	Cl	$C_{18}H_{14}Cl_2N_4O_2$ (f)	55.11 (55.18)	4.55 (4.63)	16.07 (16.29)	12.64 (12.87)
12	-NHN=C(CH_3)COOCH_3	Cl	$C_{19}H_{16}Cl_2N_4O_2$ (g)	54.68 (55.38)	4.30 (4.54)	16.49 (16.47)	12.95 (13.01)
13	-NHN=C(CH_3)COOC_2H_5	(h)	$C_{19}H_{18}BrN_5O_2$ (h)	53.33 (53.28)	4.20 (4.24)	Br, 18.87 (Br, 18.66)	16.34 16.35
14		H	$C_{20}H_{17}ClN_4O_4$	57.65 (58.18)	4.34 (4.15)	8.45 (8.59)	13.25 (13.57)
15	-NHNHCOCOOC_2H_5	H	$C_{19}H_{17}ClN_4O_3$	59.26 (59.30)	4.41 (4.45)	9.21 (9.21)	14.44 (14.56)
16	-N(CH_3)NHCOCOOC_2H_5	H	$C_{20}H_{19}ClN_4O_3$	60.27 (60.23)	4.95 (4.80)	8.98 (8.89)	14.02 (14.05)
17	-N(CH_3)NHCH_3	H	$C_{17}H_{17}ClN_4$	65.14 (65.28)	5.73 (5.48)	11.32 (11.33)	18.00 (17.91)
18	-NHN=CHCH_2Cl	H	$C_{17}H_{14}Cl_2N_4$	59.04 (59.14)	4.17 (4.09)	20.51 (20.54)	16.14 (16.23)
19		H	$C_{20}H_{18}Cl_2N_4$	62.04 (62.35)	4.81 (4.70)	17.86 (18.40)	14.36 (14.54)
20		H	$C_{21}H_{22}Cl_3N_4O$	60.31 (60.44)	5.16 (5.31)	17.50 (16.99)	13.55 (13.42)
21	 (i)	H	$C_{18}H_{17}ClN_4$ (j)				

Table I (continued)

No.	R	X	Formula (a)	Analysis (b) C	H	Cl	N
22	-NHN=C(CH$_3$)(CH$_3$) (i)	Cl	$C_{18}H_{16}Cl_2N_4$	59.88 (60.18)	4.44 (4.49)	19.78 (19.74)	15.37 (15.60)

(a) When the analyzed sample contained solvent that could not be removed by drying, the amount was determined by melt solvate and nmr and the calculated values were corrected for this amount. (b) The values in parentheses are calculated. (c) First prepared by J. B. Hester and J. R. Greene in these laboratories. (d) Melt solvate and nmr showed the presence of methanol of solvation. The calculated values are based on 1.44 methanol: Melt solvate found 11.90%. (e) Melt solvate showed the presence of 1.95% of chloroform (approximately 0.06 mole) which could not be removed even on long drying *in vacuo*. The calculated values are corrected for this. (f) Nmr shows the presence of 1 mole of ethanol. The calculated values are corrected for this. (g) Melt solvate shows the presence of methanol of solvation and nmr indicates the amount is about 0.85 mole, for which the calcualted values are corrected. (h) Br in place of Cl and 2-pyridyl in place of *o*-X-C_6H_4. (i) Although **21** and **22** are not intermediates, they are included since they show CNS activity but can not cyclize to triazines. (j) See reference (9).

Scheme III



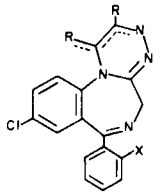
they were uniformally inactive in measurements of analgesic, antidepressant-like and antipsychotic-like activities, some displayed extremely potent activity in tests of anxiolytic and sedation-hypnotic potential. The results of these latter tests are listed in Table III. The standard benzodiazepine, diazepam, is included as a reference compound. It is apparent from these data that several compounds (No. **5**, **11**, **25**, **28**, **30**, **32**, **34**, **35**, **36**, and **42**) are more potent than diazepam in one or more of these tests. Although the significance of the differences in activities on these various tests is not known, the marked potency of No. **30** and **35** in the bicucullin antagonism test is particularly noteworthy. Bicucullin is known to be an antagonist of γ-aminobutyric acid (GABA) receptors in the CNS (6) and benzodiazepine anxiolytics have been suggested to potentiate GABA (7). Thus, the antagonism of bicucullin may be closely related to the mechanism of action of these compounds.

It is interesting that several of the intermediate hydrazones, notably No. **11**, show considerable activity. This might be thought to be due to cyclization to No. **35** either *in vitro* or *in vivo*; however, this cyclization does not take place chemically under mild conditions. Furthermore, the analogous hydrazone of acetone, No. **22**, which can not cyclize, also shows appreciable activity. It is therefore likely that the hydrazones have intrinsic activity themselves.

Biological Test Methods.

The compounds were evaluated in mice using a battery of eleven tests to identify different types of CNS activities. Anxiolytic and sedative-hypnotic activity were determined using the hypoxic stress antagonism (1), pentylenetetrazole (Metrazol ®) convulsion antagonism (2), bicucullin convulsion antagonsim, and γ-butyrolacetone sleep potentiation tests. Bicucullin antagonism measures the ability of the test compound (i.p. 30 minutes previously) to antagonize the tonic-extensor convulsion induced by bicucullin (1 mg./kg. i.v.). The potentiation of a subthreshold hypnotic γ-butyrolacetone dose (200 mg./kg. i.p.) was assessed 40 minutes after injection (i.p.) of the test compound and 10 minutes after γ-butyrolacetone by observing the loss of righting reflex. Antipsychotic-like activity was identified by the antagonism of apormorphine induced cage climbing, antagonism of amphetamine aggregation toxicity and the ability of the compound to cause hypothermia. Antidepressant-like activity was determined by the potentiation of yohimbine toxicity, potentiation of apomorphine induced gnawing and the antagonism of oxotremorine induced hypothermia. Analgesia was evaluated by the hydrochloric acid writhing antagonism test. The compounds were tested at 25 and 50 mg./kg. If significant activity (3/4 or 4/4 responders) was observed additional doses (.3 log intervals) were tested until no activity (1/4 or 0/4 responders) was noted. The number of responders at each dose was used to calculate the ED_{50} by the method of Spearman and Karber (8).

Table II



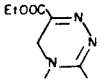
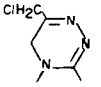
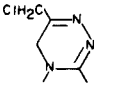
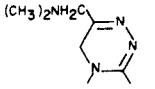
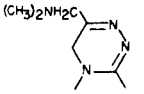
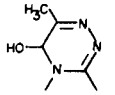
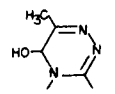
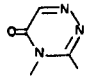
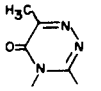
No.		X	Salt (if any)	Formula (a)	Analysis (b) C	H	Cl	N
23		H	base	$C_{18}H_{15}ClN_4$ (c)	65.94 (66.01)	4.67 (4.62)	12.32 (12.32)	17.41 (17.06)
24		H	·HCl	$C_{18}H_{16}Cl_2N_4$	60.08 (60.18)	4.53 (4.49)	19.58 (19.74)	15.82 (15.60)
25		Cl	·HCl	$C_{18}H_{15}Cl_3N_4$	54.75 (54.91)	4.09 (3.84)	26.94 (27.01)	14.33 (14.23)
26		H	·HBr	$C_{20}H_{18}BrClN_4O_2$	51.93 (52.02)	4.14 (3.93)	7.01 (d) (7.68)	12.19 (12.13)
27		H	·HCl	$C_{18}H_{15}Cl_3N_4$	54.61 (54.91)	3.92 (3.84)	27.13 (27.01)	14.17 (14.23)
28		Cl	·HCl	$C_{18}H_{14}Cl_4N_4$	50.57 (50.50)	3.24 (3.30)	33.05 (33.12)	13.04 (13.09)
29		H	base	$C_{20}H_{20}ClN_5$	65.57 (65.66)	5.65 (5.51)	9.70 (9.69)	18.83 (19.14)
30		Cl	base	$C_{20}H_{19}Cl_2N_5$	59.97 (60.01)	4.70 (4.78)	17.33 (17.71)	16.63 (17.50)
31		H	base	$C_{18}H_{15}ClN_4O$ (e)	61.54 (61.96)	5.02 (5.03)	9.73 (9.73)	15.69 (15.37)
32		Cl	base	$C_{18}H_{14}Cl_2N_4O$ (f)	57.00 (57.62)	3.72 (3.87)	18.58 (19.01)	14.71 (14.64)
33		H	base	$C_{17}H_{11}ClN_4O$	63.00 (63.26)	3.61 (3.44)	10.68 (10.99)	17.40 (17.36)
34		H	base	$C_{18}H_{13}ClN_4O$	63.99 (64.20)	4.23 (3.89)	10.56 (10.53)	16.26 (16.64)

Table II (continued)

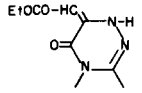
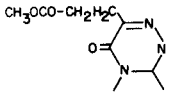
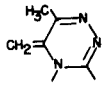
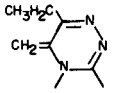
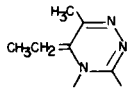
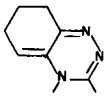
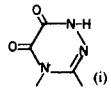
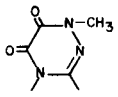
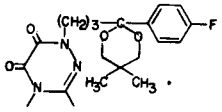
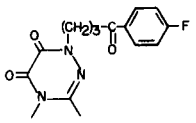
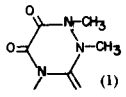
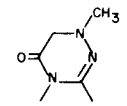
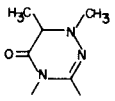
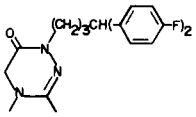
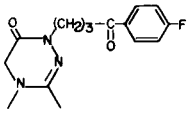
No.		X	Salt (if any)	Formula (a)	Analysis (b) C	H	Cl	N
35		Cl	base	$C_{18}H_{12}Cl_2N_4O$	58.46 (58.24)	3.45 (3.26)	18.84 (19.10)	15.00 (15.09)
36		(g)	base	$C_{17}H_{12}BrN_5O$	53.40 (53.42)	3.12 (3.17)	Br, 20.69 Br, (20.91)	18.39 (18.32)
37		H	base	$C_{17}H_{17}ClN_4O_3$	61.36 (61.69)	4.28 (4.19)	8.59 (8.67)	13.77 (13.70)
38		H	base	$C_{21}H_{17}ClN_4O_3$	61.86 (61.69)	4.45 (4.19)	8.69 (8.67)	13.53 (13.70)
39		H	base	$C_{19}H_{15}ClN_4$	67.99 (68.16)	4.71 (4.52)	10.69 (10.59)	16.78 (16.74)
40		H	base	$C_{20}H_{17}ClN_4$	68.59 (68.86)	4.88 (4.91)	10.15 (10.16)	16.01 (16.06)
41		H	base	$C_{20}H_{17}ClN_4$	68.73 (68.86)	4.86 (4.91)	10.34 (10.16)	16.07 (16.06)
42		H	base	$C_{21}H_{17}ClN_4$ (h)	67.94 (68.23)	5.15 (5.23)	8.90 (8.76)	13.86 (13.84)
43	 (i)	H	base	$C_{17}H_{11}ClN_4O_2$	60.18 (60.28)	3.18 (3.27)	10.45 (10.46)	16.47 (16.54)
44		H	base	$C_{18}H_{13}ClN_4O_2$	61.23 (61.28)	3.70 (3.71)	10.15 (10.05)	16.15 (15.88)
45		H	base	$C_{32}H_{30}ClFN_4O_4$ (j)	65.49 (65.25)	5.33 (5.13)	6.01 (6.02)	9.50 (9.51)
46		H	base	$C_{27}H_{20}ClFN_4O_3$ (k)	64.24 (64.48)	4.26 (4.01)	6.95 (7.05)	10.91 (11.14)
47	 (l)	H	base	$C_{19}H_{15}ClN_4O_2$	62.04 (62.21)	4.15 (4.12)	9.72 (9.66)	15.41 (15.28)

