Synthesis of *s*-Triazolocycloalkyl-, *s*-Triazolobenzocycloalkyl-, and *s*-Triazolocycloalkylhydrothiadiazines

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The reaction of cyclic-α-haloketones with 5-substituted-4-amino-4*H*-1,2,4-triazole-3-thiols gave *s*-triazolocycloalkylhydrothiadiazines and *s*-triazolobenzocycloalkylthiadiazines. Reduction of the 5,5a-imine bond of the *s*-triazolocycloalkylthiadiazines gave *s*-triazolocycloalkylhydrothiadiazines.

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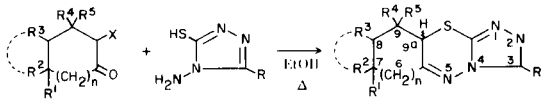
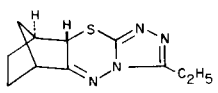
Synthesis of condensed triazole heterocycles, particularly *s*-triazolothiadiazines have been reported (1-3). Pharmacologic evaluation as potential anti-inflammatory and analgesic agents also has been reported (4). We have prepared a series of *s*-triazolocycloalkylthiadiazines, *s*-triazolobenzocycloalkylthiadiazines and their reduction products, the *s*-triazolocycloalkylhydrothiadiazines, for pharmacologic evaluation and wish to report the synthesis of these compounds.

The *s*-triazolocycloalkylthiadiazines (Table I) and the *s*-triazolobenzocycloalkylthiadiazines (Table II) were prepared by cyclization of the appropriate α-haloketone I with a substituted 4-amino-4*H*-1,2,4-triazole-3-thiol II in absolute ethanol.



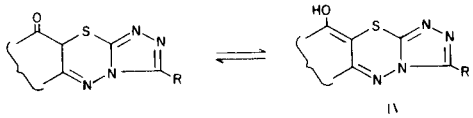
I II III

The ^{1}H nmr chemical shift of the methine proton adjacent to the sulfur atom was very characteristic for the *s*-triazolocycloalkylthiadiazines (Table I). It appeared in the ^{1}H nmr spectrum between 3.7 and 4.8 δ (deuteriochloroform) generally as a complex multiplet. The identification of this proton (9a position for compounds in which n = 1) allowed a stereochemical assignment to be made for the bicyclic compound **13**. The structure of **13** was assigned as the *endo* isomer with the 9a proton on the β face of the molecule. This structural assignment was based on the appearance of a sharp doublet at 3.75 δ (J = 5.0 Hz) for the 9a proton (5).

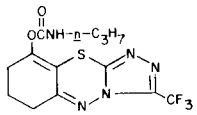


13

In examples in which an α-halo-β-diketone (I, where R^4, R^5 = oxo) was allowed to react with II the resulting products existed predominantly in the enolic form IV. The carbonyl stretching frequency in the ir spectra was absent and the characteristic 9a methine proton did not appear in the ^{1}H nmr spectra of these compounds. When **7** was treated with *n*-propylisocyanate, the carbamate **8** was obtained; this reaction product provided chemical evidence of the enol tautomer for compounds **7** as well as **5**, **12**, **21** and **24**.



IV



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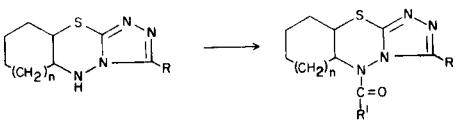
Compounds in Tables I and II are weak bases and in general form hydrohalide salts. The basicity is dependent upon the R substituent (Formula III) in that neither **6** (R = CF_3) nor **25** (R = C_6H_5) could be converted into their respective hydrochloride salts.

The triazolocycloalkylhydrothiadiazines V (Table III) were obtained by the reduction of certain compounds in Table I with either sodium borohydride or vitride. The reduction products were obtained as a mixture of *cis* and *trans* isomers. Enolic derivatives such as **5** could not be reduced with sodium borohydride under the same conditions.

V

The reactivity of the reduced compounds was demonstrated by the susceptibility of **48**, **53** and **55** to acylation with either acid chlorides, acid anhydrides or isocyanates.



48, R = C_2H_5, n = 1
53, R = CH_3, n = 2
55, R = C_2H_5, n = 2

49, R = C_2H_5, n = 1, R^1 = CHCHC_6H_5
50, R = C_2H_5, n = 1, R^1 = $NHCH_2CO_2C_2H_5$
54, R = CH_3, n = 2, R^1 = NHC_6H_5
56, R = C_2H_5, n = 2, R^1 = CH_3

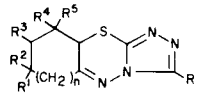
In conclusion, this research has demonstrated the very general facile cyclization reaction between substituted 4-amino-4*H*-1,2,4-triazole-3-thiols and α-haloketones. It has also provided novel compounds for pharmacologic evaluation.

EXPERIMENTAL

Melting points were determined in open capillaries in a Thomas-Hoover apparatus and are uncorrected. The infrared and ultra-

Table I

Triazolocycloalkylthiadiazines



Compound	R	R^1	R^2	R^3	R^4, R^5	n	Preparative Method (a)	M.p., °C	Crystallization Solvent	Formula	% Yield
1	C_2H_5	H	H	H	H, H	0	A	83-85	Ether	$C_{13}H_{20}N_4S$	53
2	H	H	H	H	H, H	1	A	146-147.5	Dichloromethane-ether	$C_8H_{10}N_4S$	43
3	CH_3	H	H	H	H, H	1	A	103-104	Ether	$C_9H_{12}N_4S$	72
4	CH_3	H	H	H	H, CH_3	1	B	124-127	Ether	$C_{10}H_{14}N_4S$	14
5	CH_3	CH_3	CH_3	H	=O	1	C	246-247	Ether	$C_{11}H_{14}N_4OS$	43
6	CF_3	H	H	H	H, H	1	B	100-101	Ether	$C_9H_9F_3N_4S$	20
7	CF_3	CH_3	CH_3	H	=O	1	C	225-226	Ethanol-water	$C_{11}H_{11}F_3N_4OS$	47
8(b)							see Exptl.	116-117.5	Ethyl acetate-hexane	$C_{15}H_{18}F_3N_5O_2S$	53
9	C_2H_5	H	H	H	H, H	1	B	69-70	Methanol-water	$C_{10}H_{14}N_4S$	95
10	C_2H_5	H	H	C_2H_5	H, H	1	B	76-79	Ether	$C_{12}H_{18}N_4S$	30
11	C_2H_5	H	H	$C(CH_3)_3$	H, H	1	B	130-132	Ether	$C_{14}H_{22}N_4S$	19
12	C_2H_5	H	H	H	=O	1	C	223-224	Ethanol	$C_{10}H_{12}N_4OS$	52
13(b)							B	120-123	THF-hexane	$C_{11}H_{14}N_4S$	29
14	C_3H_7-*n*	H	H	H	H, H	1	B	73-74	Ether-hexane	$C_{11}H_{16}N_4S$	53
15	cyclo-C_3H_5	H	H	H	H, H	1	B	118-119	Methanol-water	$C_{11}H_{14}N_4S$	34
16	C_4H_9-*n*	H	H	H	H, H	1	A	160-162	Methanol-ether acetate	$C_{12}H_{18}N_4S$·HCl	61
17	C_7H_{15}-*n*	H	H	H	H, H	1	B	66-67	Dichloromethane-pentane	$C_{15}H_{24}N_4S$	72
18	$C_{13}H_{27}$-*n*	H	H	H	H, H	1	B	84-85	Dichloromethane-pentane	$C_{21}H_{36}N_4S$	34
19	CH_2OCH_3	H	H	H	H, H	1	B	62-63	Dichloromethane-hexane	$C_{10}H_{14}N_4OS$	67
20	$CH_2OC_2H_5$	H	H	H	H, H	1	B	78.5-79.5	Dichloromethane-heptane	$C_{11}H_{16}N_4OS$	42
21	$CH_2OC_2H_5$	H	H	H	=O	1	C	205-207	Ethanol	$C_{11}H_{14}N_4O_2S$	57
22	$CH_2OC_6H_5$	H	H	H	H, H	1	B	116-117	Dichloromethane-methanol	$C_{15}H_{16}N_4OS$	30
23	$CH_2CH_2OC_2H_5$	H	H	H	H, H	1	B	78-79	Dichloromethane-hexane	$C_{12}H_{18}N_4OS$	43
24	$CH_2CH_2OC_2H_5$	CH_3	CH_3	H	=O	1	C	206-207	Methanol	$C_{14}H_{20}N_4O_2S$	36
25	C_6H_5	H	H	H	H, H	1	B	187-188	Ethanol-water	$C_{14}H_{14}N_4S$	32
26	H	H	H	H	H, H	2	A	173-174.5	Methanol-ethyl acetate	$C_9H_{12}N_4S$·HCl	62
27	CH_3	H	H	H	H, H	2	A	170-171	Methanol-ethyl acetate	$C_{10}H_{14}N_4S$·HCl	73
28	CF_3	H	H	H	H, H	2	B	100-101	Ether-hexane	$C_{10}H_{11}F_3N_3S$	70
29	C_2H_5	H	H	H	H, H	2	A	143-144	Methanol-ethyl acetate	$C_{11}H_{16}N_4S$·HCl	57
30	C_3H_7-*n*	H	H	H	H, H	2	A	123-124	Methanol-ethyl acetate	$C_{12}H_{18}N_4S$·HCl	60
31	C_7H_{15}-*n*	H	H	H	H, H	2	A	96-97	Methanol-ethyl acetate	$C_{16}H_{26}N_4S$·HCl	33
32	$CH_2OC_6H_5$	H	H	H	H, H	2	A	155-157	Methanol-ethyl acetate	$C_{16}H_{18}N_4OS$·HCl	77
33	CH_3	H	H	H	H, H	3	A	187-189	Methanol-ethyl acetate	$C_{11}H_{16}N_4S$·HCl	56
34	C_2H_5	H	H	H	H, H	3	B	94-95	Dichloromethane-hexane	$C_{12}H_{16}N_4S$	68
35	C_3H_7-*n*	H	H	H	H, H	3	A	144-145	Methanol-ethyl acetate	$C_{12}H_{18}N_4S$·HCl	60
36	C_7H_{15}-*n*	H	H	H	H, H	3	A	119-120	Ether	$C_{17}H_{28}N_4S$·HCl	38