Table II (continued)

No.		X	Salt (if any)	Formula (a)	Analysis (b) C	H	Cl	N
48		H	base	$C_{18}H_{15}ClN_4O$	63.70 (63.81)	4.39 (4.46)	10.67 (10.47)	16.71 (16.54)
49		H	base	$C_{19}H_{17}ClN_4O$	64.52 (64.68)	4.79 (4.86)	10.11 (10.05)	15.90 (15.88)
50		Cl	base	$C_{33}H_{26}ClF_2N_4O$ (m)	65.19 (65.36)	4.46 (4.48)	10.90 (11.42)	9.02 (9.02)
51		Cl	base	$C_{27}H_{21}ClFN_4O_2$ (n)	61.86 (61.90)	4.06 (4.09)	12.99 (13.43)	10.49 (10.61)

(a) See footnote (a), Table I. (b) The values in parentheses are calculated. (c) Melt solvate and nmr showed the presence of chloroform of solvation and the Cl analysis indicated the amount was about 0.0471 mole. (d) Bromine: Calcd.: 17.31. Found: 17.53. Chlorine, found by difference from total halogen, 7.07. (e) Melt solvate and nmr showed the presence of methanol of solvation. The calculated values are based on 0.8 methanol: Melt solvate, Calcd: methanol, 7.03. Found: 6.81. (f) Melt solvate showed the presence of about 0.08 mole of ethyl acetate and 0.04 mole of methylene chloride in the analytical sample. Melt solvate, calcd.: ethyl acetate, 1.84; dichloromethane, 0.89. Found: ethyl acetate, 1.68; dichloromethane, 0.82. (g) Br in place of Cl and 2-pyridyl in place of *o*-X-C_6H_4. (h) Nmr and melt solvate show the presence of approximately 0.5 mole of ethyl acetate of solvation. Melt solvate: Calcd. for 0.5 ethyl acetate, 10.88%. Found: 11.13%. (i) First prepared in these laboratories by J. R. Greene as a byproduct in the reaction of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thione with ethyl oxalylhydrazide. (j) Fluorine: Calcd.: 3.23. Found: 3.39. (k) Fluorine: Calcd.: 3.78. Found: 3.90. (l) Double bond in 4a-5 position instead of 4-4a position. (m) Nmr and melt solvate show the presence of approximately 0.2 mole of ethyl acetate of solvation. Melt solvate: Calcd. for 0.2 ethyl acetate, 2.84%. Found: 2.66%. (n) Nmr and melt solvate show the presence of approximately 0.052 mole (0.87%) of ethyl acetate.

EXPERIMENTAL

(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)hydrazone of 1-Chloro-2-propanone (**1**).

A solution of 2.85 g. (0.01 mole) of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine (**9**) in 75 ml. of tetrahydrofuran was cooled to 0°, under nitrogen, and 1 ml. (1.15 g., 0.0124 mole) of 1-chloro-2-propanone was added with stirring during 10 minutes. After stirring at 0° for 0.5 hours and at room temperature for 2 hours tlc (silica, 20% methanol/benzene) showed one spot. The mixture was evaporated at room temperature and the residue was dissolved in 150 ml. of ethyl acetate, filtered hot, concentrated to 50 ml. and cooled giving 2.93 g. (79%) of crystals, m.p. 210-227° dec.; ir (Nujol): 3320 (NH), 1640, 1610 (C=N), 825, 695 (arom.) cm^{-1}; nmr (deuteriochloroform): δ 2.19 (s, 3, CH_3), 4.19 (s, 2, (CH_2Cl), 4.50 (s, 2, 3-CH_2), 8.38 (s, 1, NH), between 6.95 and 7.65 (m, 8, arom. H's); ms: M^+ 358 (2 Cl).

9-Chloro-1,5-dihydro-2-methyl-7-phenyl-*as*-triazino[4,3-*a*][1,4]-benzodiazepine Hydrochloride (**24**).

A solution of 0.72 g. (0.002 mole) of **1** in 25 ml. of toluene, under nitrogen, was stirred under reflux for 4 hours. After standing overnight the resulting crystals were collected, washed with toluene and ether and dried giving 0.32 g. of brown solid. This was dissolved in 20 ml. of methanol, treated with decolorizing charcoal, filtered, concentrated and diluted with 2-propanol. The solution was further concentrated until crystallization started. After cooling the product was collected, washed with 2-propanol and ether and dried yielding 0.2 g. (28%) of nearly white crystals, m.p. 235-245° dec.; ir (Nujol): 2600 (NH^+), 1600, 1580, 1480 (C=N/C=C), 825, 710, 695 (arom./other) cm^{-1}.

Free Base (**23**).

Crude hydrochloride, prepared as above, was basified with sodium hydroxide and extracted with chloroform. The solution was treated with decolorizing charcoal, filtered, concentrated and diluted with ether giving tan crystals, m.p. 170-197° dec.; tlc (silica, 10% methanol/chloroform) showed only one spot, ir (Nujol): 1610, 1560, 1485 (C=N/C=C), 1340, 1320, 1300, 1210 (C-H/other), 820, 740, 700 (arom.) cm^{-1}; nmr (deuteriochloroform): δ 2.17 (s, 3, CH_3), 4.10 (broad s, 2, 1-CH_2), about 5.0 (very broad s, 5-CH_2), 7.27 (s, $CHCl_3$), between 7.0 and 7.8 (m, 8, arom. H's); ms: M^+ 322 (1 Cl).

[7-Chloro-5-(*o*-chlorophenyl)-3*H*-1,4-benzodiazepin-2-yl]hydrazone of 1-Chloro-2-propanone (**2**).

This was prepared by the procedure used for **1** from 3.19 g. (0.01 mole) of 7-chloro-5-(*o*-chlorophenyl)-2-hydrazino-3*H*-1,4-benzodiazepine (**10**), 1 ml. (1.15 g., 0.0124 mole) of 1-chloro-2-

Table III

Anxiolytic and Sedative Hypnotic Activity
ED_{50} mg./kg.

No. from Tables I-II	Bicuculin Antagonism	Metrazol Antagonism	γ-Butyrolacetone Sleep Potentiation	Hypoxic Stress Antagonism
1	>50	>50	>50	>50
2	>50	35.4	8.8	>50
3	>50	>50	2.6	>50
4	>50	3.0	3.0	>50
5	2.0	0.7	0.7	20.0
6	3.1	12.5	1.3	25.0
7	3.1	8.8	6.3	21.0
9	29.7	21.0	1.3	3.7
10	21.0	10.5	0.1	0.2
11	0.3	0.2	0.1	0.7
12	8.8	37.0	5.3	21.0
13	>50	>50	>50	>50
14	>50	10.5	21.0	17.7
15	40.0	20.0	20.0	>50
16	>50	>50	>50	>50
18	>50	>50	>50	>50
19	>50	>50	>50	>50
20	10.0	10.0	9.0	30.0
21	>50	42.0	21.0	>50
22	3.7	3.7	0.2	8.8
24	5.3	1.6	0.6	1.1
25	1.3	0.24	0.042	0.3
26	29.7	12.5	6.3	35.4
27	29.7	35.4	5.3	25.0
28	17.7	0.7	3.1	6.2
29	5.3	6.3	0.6	8.8
30	0.03	0.1	0.0125	0.4
31	7.0	7.0	2.0	>50
32	0.7	1.0	1.0	>50
33	8.8	1.3	0.7	2.6
34	1.6	0.3	0.1	3.7
35	0.04	0.029	0.01	0.09
36	0.4	0.5	0.9	10.0
37	>50	>50	>50	>50
38	>50	29.7	10.5	50.0
39	30.0	20.0	10.0	>50
40	20.0	5.0	9.0	5.0
41	30.0	10.0	2.0	>50
42	3.0	3.0	1.0	>50
43	3.0	2.0	5.0	6.0
44	>50	40.0	20.0	>50
45	>50	>50	>50	>50
46	>50	30.0	>50	>50
47	>50	>50	>50	>50
48	20.0	7.0	2.0	>50
49	>50	10.0	8.0	>50
50	>50	>50	>50	>50
51	3.0	2.0	3.0	>50
Diazepam	2.6	0.8	0.035	0.2

propanone, and 100 ml. of tetrahydrofuran. The residue after evaporation was dissolved in ether, filtered, concentrated, and diluted with pentane. After cooling in the refrigerator the product was collected, washed with a mixture of ether and pentane and dried yielding 3.82 g. (97%) of tan solid, m.p. 202-217° dec. A sample recrystallized from 2-propanol had the same ir and decomposition point; ir (Nujol): 3380, 3350 (NH), 1635, 1615, 1660, 1485 (C=N/C=C), 1435, 1365, 1325, 1280, 1220 (CH/C-N/other), 840, 775, 755, 735, 710 (arom./C-Cl/other) cm^{-1}; nmr (deuteriochloroform): δ 2.19 (s, 3, CH_3), 4.19 (s, 2, CCH_2Cl), 4.53 (s, 2, 3-CH_2), between 6.9 and 7.5 (m, 7, arom. H's); ms: M^+ 393 (very weak).

9-Chloro-7-(*o*-chlorophenyl)-1,5-dihydro-2-methyl-*as*-triazino-[4,3-*a*][1,4]benzodaizepine Hydrochloride (**25**).

This was prepared by the procedure used for **24** from 3.15 g. (0.008 mole) of **2** in 50 ml. of toluene. After decolorizing treatment the methanol solution was concentrated to 15 ml., diluted to 50 ml. with ether and cooled yielding 1.22 g. (38.8%) of tan crystals, m.p. 250-260° dec.; ir (Nujol): 2060, 2640 ($\overset{+}{N}H$), 1820, 1490 (C=N/C=C), 1300, 1110 (CH/C-N other), 830, 745 (arom.) cm^{-1}; nmr (DMSO-d_6): δ 2.07 (s, 3, CH_3), between 4.2 and 5.5 (very broad, 4, two CH_2's), between 7.0 and 8.0 (m, 7, arom. H's); ms: M^+ (free base) 356 (2 Cl).

2-Carbethoxy-9-chloro-1,5-dihydro-7-phenyl-*as*-triazino[4,3-*a*]-[1,4]benzodiazepine Hydrobromide (**26**).