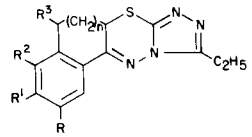
Table I (Continued)

Compound	R	R^1	R^2	R^3	R^4, R^5	n	Preparative Method (a)	M.p., °C	Crystallization Solvent	Formula	% Yield
					H, H	3	B	93-94	Dichloromethane-heptane	$C_{13}H_{20}N_4S$	75
37	$CH_2OC_2H_5$	H	H	H	H, H	7	B	138-139	Dichloromethane-hexane	$C_{15}H_{24}N_4S$	21
38	CH_3	H	H	H	H, H	7	A	155-157	Methanol-ethyl acetate	$C_{16}H_{26}N_4S \cdot HCl$	15
39	C_2H_5	H	H	H							

(a) See Experimental for details. (b) Structure given in text.

Table II

Triazolobenzocycloalkylthiadiazines

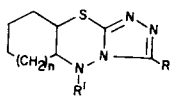


Compound	R	R^1	R^2	R^3	n	Preparative Method (a)	M.p., °C	Recrystallization Solvent	Molecular Formula	% Yield
40	H	H	H	H	0	B	163-164	Ethanol-water	$C_{13}H_{12}N_4S$	56
41	OCH_3	OCH_3	H	H	0	B	211-212	Ethanol-water	$C_{15}H_{16}N_2O_2S$	28
42	H	H	H	H	1	B	130-132	Benzene-hexane	$C_{14}H_{14}N_4S$	72
43	H	H	H	CH_3	1	B	156-158	Ethanol-water	$C_{15}H_{16}N_4S$	8
44	H	OCH_3	H	H	1	B	125-126	Benzene-hexane	$C_{15}H_{16}N_4OS$	26
45	H	H	OCH_3	H	1	B	163-164	Ethanol-water	$C_{15}H_{16}N_4OS$	35

(a) See Experimental for details.