To a solution of 2.85 g. (0.01 mole) of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine (**9**) in 75 ml. of tetrahydrofuran, under nitrogen, was added 2.0 ml. (0.0157 mole) of ethyl bromopyruvate. The solution became dark and solid and soon separated. After standing 5 days the solid was collected, washed with tetrahydrofuran and dried giving 2.07 g. of tan solid, m.p. 205-215° dec., and showing essentially one spot on tlc (silica, 10% methanol/chloroform). This was dissolved in 250 ml. of ethanol, treated at the boiling point with decolorizing charcoal, filtered, and concentrated to 180 ml. After standing overnight the product was collected, washed with ethanol and dried yielding 0.95 g. (20.3%) of white crystals, m.p. 216-223° dec.; ir (Nujol): 2700 (N^+H), 1720 (C=O), 1610, 1540, 1480 (C=N/C=C), 1315, 1290, 1140, 1085 (C-O/C-N/other), 730, 695 (arom.) cm^{-1}; nmr (DMSO-d_6): δ 1.24 (t, 3, CH_2CH_3), between 3.9 and 5.3 (m, 6, three CH_2's), between 7.3 and 8.1 (m, 8, arom. H's); ms: M^+ (free base) 380 (1 Cl).

(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)hydrazone of 1,3-Dichloro-2-propanone (**3**).

This was prepared by the procedure used for **1** from 4.7 g. (0.0165 mole) of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine (**9**), 3.1 g. (0.025 mole) of 1,3-dichloro-2-propanone in 100 ml. of tetrahydrofuran. The evaporated reaction mixture was dissolved in methylene chloride, filtered and concentrated to 90 ml. Dilution to 100 ml. with methanol and cooling gave 4.57 g. (64.5%) of nearly white solid, m.p. 165-250° dec.; ir (Nujol): 3300, 3250 (NH), 630, 1605, 1590, 1485 (C=N/C=C), 1450, 1320, (CH/C-N other), 825, 695, 685 (arom.) cm^{-1}; nmr (deuteriochloroform): δ 4.38 and 4.47 (two s's, 4, two CH_2Cl's), 4.63 (s, 2, 3-CH_2), between 6.9 and 7.65 (m, 8, arom. H's); ms: M^+ 393.

9-Chloro-2-chloromethyl-1,5-dihydro-7-phenyl-*as*-triazino[4,3-*a*]-[1,4]benzodiazepine Hydrochloride (**27**).

The hydrazone **3** was prepared as above from 5.7 g. (0.02 mole) of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine (**9**) and 2.8 g. (0.022 mole) of 1,3-dichloro-2-propanone in 125 ml. of tetrahydrofuran. After 4 hours at room temperature, tlc (silica, 10% methanol/chloroform) showed one spot, same as for that of **3**. Without isolation the mixture was kept under nitrogen at room temperature for 14 days. After concentration to about 100 ml.,

the resulting solid was collected and dried, giving 4.66 g. of tan solid, tlc (silica, 10% methanol/chloroform) showed one spot moving slower than that of the hydrazone **3**. This was recrystallized from methanol, with decolorizing charcoal treatment, yielding 3.3 g. (44%) of white fluffy crystals, m.p. 215-260° dec.; ir (Nujol): 2570 ($\overset{+}{N}H$), 1610, 1575, 1565, 1485 (C=N/C=C), 1325, 1305 (C-N/other), 825, 785, 695 (arom.) cm^{-1}; nmr (DMSO-d_6): δ 4.49 (s, 2, CH_2Cl), between 4.0 and 5.4 (m, 4, two CH_2's), between 7.2 and 8.0 (m, 8, arom. H's); ms: M^+ (free base) 357 (3 Cl).

9-Chloro-2-chloromethyl-7-(*o*-chlorophenyl)-1,5-dihydro-*as*-triazino[4,3-*a*][1,4]benzodiazepine Hydrochloride (**28**).

[7-Chloro-5-(*o*-chlorophenyl)-3*H*-1,4-benzodiazepin-2-yl]hydrazone of 1,3-dichloro-2-propanone was prepared *in situ* by the procedure used for **1** from 3.19 g. (0.01 mole) of 7-chloro-5-(*o*-chlorophenyl)-2-hydrazino-3*H*-1,4-benzodiazepine (**10**) and 1.4 g. (0.011 mole) of 1,3-dichloro-2-propanone in 150 ml. of tetrahydrofuran. Without isolation the mixture was stirred, at reflux, under nitrogen for 3 hours and concentrated to 75 ml. After standing overnight the resulting crystalline product was collected, washed with tetrahydrofuran and dried giving 1.54 g. (36%) of tan solid. This was recrystallized from methanol, with decolorizing charcoal treatment, yielding 0.65 g. of white crystals, m.p. 230-240° dec.; ir (Nujol): 2620 ($\overset{+}{N}H$), 1665, 1630 (C=N/C=C), 850, 765 (arom.) cm^{-1}; ms: M^+ 390 (3 Cl).

9-Chloro-1,5-dihydro-2-(dimethylaminomethyl)-7-phenyl-*as*-triazino[4,3-*a*][1,4]benzodiazepine (**29**).

To a solution of 1.85 g. (0.005 mole) of **27** in 250 ml. of methanol and 40 ml. of water, under nitrogen, was added with stirring 10 ml. (0.05 mole) of 20% aqueous dimethylamine. After 5 hours at room temperature the solution was evaporated *in vacuo*. The residue was dissolved in methylene chloride, washed with cold dilute sodium hydroxide, water, and saturated sodium chloride solution. After drying over sodium sulfate, filtering, and evaporating the product was crystallized from 2-propanol, yielding 0.93 g. (59%) of tan crystals, m.p. 169-190° dec.; ir (Nujol): 2770 (CNH), 1610, 1560, 1545 (C=N/C=C), 1340, 1320 (C-N/other), 835, 700 (arom.) cm^{-1}; nmr (deuteriochloroform): δ 2.30 (s, 6, two CH_3's), 3.28 (s, 2, CH_2N), 4.24 (broad, s, 2, 1-CH_2), between 7.5 and 7.75 (m, 8, arom. H's); ms: M^+ 365 (1 Cl).

9-Chloro-7-(*o*-chlorophenyl)-1,5-dihydro-2-dimethylaminomethyl)-*as*-triazino[4,3-*a*][1,4]benzodiazepine (**30**).

This was prepared by the procedure used for **29** from 0.856 g. (0.002 mole) of **28**, 4 ml. (0.02 mole) of 25% aqueous dimethylamine in 100 ml. of methanol. After evaporation of the methylene chloride solution, the residue was triturated with ether and collected giving 0.6 g. of tan solid. This was dissolved in 700 ml. of ether at the boiling point, filtered, concentrated to 50 ml., and cooled giving 0.4 g. (50%) of yellow crystals, m.p. 170-174° dec.; ir (Nujol): 2780 (CHN), 1615, 1595, 1565, 1540, 1490 (C=N/C=C), 1410, 1325 (other), 840, 815, 765, 745, 740 (arom./other) cm^{-1}; nmr (deuteriochloroform): δ 2.29 (s, 6, two CH_3's), 3.29 (s, 2, CH_2N), 4.26 (s, 2, 1-CH_2), 4.5 (broad, s, 2, 5-CH_2), between 6.9 and 7.7 (m, 7, arom. H's); ms: M^+ 399 (2 Cl).

(7-(Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)hydrazone of 1,1-Dimethoxy-2-propanone (**4**).

A solution of 2.8 g. (0.01 mole) of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine (**9**) and 2.6 g. (0.022 mole) of 1,1-dimethoxy-2-propanone in 100 ml. of tetrahydrofuran was stirred at room temperature for 18 hours and evaporated *in vacuo*. The residue was dissolved in methylene chloride, washed with water and dried over sodium sulfate. After filtration and concentration the product was chromatographed on silica gel, eluting with a mixture of hexane 70%, methylene chloride 25% and 2-propanol 5%. The product was crystallized from a mixture of ethyl acetate and hexane yielding 2.3 g. (60%) of crystals, m.p. 182-183°; ir (Nujol): 3280 (NH), 1640, 1610 (C=N), 1580, 1480 (C=C), 1350, 1220, 1115 (other), 1075 (CO), 940, 825, 735, 694 (arom./other) cm^{-1}; nmr (deuteriochloroform): δ 2.03 (s, 3, CCH_3), 3.20 (s, 6, two OCH_3), 4.25 (s, 2, 3-CH_2), 4.35 (s, 1, CHO_2), 8.21 (s, 1, NH), between 6.9 and 7.7 (m, 8, arom. H's).

9-Chloro-1,5-dihydro-2-methyl-7-phenyl-*as*-triazino[4,3-*a*][1,4]-benzodiazepin-1-ol Methanol Solvate (**31**).

To 15 ml. of concentrated sulfuric acid, at 0° under nitrogen, was slowly added with stirring 2.52 g. (0.065 mole) of **4**. The solution was allowed to warm to room temperature, stirred for 2 hours, quenched with ice and sodium bicarbonate solution, and extracted with methylene chloride. After washing with water, drying over sodium sulfate and evaporating *in vacuo*, the residue was crystallized from a mixture of methylene chloride, methanol and then from ethyl acetate. More product was obtained by chromatographing the filtrate on silica gel, eluting with 10% methanol in chloroform, and crystallizing from ethyl acetate. The total yield was 1.15 g. (about 50%) of white solid containing ethyl acetate of crystallization, m.p. 170-172° dec. The compound seems to solvate with many solvents and the decomposition points varied widely. A sample for analysis was crystallized from ethyl acetate-methanol and was found to contain about 0.8 mole of methanol even after long drying *in vacuo*, m.p. 170-174° dec.; ir (Nujol): 3000 (broad), 2720 (OH), 1615, 1595, 1555, 1480, (C=N/C=C), 1325, 1195, 1095, 1045, 885 (other), 825, 815, 785, 745, 705 (arom.) cm^{-1}; nmr (deuteriochloroform + methanol-d_4 + deuterium oxide): δ 2.30 (s, 3, CH_3), 3.37 (s, methanol of solvation), ab centered at 3.97 and 4.9 (2, J = -11Hz, 5-CH_2), 5.5 (s, 1, HCO), between 7.1 and 8.2 (m, 8, arom. H's); ms: M^+ 338 (1 Cl).

(7-Chloro-5-(*o*-chlorophenyl)-3*H*-1,4-benzodiazepin-2-yl)hydrazone of 1,1-dimethoxy-2-propanone (**5**).

This was prepared by the procedure used for **4** from 15.96 g. (0.05 mole) of 7-chloro-5-(*o*-chlorophenyl)-2-hydrazino-3*H*-1,4-benzodiazepine (**10**) and 11.8 g. (0.1 mole) of 1,1-dimethoxy-2-propanone in 250 ml. of tetrahydrofuran. The product was crystallized from ethyl acetate-hexane and additional material was obtained by chromatographing the filtrate on silica gel, eluting with 5% methanol in chloroform. The total yield was 17.0 g. (81%), m.p. 153-158°. The sample for analysis was recrystallized from ethyl acetate-hexane, m.p. 157-158°; ir (Nujol): 3220, 3160 (NH), 1645, 1625, 1595, 1560, 1480 (C=N/C=C), 1115, 1070, 1055, 940, 830, 755 (other) cm^{-1}; nmr (deuteriochloroform): δ 2.8 (s, 3, CCH_3), 3.43 (s, 6, OCH_3), 4.54 (s, 2, 3-CH_2), 4.69 (s, 1, CHO_2), 8.4 (broad s, 1, NH), between 6.85 and 7.6 (m, 7, arom. H's).

9-Chloro-7-(*o*-chlorophenyl)-1,5-dihydro-2-methyl-*as*-triazino[4,3-*a*][1,4]benzodiazepin-1-ol (**32**).

This was prepared by the procedure used for **31** from 7.57 g. (0.018 mole) of **5** and 30 ml. of concentrated sulfuric acid. The product was crystallized from ethyl acetate yielding 4.08 g. (60%) of crystalline solid, m.p. 170-173° dec. Nmr showed the presence of ethyl acetate of crystallization. A sample for analysis was crystallized from a mixture of ethyl acetate and methylene chloride, m.p. 165-170° dec.; ir (Nujol): ~3000, 2720 (OH), 1615, 1595,

1570, 1555, 1485 (C=N/C=C), 1040 (C-O), 885, 830, 765, 735 (arom.) cm^{-1}; nmr (on sample from ethyl acetate) (deuteriochloroform + methanol-d_4): δ 1.27 (t, 1.5, CH_3CH_2O of ½ ethyl acetate), 2.03 (s, 1.5, CH_3CO of ½ ethyl acetate), 2.33 (s, 3, 2-CH_3), 4.16 (q, CH_3CH_2O of ½ ethyl acetate), ab centered at 4.0 and 4.95 (2, J = 10 Hz, 5-CH_2), 5.4 (s, 1, HCL), between 6.95 and 7.85 (m, 7, arom. H's).

(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)hydrazone of Glyoxylic Acid, Methanol Solvate (**6**).

To a solution of 5.41 g. (0.019 mole) of 7-Chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine (9) in 100 ml. of methanol, under nitrogen, was added with stirring 3.0 g. (0.04 mole) of glyoxylic acid hydrate. Solid separated and after stirring for 1 hour, it was collected, washed with methanol and ether and dried giving 5.66 g. (77%) of solid, m.p. 164-166° dec.; ir (Nujol): 3420, 3340, 3220 (OH/NH), ~ 2570 (broad) (acid OH), 1655, 1615, 1600, 1580, 1550, 1480 (CO/C=N/C=N), 1325, 1230, 1080, 1020 (C-O/C-N), 985, 945 (other), 740, 700 (vinyl CH) cm^{-1}.

(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)hydrazone of Methyl Glyoxylate (**7**).

To a stirred suspension of 6.29 g. (0.017 mole) of **6** in 300 ml. of methylene chloride was slowly added an ethereal solution containing (by titration) 0.22 moles of diazomethane. After standing for an hour the solution was evaporated *in vacuo* and the residue was crystallized from ethyl acetate giving 3.20 g. (53%) of the methyl ester, m.p. 171.5-176°. A sample for analysis was recrystallized from ethyl acetate-hexane, m.p. 173.5-176°; ir (Nujol): 3300 (NH), 3060 (=CH), 1720 (C=O), 1630 (C=N), 1580, 1555, 1490 (C=N/C=C), 1280, 1045 (C-O/C-N), 815, 795, 710 (arom./other) cm^{-1}; nmr (deuteriochloroform): δ 3.85 (s, 3, OCH_3), 4.5 (s, 2, 3-CH_2), between 7.05 and 7.6 (m, 8, arom. H's), 7.8 (s, 1, N=CH), 8.9 (s, 1, NH).

9-Chloro-1,5-dihydro-7-phenyl-*as*-triazino[4,3-*a*][1,4]benzodiazepin-1-one (**33**).

A solution of 1.71 g. (0.005 mole) of the methanol solvate, **6**, in tetrahydrofuran was evaporated to dryness *in vacuo*. The residue was dissolved in more tetrahydrofuran and reevaporated several times until nmr showed no more methanol present. The residue was then taken up in 40 ml. of tetrahydrofuran and treated, under nitrogen, with 0.81 g. (0.005 mole) of 1,1'-carbonyldiimidazole. After stirring for 1 hour at room temperature and 2 hours under reflux the mixture was evaporated *in vacuo*, treated with water, and extracted with methylene chloride. The extract was washed with water, dried, concentrated and chromatographed on silica gel, eluting with chloroform. The product was crystallized from ethyl acetate-hexane yielding 0.33 g. (20.5%) of white solid, m.p. 191-195°, ir (Nujol): 3100, 3060 (=CH), 1710 (C=O), 1610, 1600, 1575, 1515, 1485 (C=N/C=C), 1325, 1310 (C-N/other), 840, 790, 700 (arom./other) cm^{-1}; nmr (deuteriochloroform): δ 8.5 (s, 1, CH=N), ab centered at 5.3 and 4.15 (2, J = -11 Hz, Hz, 5-CH_2), between 7.3 and 7.9 (m, 8, arom. H's).

Acetyl-(7-chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)hydrazone of Methyl Glyoxylate (**8**).

In an attempt to cyclize **7** to **33** (see preparation of **34** below), 1.06 g. (0.003 mole) of **7** in 15 ml. of glacial acetic acid and 1.06 g. (0.003 mole) of acetic anhydride, under nitrogen, was refluxed for 2 hours. After cooling and neutralizing with sodium bicarbonate the product was extracted with methylene chloride, washed with water, dried and evaporated. Crystallization from ethyl acetate-hexane gave 0.36 g. (30%) of crystals, m.p. 195-210° dec., which was found by ir and nmr to be the acetyl derivative of **7**, ir (Nujol): 1755 (C=O), 1660, 1640 (C=O/C=N), 1610, 1575, 1565, 1495, 1485 (C=N/C=C), 1400, 1320, 1300, 1275, 1015 (C-O/C-N/other), 840, 705 (arom./other) cm^{-1}; nmr (deuteriochloroform): δ 2.3 (s, 3, CH_3CO), 3.7 (s, 3, CH_3O), ab centered at 4.2 and 4.9 (2, J = -13 Hz, 3-CH_2), 6.5 (s, 1, N=CH), between 7.2 and 7.7 (m, 8, arom. H's).

(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)hydrazone of Pyruvic Acid (**9**).

A mixture of 2.85 g. (0.01 mole) of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine (9) and 0.847 ml. (0.012 mole) of pyruvic acid in 100 ml. of methanol, under nitrogen, was stirred at room temperature for 2.5 hours, heated to the boiling point to dissolve the solid. On cooling 3.47 g. of yellow-tan crystals was obtained, m.p. 145-165° dec. This was shown by nmr and melt solvate to contain methanol of crystallization. Recrystallization from ethyl acetate gave 2.68 g. (76%) of yellow crystals, m.p. 183-185° dec.; ir (Nujol): 3260 (NH), 2460 (OH), 1695 (C=O), 1640 (C=N), 1555, 1485 (C=N/C=C), 1325, 1215, 1170, 1160 (C-O/C-N/other), 820, 780, 700 (arom./other) cm^{-1}; nmr (DMSO-d_6): δ 2.14 (s, 3, CH_3), 4.44 (broad s, 2, 3-CH_2), between 7.1 and 7.8 (m, 8, arom. H's).

(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)hydrazone of Methyl Pyruvate (**10**).

A mixture of 5.7 g. (0.02 mole) of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine (9) and 6 ml. (0.08 mole) of methyl pyruvate in 50 ml. of methanol was stirred, under nitrogen, for 24 hours. After filtration and evaporation *in vacuo* the residue was chromatographed on silica gel, eluting with 1% methanol in chloroform. The product was crystallized from chloroform-ether yielding 3.5 g. (67%) of white crystals, m.p. 156-157°; ir (Nujol): 3220 broad (NH), 1735, 1725 (C=O), 1635, 1580, 1550, 1480 (C=N/C=C), 1285, 1150, 1065, 940 (C-O/C-N/other), 830, 740, 705 (arom.) cm^{-1}; nmr (deuteriochloroform): δ 2.05 (s, 3, CCH_3), 3.80 (s, 3, OCH_3), 4.52 (s, 2, 3-CH_2), between 6.9 and 7.65 (m, 8, arom. H's); ms: M^+ 368 (1 Cl).

This same methyl ester **10** was also prepared from the corresponding acid **9** using diazomethane, and also using 3-methyl-1-*p*-tolyltriazine.

9-Chloro-1,5-dihydro-2-methyl-7-phenyl-*as*-triazino[4,3-*a*][1,4]-benzodiazepin-1-one (**34**).

A solution of 0.37 g. (0.001 mole) of the methyl ester, **10**, in 5 ml. of glacial acetic acid was stirred under reflux, under nitrogen, for 45 minutes and evaporated *in vacuo*. The residue was neutralized with sodium bicarbonate, extracted with methylene chloride, washed with water, dried, and evaporated *in vacuo*. The residue was chromatographed on silica gel, eluting with 2% methanol in chloroform, and crystallized from ethyl acetate-hexane yielding 0.18 g. (52%) of **34**, m.p. 194-196°. A sample for analysis was recrystallized from 2-propanol; ir (Nujol): 1685 (C=O), 1605, 1595, 1575, 1565, 1515 (C=N/C=C), 1320 (C-N), 820, 785, 765, 735, 695 (arom./other) cm^{-1}; nmr (deuteriochloroform): δ 2.53 (s, 3, CH_3), ab centered at 4.07 and 5.22 (2, J = -12 Hz, 5-CH_2), between 7.2 and 7.9 (m, 8, arom. H's); ms: M^+ 336 (1 Cl).

This same compound was prepared in lower yield by heating the ester **10** at reflux in 1,2,4-trichlorobenzene for 8 hours. It was also prepared in excellent yield from the acid **9** by cyclization with 1,1'-carbonyldiimidazole or with polyphosphoric acid.

[7-Chloro-5-(*o*-chlorophenyl)-3*H*-1,4-benzodiazepin-2-yl]hydrazone of Pyruvic Acid Ethanol Solvate (**11**).

A mixture of 1.6 g. (0.005 mole) of 7-chloro-5-(*o*-chlorophenyl)-2-hydrazino-3*H*-1,4-benzodiazepine (10) and 0.5 ml.

(0.007 mole) of pyruvic acid in 50 ml. of ethanol was heated to the boiling point, cooled and stirred at room temperature for 2 hours. The solid was collected, washed with ethanol and dried for 1.5 hours at room temperature and 0.02 mm. pressure yielding 2.04 g. (94%) of light yellow solid, m.p. 147-151° dec.; ir (Nujol): 3200 broad (NH/OH), 1725 (C=O), 1630 (C=N), 1590, 1555, 1485 (C=N/C=C), 1325, 1190, 1055 (C-N/C-O/other), 830, 750 (arom./other) cm^{-1}; nmr (DMSO-d_6): δ 1.05 (t, 3, CH_3 of ethanol of solvation), 2.15 (s, 3, CH_3), 3.45 (q, 2, CH_2 of ethanol of solvation), 4.45 (s, 2, 3-CH_2), between 6.8 and 7.75 (m, 7, arom. H's).

[7-Chloro-5-(*o*-chlorophenyl)-3*H*-1,4-benzodiazepin-2-yl]hydrazone of Methyl Pyruvate Methanol Solvate (**12**).

This was prepared by the procedure used for **10** from 4.35 g. (0.01 mole) of **11** in dichloromethane and adding 0.011 mole of ethereal diazomethane. Evaporation and crystallization from methanol yielded 3.1 g. (77%) of yellow needles, m.p. 108-127° dec.; ir (Nujol): 3520, 3260 (NH/OH), 1720 (C=O), 1625 (C=N), 1580, 1545, 1480 (C=N/C=C), 1290, 1055 (C-O/C-N/other), 825, 772 (arom./other) cm^{-1}; nmr (deuteriochloroform): δ 2.3 (s, 3, CCH_3), 3.46 (s, ~ 2.55, OCH_3 of 0.85 moles of methanol of solvation), 3.35 (s, 3, OCH_3 of ester), 4.56 (s, 2, 3-CH_2), between 6.9 and 7.6 (m, 7, arom. H's); ms: M^+ 403 (2 Cl).

9-Chloro-7-(*o*-chlorophenyl)-1,5-dihydro-2-methyl-*as*-triazino[4,3-*a*][1,4]benzodiazepin-1-one (**35**).

A solution of 4.5 g. (0.0113 mole) of **12** in 125 ml. of 1,2,4-trichlorobenzene was stirred under reflux, under nitrogen, for 10 hours using a short air condenser. After evaporation of the solvent *in vacuo* the dark residue was crystallized from ethyl acetate yielding 1.93 g. (46%) of yellow needles, m.p. 211.5-213°; ir (Nujol): 1685 (C=O), 1620, 1600, 1570, 1520 (C=N/C=C), 1320 (C-N/other), 830, 775, 770, 740 (arom./C-Cl/other) cm^{-1}; nmr (deuteriochloroform): δ 2.52 (s, 3, CH_3), ab centered at 4.14 and 5.23 (2, J = -12 Hz, 5-CH_2), between 7.05 and 7.85 (m, 7, arom. H's); ms: M^+ 370 (2 Cl).

This same compound (**35**) was also prepared in 50% overall yield by treating 7-chloro-5-(*o*-chlorophenyl)-2-hydrazino-3*H*-1,4-benzodiazepine (**10**) with ethyl pyruvate and refluxing the non-crystalline ethyl ester hydrazone for 3 hours in glacial acetic acid.

[7-Bromo-1,3-dihydro-5-(2-pyridyl)-2*H*-1,4-benzodiazepin-2-yl]-hydrazone of Ethyl Pyruvate (**13**).

A mixture of 3.30 g. (0.01 mole) of 7-bromo-2-hydrazino-5-(2-pyridyl)-3*H*-1,4-benzodiazepine (**10**) and 1.16 g. (0.01 mole) of ethyl pyruvate in 50 ml. of tetrahydrofuran, under nitrogen, was stirred at room temperature for 2 hours. After evaporation *in vacuo* the residue was dissolved in methylene chloride, washed with water, dried, and evaporated. Trituration with ethyl acetate gave a crystalline solid which was collected, washed with ethyl acetate-hexane and dried yielding 3.10 g. (72%) of **13**, m.p. 220-227° dec. A sample for analysis was recrystallized from methylene chloride-methanol-ethyl acetate, m.p. 230-233° dec.; ir (Nujol): 3220 (NH), 1705 (C=O), 1630 (C=N), 1585, 1535 (C=N/C=C), 1300, 1145 (other) cm^{-1}; nmr (deuteriochloroform + methanol-d_4): δ 1.4 (t, 3, OCH_2CH_3), 2.3 (s, 3, CCH_3), 4.4 (q, 2, OCH_2CH_3), between 7.2 and 8.0 (m, 7, arom. H's).

9-Bromo-1,5-dihydro-2-methyl-7-(2-pyridyl)-*as*-triazino[4,3-*a*]-[1,4]benzodiazepin-1-one (**36**).

A solution of 1.6 g. (0.0037 mole) of **13** in 15 ml. of glacial acetic acid, under nitrogen, was heated under reflux for 2 hours, cooled, neutralized with ice and sodium bicarbonate and extracted with methylene chloride. After washing with water, drying, and evaporating *in vacuo* the product was chromatographed on silica gel, eluting with 1.5% methanol in chloroform. The product was crystallized first from ethyl acetate-hexane and then from methylene chloride/ethyl acetate yielding 0.16 g. (11%) of yellow crystals, m.p. 224-227°; ir (Nujol): 1710, 1690 (C=O), 1610, 1590, 1575, 1570, 1525 (C=N/C=C) cm^{-1}; nmr (deuteriochloroform): δ 2.5 (s, 3, CH_3), ab centered at 4.2 and 5.3 (2, J = -12 Hz, 5-CH_2), between 7.25 and 8.78 (m, 7, arom. H's).

9-Chloro-3,5-dihydro-1-oxo-7-phenyl-*as*-triazino[4,3-*a*][1,4]benzodiazepine-Δ^2(1*H*),α-acetic Acid, Ethyl Ester (**37**).

Diethyl oxalacetate was liberated from 1.26 g. (0.006 mole) of its sodium salt by neutralization with hydrochloric acid and extraction with methylene chloride. The extract was dried over sodium sulfate, evaporated *in vacuo*, dissolved in 50 ml. of methanol, and mixed with 0.812 g. (0.003 mole) of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine (**9**). After stirring for 1.5 hours the solution was evaporated *in vacuo*. The residue was dissolved in methylene chloride, washed with 5% sodium hydroxide solution, dried over magnesium sulfate, filtered and evaporated *in vacuo* giving (7-chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)hydrazone of diethyl oxalacetate which failed to crystallize but was found by nmr to be essentially this hydrazone, nmr (deuteriochloroform): δ 1.21 and 1.23 (2, t's, 6, two OCH_2CH_3's), 3.95 (s, 2, CH_2CO), 4.14 and 4.27 (2 q's, 4, two OCH_2CH_3's), 4.5 (s, 2, 3-CH_2), between 6.9 and 7.7 (m, 8, arom. H's).

This hydrazone was dissolved in 10 ml. of glacial acetic acid and refluxed under nitrogen for 1.5 hours. After evaporation *in vacuo* the residue was mixed with methylene chloride and washed with dilute sodium bicarbonate solution, then with water and dried over sodium sulfate. The solution was again evaporated, crystallized from ethyl acetate with decolorizing charcoal treatment and then recrystallized twice from ethyl acetate-hexane yielding 1.15 g. of yellow crystals, m.p. 216-219.5°. The ir, uv, and nmr indicates this exists with the double bond exo to the triazino ring as indicated for No. 37, Table II; ir (Nujol): 3280 (NH/OH), 3080, 3040 (=CH), 1705 (C=O), 1650 (C=O/C=N), 1605, 1580, 1570, 1480 (C=N/C=C), 1335, 1320, 1295, 1275, 1190, 1170 (C-O/C-N/other), 890, 820, 780, 775, 765, 745, 690 (arom./other) cm^{-1}; uv max (ethanol): end absorption 208 mμ, sh (ε 38.500), 253 sh (15,550), 285 (15,800), 358 sh (11,000), 370 (11,500), 390 sh (7,450); nmr (deuteriochloroform): δ 1.3 (t, 3, OCH_2CH_3), 4.2 (q, 2, OCH_2CH_3), ab centered at 4.1 and 4.9 (2, J = -12 Hz, 5-CH_2), 5.6 (s, 1, =CH), between 7.3 and 7.8 (m, 8, arom. H's), 11.3 (broad s, 1, NH); ms: M^+ 408 (1 Cl).

(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)hydrazone of α-Ketoglutaric Acid (**14**).

A solution of 2.92 g. (0.02 mole) of α-ketoglutaric acid in 30 ml. of methanol was slowly added at room temperature to a stirred suspension of 2.86 g. (0.01 mole) of 7-chloro-2-hydrazono-5-phenyl-3*H*-1,4-benzodiazepine (**9**) in 70 ml. of methanol. After stirring for 1.5 hours the product was collected yielding 3.88 g. (94%) of yellow solid, m.p. 212° dec.; ir (Nujol): 3200 (NH), 2800 to 2350 (broad) (acid OH), 1735 (CO), 1625, 1585, 1550, 1490 (C=N/C=C), 1310, 1230, 1170, 1065 (C-O/C-N), 835, 695 (arom./other) cm^{-1}; ms: dehydrated in instrument to anhydride showing a strong peak at 394 m/e.

2-[2-(Carbomethoxy)ethyl]-9-chloro-1,5-dihydro-7-phenyl-*as*-triazino[4,3-*a*][1,4]benzodiazepin-1-one (**38**).

The dimethyl ester of **14** was prepared by adding an excess of ethereal diazomethane to a stirred suspension of 14.24 g. (0.0345 mole) of **14** in 200 ml. of methylene chloride. Evaporation *in vacuo* gave an oil which failed to crystallize; nmr (deuteriochloroform): δ between 2.5 and 3.35 (m, 4, CH_2CH_2CO), 3.66 and 3.84 (2s's, 6, two OCH_3), 4.53 (s, 2, 3-CH_2), between 7.0 and 8.0 (m, 8, arom. H's).

This methyl ester was dissolved in 50 ml. of glacial acetic acid and refluxed under nitrogen for 1 hour. After cooling the solution was neutralized with ice water and sodium bicarbonate, and extracted with methylene chloride. After evaporation *in vacuo* the residue was crystallized from ethyl acetate-hexane yielding 7.2 g. (51%) of white solid, m.p. 145-148°. A sample for analysis was recrystallized from ethyl acetate-hexane, m.p. 146-150°; ir (Nujol): 1735 (O-C=O), 1705 (N-C=O), 1580, 1525 (C=N/C=C), 1320, 1205, 1180 (C-O/C-N/other), 825, 790, 695 (arom./other) cm^{-1}; nmr (deuteriochloroform): δ between 2.7 and 3.4 (m, 4, CH_2CH_2CO), 3.7 (s, 3, OCH_3), ab centered at 4.1 and 5.25 (2, J = -12 Hz, 5-CH_2), between 7.3 and 7.85 (m, 8, arom. H's).

9-Chloro-1,5-dihydro-2-methyl-1-methylene-7-phenyl-*as*-triazino-[4,3-*a*][1,4]benzodiazepine (**39**).

A solution of 14.24 g. (0.05 mole) of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine (9) in 200 ml. of tetrahydrofuran, under nitrogen, was cooled to 0° and a solution of 5.16 g. (0.06 mole) of 2,3-butanedione in 100 mL of tetrahydrofuran was added with stirring. After 3 hours the solution was evaporated *in vacuo* giving (7-chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)monohydrazone of 2,3-butanedione as a light yellow non-crystalline solid showing two close spots on tlc (silica, 70% hexane/25% dichloromethane/5% 2-propanol). The nmr shows two close peaks for each of the methyl groups from which it is construed that the compound exists in *syn* and *anti* forms. These could be partially separated by chromatography, upfield isomer; nmr (deuteriochloroform): δ 2.10 (s, 3, N=CCH_3), 2.42 (s, 3, CH_3CO), 4.4 (s, 2, 3-CH_2), between 6.9 and 7.7 (m, 8, arom. H's); downfield isomer, nmr (deuteriochloroform): δ 2.1 (s, 3, N=CCH_3), 2.48 (s, 3, CH_3CO), 4.54 (s, 2, 3-CH_2), between 6.95 and 7.7 (m, 8, arom. H's).

A 5.5 g. (0.017 mole) portion of the above crude hydrazone was added, under nitrogen, to 20 ml. of liquid hydrogen fluoride at -80° and the solution was allowed to warm at room temperature and evaporate overnight in the hood. The residue was mixed with aqueous sodium bicarbonate, extracted with methylene chloride, washed with water, dried over sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on silica gel, eluting with 60% hexane, 35% methylene chloride and 5% 2-propanol. The product was crystallized from ethyl acetate-hexane yielding 2.04 g. (37%) of light yellow solid, m.p. 190-196° dec. A sample for analysis was recrystallized from methylene chloride-ethyl acetate, m.p. 194-196°; ir (Nujol): 1610, 1590, 1560, 1540, 1475 (C=N/C=C), 880 (=CH_2), 835, 815, 745, 700 (arom./other) cm^{-1}; uv max (ethanol): 219 mμ (ε 40,400), 333 (3,700); nmr (deuteriochloroform): δ 2.2 (s, 3, CH_3), 4.3 (s, =CH_2), ab centered at 3.9 and 4.8 (2, J = -13 Hz, 5-CH_2), between 7.3 and 7.8 (m, 8, arom. H's).

Other runs using a mixture of methanesulfonic acid and phosphorus pentoxide as the cyclizing reagent gave similar results but lower yield. Among the chromatographic fractions was found a considerable amount of unreacted hydrazone. This was shown by tlc and nmr to be the downfield isomer in the nmr. Little, if any, of the upfield isomer remained after treatment with HF indicating that the upfield isomer is much more easily cyclized than the other.

9-Chloro-1,5-dihydro-2-ethyl-1-methylene-7-phenyl-*as*-triazino-[4,3-*a*][1,4]benzodiazepine (**40**) and 9-Chloro-1,5-dihydro-1-ethylidene-2-methyl-7-phenyl-*as*-triazino[4,3-*a*][1,4]benzodiazepine (**41**).

By a procedure similar to that used for the preparation of **39**, 2.84 g. (0.01 mole) of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine (9) was condensed with 2,3-pentanedione in tetrahydrofuran. After evaporation the residue was dissolved in methylene chloride, washed with water, dried over sodium sulfate, evaporated and chromatographed on silica gel, eluting with hexane 70%/dichloromethane/25% 2-propanol/5%. The product was an oil whose nmr was consistent with that of a mixture of the two monohydrazones, probably *syn* and *anti* forms. The yield was about 90%. This oil was added to liquid hydrogen fluoride at -80°, allowed to evaporate overnight, and worked up as for the above. Chromatography yielded two cyclized products, **40** and **41**, which were identified by nmr. Product **40** crystallized from ethyl acetate-hexane giving 0.44 g. (11%) of yellow crystals which were found by melt solvate to contain 14% solvent, m.p. 104-117° dec. Recrystallization from methylene chloride-ether gave an unsolvated product, m.p. 155-163° dec.; ir (Nujol): 1610, 1595, 1565 (C=N/C=C), 1445, 1360, 1320, 835, 695 (other); uv max (ethanol): 219 mμ (ε 35,850), 331 (3,400); nmr (deuteriochloroform): δ 1.3 (t, 3, CH_2CH_3), 2.5 (q, 2, CH_2CH_3), ab centered at 3.9 and 4.9 (2, J = -7 Hz, 5-CH_2), between 4.3 and 4.4 (m, 2, =CH_2), between 7.3 and 7.8 (m, 8, arom. H's); ms: M^+ 348 (1 Cl). Product **41** from the column was crystallized from ethyl-acetate-hexane giving 0.16 g. (4.6%) of yellow crystals, m.p. 180-193° dec.; ir (Nujol): 1610, 1595, 1580, 1565, 1545 (C=N/C=C), 1475, 1445, 1395, 1350, 1290, 695 (other); uv max (ethanol): 313 mμ (ε 38,350), 350 (sh) (16,950), 328 (4,650); nmr (deuteriochloroform): δ 1.2 (d, 3, CH_3CH=C), 2.2 (s, 3, CH_3-C=N), ab centered at 4.1 and 4.9 (2, J = -8 Hz, 5-CH_2), 5.15 (m, 1, HCCH_3), between 7.2 and 7.8 (m, 8, arom. H's).

10-Chloro-1,2,3,6-tetrahydro-9-phenyl[1,2,4]benzotriazino[4,3-*a*]-[1,4]benzodiazepine Ethyl Acetate Solvate (**42**).

To a solution of 5.69 g. (0.02 mole) of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine (9) in 75 ml. of tetrahydrofuran, under nitrogen, was slowly added with stirring 2.24 g. (0.02 mole) of 1,2-cyclohexanedione. After refluxing for 4 hours the solution was evaporated *in vacuo*, dissolved in methylene chloride, washed with water and dried over sodium sulfate. Filtration and evaporation *in vacuo* gave crude (7-chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)monohydrazone of 1,2-cyclohexanedione which failed to crystallize.

This crude hydrazone was added to 20 ml. of liquid hydrogen fluoride at -80°, and the solution was allowed to evaporate overnight in the hood. The residue was mixed with ice and sodium bicarbonate and extracted with methylene chloride. After evaporation *in vacuo* the residue was chromatographed on silica gel eluting with 2% methanol in chloroform. The product crystallized from ethyl acetate yielding 0.52 g. (7%) of yellow solid, m.p. 180-182° (after softening at 130°). A sample for analysis, recrystallized from methylene chloride-ethyl acetate, had the same melting point; ir (Nujol): 1730 (ethyl acetate of solvation), 1625, 1610, 1595, 1570, 1540, 1480 (C=N/C=C), 1345, 1325, 1240 (other); uv max (ethanol): 218 mμ (ε, 34,100), 250 sh (16,000), 350 (3,200); nmr (deuteriochloroform): δ 1.25 (t, $CH_3CH_2OCOCH_3$ of solvation), between 1.5 and 2.3 (m, -CH_2CH_2- and $CH_3CH_2OCOCH_3$ of solvation), 2.6 (q, 2, CH_2CH), 4.13 (q, $CH_3CH_2OCOCH_3$ of solvation), ab centered at 3.9 and 4.8 (2, J = -11 Hz, 6-CH_2), 5.0 (m, 1, CH_2CH=), between 7.3 and 7.8 (m, 8, arom. H's).

2-(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)hydrazide of Oxalic Acid Ethyl Ester (**15**).

A solution of 1.42 g. (0.005 mole) of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine (9) and 0.8 ml. (0.0055 mole) of dried triethylamine in 25 ml. of tetrahydrofuran, under nitrogen, was cooled to -80° and a solution of 0.615 ml. (0.0055 mole) of ethyl oxalyl chloride in 25 ml. of tetrahydrofuran was added dropwise with stirring during 20 minutes. After stirring at -80° for 1 hour and at room temperature for 2 hours the mixture was

evaporated *in vacuo*, well mixed with ice, aqueous sodium bicarbonate and methylene chloride. Part of the product remained as a crystalline solid and more was obtained by concentration of the methylene chloride solution. The yield was 1.03 g. (53.5%) of white solid. A sample for analysis was recrystallized from ethanol, m.p. 173-175° dec.; ir (Nujol): 3180, 3140, 3060 (NH/OH), 1760, 1740, 1685 (C=O), 1625 (C=O/C=N), 1580, 1565, 1520, 1480 (C=N/C=C), 1400, 1325, 1295, 1205 (other) cm^{-1}; nmr (DMSO-d_6): δ 1.3 (t, 3, CH_2CH_3), between 3.9 and 4.8 (m, 4, two CH_2's), between 7.05 and 7.08 (m, 8, arom. H's), 9.6 and 10.8 (two broad exchangeable bands, 1 each, NH's); ms: M^+ 384 (1 Cl).

9-Chloro-3,5-dihydro-7-phenyl-*as*-triazino[4,3-*a*][1,4]benzodiazepine-1,2-dione (**43**).

A solution of 1.0 g. (0.0026 mole) of **15** in 25 ml. of dried pyridine was stirred, under nitrogen, under reflux for 2 hours and allowed to stand at room temperature overnight. Evaporation *in vacuo* below 45° gave a gum which was dissolved in methylene chloride, filtered, again evaporated, and crystallized from ethyl acetate yielding 0.76 g. (86%) of white crystals, m.p. 260-263° dec. Recrystallization from 2-propanol gave white crystals, m.p. 267-273° dec., and recrystallization from dioxane gave white crystals, m.p. 289-294° dec. All samples contained solvent of crystallization and all melting points showed sintering much below the decomposition. Prolonged drying at 100°, *in vacuo*, reduced the solvent to less than 0.1 mole; ir (Nujol): 3180, 3100 (NH/=CH), 1725, 685 (C=O), 1650 (C=N), 1595, 1580, 1485, 1450 (C=N/C=C), 820, 790, 745, 695 (arom./other) cm^{-1}; uv max (ethanol): 223 mμ (ε, 32,950), 255 sh (14,350), 269 sh (12,500), 315 sl. sh (4,750), 330 sl. sh (2,100); nmr (DMSO-d_6): δ ab centered at 4.1 and 4.8 (2, J = -12 Hz, 5-CH_2), between 7.25 and 8.0 (m, 8, arom. H's), ms: M^+ 338 (1 Cl).

9-Chloro-3,5-dihydro-3-methyl-7-phenyl-*as*-triazino[4,3-*a*][1,4]-benzodiazepine-1,2-dione (**44**).

To a solution of 0.678 g. (0.002 mole) of **43** in 30 ml. of tetrahydrofuran, under nitrogen, was added with stirring 0.1 g. (0.0022 mole) of 50% sodium hydride in mineral oil. After 5 minutes, 0.62 ml. (0.01 mole) of methyl iodide was added dropwise during 10 minutes. The solution was stirred for 3 hours, evaporated *in vacuo* and well shaken with ice water and ether. The resulting crystalline solid was collected, washed with water and ether and dried yielding 0.48 g. (68%) of white solid, m.p. 261-265°. A sample for analysis was recrystallized from methanol, m.p. 266-267°; ir (Nujol): 1730, 1680 (C=O), 1635, 1605 (C=N), 1480 (C=C), 1345, 1320, 700 (other) cm^{-1}; nmr (deuteriochloroform): δ 3.59 (s, 3, CH_3), ab centered at 4.05 and 4.9 (2, J = -12 Hz, 5-CH_2), between 7.25 and 7.85 (m, 8, arom. H's), ms: M^+ 352 (1 Cl).

9-Chloro-3-[3-[2-(*p*-fluorophenyl)-5,5-dimethyl-1,3-dioxan-2-yl]-propyl]-3,5-dihydro-7-phenyl-*as*-triazino[4,3-*a*][1,4]benzodiazepine-1,2-dione (**45**).

To a solution of 0.678 g. (0.002 mole) of **43** in 15 ml. of dimethylformamide, under nitrogen, was added with stirring 0.11 g. (0.0025 mole) of 50% sodium hydride in mineral oil. After stirring for 30 minutes, 0.42 g. (0.0025 mole) of potassium iodide and 0.63 g. (0.0022 mole) of 2-(3-chloropropyl)-2-(*p*-fluorophenyl)-2,2-dimethyl-1,3-dioxane were added. The mixture was stirred for 3.5 hours on a steam bath and allowed to stand at room temperature overnight. The mixture was evaporated *in vacuo* and the residue was shaken with ice water and ether. The ether solution was washed with sodium bicarbonate, water, saturated sodium chloride solution, and dried over sodium sulfate. After filtration the solution was evaporated, the residue was crystallized from ether, and dried *in vacuo* yielding 0.54 g. (46%) of white solid, m.p. 155-160°; ir (Nujol): 1720, 1680 (C=O), 1635, 1610 (C=N), 1580, 1565, 1505 (C=C), 1320, 1225, 1175, 1080, 835, 700, 695 (arom./other) cm^{-1}; nmr (deuteriochloroform): δ 0.56 (s, 3, CH_3), 1.25 (s, 3, CH_3), 1.82 (m, 4, two CH_2's), 3.38 (s, 4, two OCH_2's), about 4.0 (broad, 2, N-CH_2), ab centered at 4.0 and 4.9 (2, J = -13 Hz, 5-CH_2), between 6.75 and 7.85 (m, 12, arom. H's); ms: M^+ 588 (1 Cl).

9-Chloro-3,5-dihydro-3-[3-(*p*-fluorobenzoyl)-propyl]-7-phenyl-*as*-triazino[4,3-*a*][1,4]benzodiazepine-1,2-dione (**46**).

Crude **45** prepared from 0.678 g. (0.002 mole) of **43** as described above was dissolved in 50 ml. of methanol, filtered and acidified (*p*H 1.3) with 5 ml. of 2.5 *N* hydrochloric acid. After standing at room temperature for 95 minutes the mixture was neutralized with 50 ml. of ice-water and 20 ml. of 5% sodium bicarbonate. The precipitate was collected, washed with water and dried giving tan solid which was chromatographed on silica gel eluting with 70% hexane, 25% methylene chloride, 5% 2-propanol. The product was dissolved in 2-propanol and concentrated yielding 0.31 g. (31%) of yellow-tan solid with no distinct melting point. Tlc (silica, 60% ethyl acetate/cyclohexane) showed only one spot (Rf. 1.5); ir (Nujol): 1725, 1680 (C=O), 1635, 1600 (C=N), 1505 (C=C), 1400, 1320, 1225, 1155, 830, 705, 695 (other); uv max (ethanol): 233 mμ (ε, 38,400), 265 sh (14,500); ms: M^+ 502 (1 Cl).

2-(7-Chloro-5-phenyl-3*H*-1,4-benozdiazepin-2-yl)-2-methylhydrazide of Oxalic Acid, Ethyl Ester (**16**).

A solution of 1.5 g. (0.05 mole) of 7-chloro-2-(1-methylhydrazino)-5-phenyl-3*H*-1,4-benzodiazepine (12) and 84 ml. (0.06 mole) of triethylamine in 25 ml. of tetrahydrofuran, under nitrogen, was cooled to -80° and 0.62 ml. (0.0055 mole) of ethyl oxalyl chloride in 10 ml. of tetrahydrofuran was added dropwise with stirring. After stirring at -80° for 0.5 hours and at 0° for 3 hours, the mixture was evaporated *in vacuo*. The residue was mixed with ice and sodium bicarbonate solution, and extracted with ether. The extract was washed with water, dried over sodium sulfate, filtered and evaporated. The residue was crystallized from absolute ether yielding 0.7 g. (35%) of white crystals, m.p. 142-146°; ir (Nujol): 3100, 2800 broad (NH), 1715 (C=O), 1610, 1585, 1530 (C=O/C=N/C=C), 1385, 1310, 1260, 1130, 1115, 1020, 785, 700 (arom./other) cm^{-1}; nmr (deuteriochloroform): δ 1.2 (t, 3, OCH_2CH_3), 3.0 (s, 3, NCH_3), 4.25 (q, 2, OCH_2CH_3), about 3.4-5.1 very broad (s, 2, -3-CH_2), between 7.0 and 7.3 (m, 8, arom. H's); ms: M^+ 502 (1 Cl).

7-Chloro-2-(1,2-dimethylhydrazino)-5-phenyl-3*H*-1,4-benzodiazepine (**17**).

A mixture of 10.8 g. (0.037 mole) of 7-chloro-1,3-dihydro-5-phenyl-7*H*-1,4-benzodiazepin-2-thione, 28 ml. (0.2 mole) of triethylamine and 10 g. (0.075 mole) of 1,2-dimethylhydrazine dihydrochloride in 600 ml. of methanol was stirred under reflux for 10 hours and allowed to stand at room temperature for 4 days. The mixture was evaporated *in vacuo*, the residue was diluted with water, and basified giving solid product. This was collected, dried and recrystallized from 2-propanol yielding 10.1 g. (95%) of crystalline solid, m.p. 170-175°. A sample for analysis was again recrystallized from 2-propanol, m.p. 175.5-176.5°, ir (Nujol): 3240 (NH), 1600, 1575, 1540, 1520 (C=N/C=C), 1285, 1255, 1250 (C-N/other), 850, 925, 780, 755, 705 (arom./other) cm^{-1}; nmr (deuteriochloroform): δ 2.63 (d, 3, $NHCH_3$), 3.22 (s, 3, NCH_3), between 7.0 and 7.7 (m, 8, arom. H's).

9-Chloro-3,4-dihydro-3,4-dimethyl-7-phenyl-*as*-triazino[4,3-*a*]-[1,4]benzodiazepine-1,2-dione (**47**).

A solution of 2.04 g. (0.0065 mole) of **17** and 1.2 ml. (0.015 mole) of dry pyridine in 50 ml. of tetrahydrofuran, under nitrogen, was cooled to -80° and 0.585 ml. (0.007 mole) of oxalyl chloride was slowly added with stirring. After stirring at -80° for 1 hour and at room temperature overnight the mixture was evaporated *in vacuo*, mixed with water, basified with ammonium hydroxide and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, filtered and evaporated. The residue was chromatographed on silica gel, eluting with 2% methanol in chloroform. The product was crystallized first from 2-propanol and then from ethanol yielding 0.46 g. (20%) of yellow crystals, m.p. 250-253.5°; ir (Nujol): 1710, 1680 (C=O), 1600 (C=N), 1325, 1100 (C-N/other), 850, 845, 790, 700 (arom./other) cm^{-1}; nmr (deuteriochloroform): δ 2.97 (s, 3, CH_3), 3.27 (s, 3, CH_3), 7.01 (s, 1, 5-=CH), between 7.1 and 7.85 (m, 8, arom. H's); ms: M^+ 366 (1 Cl).

9-Chloro-3,5-dihydro-3-methyl-7-phenyl-*as*-triazino[4,3-*a*][1,4]-benzodiazepin-1(2*H*)one (**48**).

Ethyl (1-methylhydrazino)-acetate was prepared by slowly adding, with stirring, 10.52 ml. (0.1 mole) of ethyl chloroacetate in 100 ml. of ethanol to a solution of 9.2 g. (0.2 mole) of methylhydrazine in 100 ml. of ethanol, under nitrogen. After refluxing for 2.5 hours the solution was evaporated *in vacuo*, mixed with methylene chloride, dried over magnesium sulfate, and filtered. Evaporation yielded 8.5 g. of oil which was shown by nmr to be essentially the desired hydrazino ester; nmr (deuteriochloroform): δ 1.24 (t, 3, OCH_2CH_3), 2.58 (s, 3, NCH_3), 3.40 (s, 2, NCH_2CO), 3.95 (s, 2, NH_2), 4.17 (q, 2, OCH_2CH_3).

A solution of 1.98 g. (0.015 mole) of this ethyl (1-methylhydrazino)acetate and 3.0 g. (0.01 mole) of 7-chloro-2-methylthio-5-phenyl-3*H*-1,4-benzodiazepine in 15 ml. of glacial acetic acid was refluxed, under nitrogen, for 1 hour. After neutralization with ice and sodium bicarbonate the product was extracted with methylene chloride, dried over sodium sulfate, filtered and evaporated *in vacuo*. The residue was chromatographed on silica gel, eluting with 50% hexane, 40% methylene chloride and 10% 2-propanol. The product was crystallized from ethyl acetate-hexane yielding 0.45 g. (13%) of light yellow crystals, m.p. 140-147°; ir (Nujol): 1720 (C=O), 1640, 1610 (C=N), 1600, 1580, 1485 (C=C), 1335, 1315 (other) cm^{-1}; uv max (ethanol): end absorption, 210 mμ, sh (ϵ, 39,050), 250 sh (18,400), 280 slight sh (7,500); nmr (deuteriochloroform): δ 2.88 (s, 3, NCH_3), ab centered at 3.15 and 3.70 (2, J = 8 Hz, 2-CH_2), ab centered at 4.15 and 4.75 (2, J = 7 Hz, 5-CH_2), between 7.3 and 7.8 (m, 8, arom. H's).

9-Chloro-3,5-dihydro-2,3-dimethyl-7-phenyl-*as*-triazino[4,3-*a*]-[1,4]benzodiazepin-1(2*H*)one (**49**).

Ethyl α-(1-methylhydrazino)propionate was prepared by slowly adding, under nitrogen, with stirring, 9.0 ml. (0.1 mole) of α-bromopropionic acid in 94 ml. of ethanol to a solution of 9.2 g. (0.2 mole) of methylhydrazine in 120 ml. of ethanol. After refluxing for 1 hour the solution was strongly acidified with hydrogen chloride gas and refluxed for 1.5 hours more. The solution was filtered, evaporated *in vacuo* and basified with aqueous sodium bicarbonate. The product was extracted with methylene chloride and the extract evaporated yielding 10.18 g. of oil which was distilled, b.p. 35-36°/0.15 mm; nmr (deuteriochloroform): δ 1.25 (t, 3, OCH_2CH_3), 1.30 (d, 3, CH_3CH), 2.58 (s, 3, NCH_3), 3.35 (q, 1, $CHCH_3$), 3.48 (s, 2, NH_2), 4.15 (q, 2, OCH_2CH_3).

A solution of 1.59 g. (0.0109 mole) of the above α-(1-methylhydrazino)propionate and 2.4 g. (0.008 mole) of 7-chloro-2-methylthio-5-phenyl-3*H*-1,4-benzodiazepine in 15 ml. of glacial acetic acid was refluxed, under nitrogen, for 1 hour. After neutralization with ice and sodium bicarbonate the product was extracted with methylene chloride, dried over sodium sulfate, filtered and evaporated *in vacuo*. The residue was chromatographed on silica gel, eluting with 50% hexane, 40% methylene chloride, and 10% 2-propanol. The product was crystallized from ethyl acetate-hexane yielding 0.83 g. (29%) of white crystals, m.p. 180-188°. A sample for analysis was recrystallized from the same solvent, m.p. 187-190°; ir (Nujol): 1715 (C=O), 1645, 1610 (C=N), 1610, 1600, 1580, 1480 (C=C), 1355, 1335, 1310, 1290 (other), 825, 780, 730, 705 (arom.) cm^{-1}; uv max (ethanol): 213 mμ (ϵ, 36,100), 245 sh (17,900), 280 slight sh (7,550); nmr indicates that this material exists in two forms (*cis* and *trans* at C-2), nmr (deuteriochloroform): δ 1.05 and 1.45 (two d's, 3, CH_3CH), 2.87 and 2.89 (two s's, 3, NCH_3), 3.08 and 3.80 (two q's, 1, CH_3CH), ab centered at 4.0 and 4.70/4.73 (disturbed) (2, J = 12 Hz, 5-CH_2), between 7.15 and 7.8 (m, 8, arom. H's).

9-Chloro-7-(*o*-chlorophenyl)-3,5-dihydro-3-[4,4-di(*p*-fluorophenyl)-butyl]-*as*-triazino[4,3-*a*][1,4]benzodiazepin-2(1*H*)one Ethyl Acetate Solvate (**50**).

A solution of 1.8 g. (0.005 mole) of 9-chloro-7-(*o*-chlorophenyl)-3,5-dihydro-*as*-triazino[4,3-*a*][1,4]benzodiazepin-2(1*H*)one (**5**) in 25 ml. of dimethylformamide, under nitrogen, was treated at room temperature with 0.132 g. (0.0055 mole) of 50% sodium hydride in mineral oil. After stirring for 30 minutes, 1.4 g. (0.005 mole) of 1-chloro-4,4-di(*p*-fluorophenyl)butane, and 0.83 g. (0.005 mole) of potassium iodide were added and the mixture was stirred at 80° for 3 hours. Most of the solvent was removed *in vacuo*, the residue was dissolved in methylene chloride, washed with aqueous sodium bicarbonate, then with water and dried over sodium sulfate. After filtration and evaporation *in vacuo* the residue was chromatographed on silica gel, eluting with 60% hexane, 35% methylene chloride, and 5% 2-propanol. The product, showing only one spot on tlc (silica, 60% hexane/35% methylene chloride/5% 2-propanol) was obtained by evaporation but could not be crystallized. An amorphous sample from ethyl acetate-hexane, dried at 50°/high vacuum overnight, was found by nmr and melt solvate to contain about 0.2 mole of ethyl acetate; ir (Nujol): 1735 (CO of ethyl acetate), 1670 (C=O), 1635 (C=N), 1605, 1505 (C=N/C=C), 1225 (C-F), 830 (arom.) cm^{-1}; nmr (deuteriochloroform): δ 1.3 (t, OCH_2CH_3 of ethyl acetate of solvation), between 1.6 and 1.8 (m, 2, -$CH_2CH_2CH_2$-), 2.0 (m, 2, -CH_2CH_2CH), 2.07 (s, CH_3CO of ethyl acetate of solvation), 3.8 (m, N-CH_2), 3.9 (m, CH_2CH), 4.15 (q, OCH_2CH_3 of ethyl acetate of solvation), 4.3 (broad s, NCH_2CO), between 4.6 and 5.2 very broad (s, 2, 5-CH_2), between 6.8 and 7.6 (m, 15, arom. H's); ms: M^+ 603 (1 Cl).

9-Chloro-7-(*o*-chlorophenyl)-3[-(*p*-fluorobenzoyl)propyl]-3,5-dihydro-*as*-triazino[4,3-*a*][1,4]benzodiazepin-2(1*H*)one (**51**).

A solution of 1.8 g. (0.005 mole) of 9-chloro-7-(*o*-chlorophenyl)-3,5-dihydro-*as*-triazino[4,3-*a*][1,4]benzodiazepin-2(1*H*)-one (5) in 25 ml. of dimethylformamide, under nitrogen, was treated at room temperature with 0.132 g. (0.0055 mole) of 50% sodium hydride in mineral oil. After stirring for 30 minutes, 1.43 g. (0.005 mole) of 2-(3-chloropropyl)-2-(*p*-fluorophenyl)-5,5-dimethyl-*m*-dioxane and 0.38 g. (0.005 mole) of potassium iodide were added and the mixture was stirred at 80° for 3 hours. Most of the solvent was removed *in vacuo*, the residue was dissolved in methylene chloride, washed with water and dried over sodium sulfate. After filtration and evaporation *in vacuo* the residue was dissolved in 100 ml. of methanol and acidified, under nitrogen, with 16 ml. of 2.5 *N* hydrochloric acid. After stirring for 18 hours at room temperature the mixture was concentrated *in vacuo* and the residue was dissolved in methylene chloride, washed with

aqueous sodium bicarbonate, then with water and dried over sodium sulfate. After filtration and evaporation *in vacuo* the residue was chromatographed on silica gel, eluting with 50% hexane, 40% methylene chloride and 10% 2-propanol. The product fraction showing only one spot on tlc (silica, 50% hexane/40% methylene chloride/10% 2-propanol) was evaporated but failed to crystallize. An amorphous sample from ethyl acetate-hexane was dried at 50°/high vacuum overnight, but still contained a trace of ethyl acetate of solvation; ir (Nujol): 1735 (weak) (ethyl acetate of solvation), 1670 (C=O), 1635 (C=N), 1600, 1505, 1490 (C=N/C=C), 1305, 1225, 1165 (C-F/other), 835 (arom.); nmr (deuteriochloroform): δ 1.25 (t, trace OCH_2CH_3 of ethyl acetate of solvation), 2.2 (m, 2, $CH_2CH_2CH_2$), 3.0 (t, 2, CH_2CH_2CO), 3.85 (t, 2, NCH_2CH_2), about 4.35 (broad s, 2, NCH_2CO), between 4.6 and 5.2 (very broad s, 2, 5-CH_2), between 6.85 and 8.15 (m, 11, arom. H's); ms: M^+ 522 (1 Cl).

(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)hydrazone of Chloroacetaldehyde (**18**).

A solution of 2.85 g. (0.01 mole) of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine (9) in 38 ml. of tetrahydrofuran was cooled, under nitrogen, to -80° and 0.82 ml. (0.013 mole) of freshly prepared anhydrous chloroacetaldehyde (13) was added dropwise with stirring. After 3 hours at -80° and 16 hours at -15° the solution was evaporated *in vacuo* and the crystalline residue was boiled with 800 ml. of absolute ether and filtered. The filtrate was concentrated to 100 ml. and cooled in the refrigerator yielding 1.8 g. (52%) of nearly white crystals, m.p. 210-235° dec.; ir (Nujol): 3280 (NH), 1645, 1610, 1605, 1580, 1485 (C=N/C=C), 820, 695 (arom. H's) cm^{-1}; nmr (deuteriochloroform): δ 4.20 (d, 2, $CHCH_2Cl$), 4.45 (s, 2, 3-CH_2), between 6.9 and 8.0 (m, 10, N=CH, NH, arom. H's); ms: M^+ 345 (1 Cl).

(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)hydrazone of 2-Chlorocyclopentanone (**19**).

A solution of 5.7 g. (0.02 mole) of 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine (9) in 75 ml. of tetrahydrofuran, under nitrogen, was cooled to 0° and a solution of 2.5 g. (0.021 mole) of 2-chlorocyclopentanone in 10 ml. of tetrahydrofuran was added dropwise, with stirring. After stirring for 5 hours at 0° the mixture was evaporated *in vacuo*. The resulting gum became solid on mixing with methanol and was collected and dried giving 5.1 g. of tan solid. This was recrystallized from ethyl acetate yielding 3.05 g. (40%) of nearly white crystals with no definite melting point; ir (Nujol): 3260 (NH), 1655, 1615, 1580, 1560, 1485 (C=N/C=C), 825, 700 (arom.) cm^{-1}; nmr (deuteriochloroform): δ 1.8-2.2 (m, 4, CH_2-CH_2CH_2CH), about 2.6 (m, 2, $=CH_2CH_2$), 4.45 (broad s, 2, 3-CH_2), 4.75 (broad t, 1, $ClCHCH_2$), between 7.0 and 7.6 (m, 8, arom. H's), 8.5 (broad s, 1, NH); ms: M^+ 385 (2 Cl).

7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)hydrazone of 2-Methoxycyclopentanone Hydrochloride (**20**).

A solution of 2.7 g. (0.007 mole) of **19** in 100 ml. of methanol was stirred under reflux for 10 minutes, concentrated to 5 ml., diluted with 50 ml. of acetone, filtered, and cooled in the refrigerator overnight. The resulting solid was collected, washed with acetone and ether and dried giving 1.4 g. (47%) of light tan solid, m.p. 174-177° dec. Melt solvate indicated 7.2% methanol which was no doubt formed by elimination of the methoxyl during the determination. Calcd: Methanol 7.68%; ir (Nujol): about 3000 and 2700 broad ($NH/\overset{+}{N}H$), 1655 (C=N), 1615, 1535, 1485 (C=N/C=C), 1090 (C-O), 785, 695 (arom.) cm^{-1}; nmr (deuteriochloroform): δ 1.4-2.1 (m, 4, $CH_2CH_2CH_2CH$), 2.4-3.1 (m, 2, $=CCH_2CH_2$), 3.5 (s, 3, OCH_3), 3.8-5.5 (m's 3, $CHOCH_3$ and 3-CH_2), between 7.1 and 8.1 (m, 8, arom. H's); ms: M^+ 380 (1 Cl).

(7-Chloro-5-(*o*-chlorophenyl)-3*H*-1,4-benzodiazepin-2-yl)hydrazone of Acetone (**22**).

A solution of 3.2 g. (0.01 mole) of 7-chloro-5-(*o*-chlorophenyl)-2-hydrazino-3*H*-1,4-benzodiazepine (10) in 75 ml. of acetone was refluxed for 40 minutes and concentrated to 10 ml. The solution was boiled while adding hexane until crystallization started. After cooling the product was collected and dried yielding 3.5 g. (97%) of white crystals, m.p. 166-168°; ir (Nujol): 3140, 3020 (NH), 1595, 1565, 1485 (C=N/C=C), 1355, 1250 (C-N/other), 820, 765, 750 (arom.) cm^{-1}; nmr (deuteriochloroform): δ 2.02 and 2.04 (two s's, 6, two CH_3's), 4.50 (s, 2, 3-CH_2), between 6.85 and 7.65 (m, 7, arom. H's); ms: M^+ 358 (2 Cl).

7-Chloro-1,3-dihydro-1-(2,2-dimethoxyethyl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**52**).

A solution of 27.1 g. (0.1 mole) of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one in 300 ml. of dry dimethylformamide, under nitrogen, was treated with 4.6 g. (0.11 mole) of 57% sodium hydride in mineral oil. After stirring at room temperature for 1 hour, 25.4 g. (0.15 mole) of bromoacetaldehyde dimethyl acetal in 10 ml. of dimethylformamide was added. The solution was stirred at 100° for 16 hours, concentrated *in vacuo* to 150 ml., mixed with ice water and extracted with methylene chloride. The extract was washed with water, dried over sodium sulfate, filtered and evaporated *in vacuo* giving a brown oil. This was crystallized from 2-propanol yielding 26.2 g. (73%) of tan crystals, m.p. 115-117.5°. A sample for analysis was chromatographed, and recrystallized from 2-propanol, m.p. 117-119°; ir (Nujol): 1670 (C=O), 1610, 1575, 1565, 1490, 1480 (C=N/C=C), 1325, 1125, 1050 (C-O/C-N), 940, 845, 820, 790, 743, 715, 700 (arom./other) cm^{-1}; nmr (deuteriochloroform): δ 3.15 and 3.31 (two s's, 6, two OCH_3's), between 3.45 and 5.0 (m, 5, two CH_2's and CH), between 7.2 and 7.85 (m, 8, arom. H's); ms: M^+ 358 (1 Cl).

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