Table III

Triazolocycloalkylhydrothiadiazines



Compound	R	R^1	n	Preparative Method (a)	M.p., °C	Recrystallization Solvent	Molecular Formula	% Yield
46	C_2H_5	H	0	D	92-94	Hexane-THF	$C_9H_{14}N_4S$	84
47	H	H	1	D	238-240	Methanol	$C_8H_{12}N_4S$	49
48	C_2H_5	H	1	D	168-169	Methanol-ethyl acetate	$C_{10}H_{16}N_4S \cdot HCl$	75
49	C_2H_5	$COCH{=}CHC_6H_5$	1	see Exptl.	140-141	Methanol-water	$C_{19}H_{22}N_4OS$	12
50	C_2H_5	$CONHCH_2CO_2C_2H_5$	1	see Exptl.	164-165	Ethanol-water	$C_{15}H_{23}N_5O_3S$	50
51	CH_2OCH_3	H	1	E	151.5-152.5	Ether	$C_{10}H_{16}N_4OS \cdot HCl$	15
52	C_6H_5	H	1	D	205-207	Ethanol-water	$C_{14}H_{16}N_4S \cdot HCl$	45
53	CH_3	H	2	D	193-194	Chloroform-methanol	$C_{10}H_{16}N_4S \cdot HCl$	57
54	CH_3	$CONHC_6H_5$	2	see Exptl.	213-215	Methanol	$C_{18}H_{23}N_5OS$	38
55	C_2H_5	H	2	D	172-175	Methanol-ethyl acetate	$C_{12}H_{20}N_4S \cdot HCl$	30
56	C_2H_5	$COCH_3$	2	see Exptl.	130-131	Ethyl acetate	$C_{13}H_{20}N_4OS$	38
57	$CH_2OC_6H_5$	H	2	D	131.5-132.5	Dichloromethane-heptane	$C_{16}H_{20}N_4OS$	42
58	C_2H_5	H	3	D	174-176	Methanol-ethyl acetate	$C_{12}H_{20}N_4S \cdot HCl$	30

(a) See Experimental for details.

Table IV

Elemental Analyses

Compound No.	*Anal.* Calcd.					*Anal.* Found				
	C	H	N	S	Cl	C	H	N	S	Cl
1	51.89	5.81	26.90			51.82	5.75	26.90		
2	49.46	5.19		16.51		49.12	5.15		16.38	
3	51.90	5.81	26.90			51.95	5.75	26.94		
4	54.02	6.35	25.21			53.83	6.30	25.43		
5	52.78	5.64		12.81		52.75	5.59		12.85	
6	41.22	3.46	21.36			41.34	3.53	21.15		
7	43.42	3.64	18.41			43.70	3.63	18.74		
8	46.27	4.66	17.98			46.35	4.63	17.85		
9	54.02	6.37		14.42		54.04	6.28		14.24	
10	57.57	7.25	22.38			57.63	7.20	22.50		
11	60.39	7.96	20.13			60.17	7.90	20.13		
12	50.83	5.12	23.71			50.83	5.07	23.67		
13	56.38	6.02	23.91			56.42	6.06	23.96		
14	55.90	6.82	23.71			56.04	6.86	23.67		
15	56.38	6.02		13.68		56.13	5.99		13.78	
16	50.25	6.68			12.36	50.13	6.69			12.36
17	61.61	8.27	19.16			61.60	8.27	19.17		
18	66.97	9.64	14.88			67.14	9.63	14.70		
19	50.40	5.92	23.51			50.29	5.93	23.82		
20	52.36	6.39	22.20			52.09	6.23	22.03		
21	49.61	5.30	21.04			49.50	5.29	21.09		
22	59.97	5.38	18.62			59.74	5.36	18.46		
23	54.09	6.82	20.97			54.13	6.75	20.97		
24	54.42	6.54	18.11			54.51	6.49	18.11		
25	62.20	5.22	20.72			62.32	5.28	21.07		
26	44.17	5.35	22.89			43.91	5.28	23.11		
27	43.47	5.84	21.65			43.47	5.80	21.83		
28	43.47	4.01	20.28			43.46	3.98	20.50		
29	48.43	6.28	20.54			48.37	6.24	20.85		
30	50.25	6.68	19.53			50.04	6.73	19.58		
31	56.04	7.94	16.34			55.97	7.91	16.50		
32	54.77	5.46	15.97			55.13	5.45	16.07		
33	48.43	6.28	20.54			48.08	6.30	20.80		
34	57.59	7.26	22.38			57.29	7.22	22.60		
35	51.90	7.04	18.62			51.76	7.08	18.60		
36	57.20	8.19	15.70			57.52	8.36	15.59		
37	55.69	7.19	19.98			55.87	7.20	20.20		
38	61.61	8.27	19.16			61.58	8.32	19.33		
39	56.04	7.94	16.33			56.01	7.96	16.33		
40	60.92	4.72	21.86			60.99	4.54	21.60		
41	56.95	5.10	17.71			56.98	4.97	17.88		
42	62.20	5.22	20.72			61.99	5.06	20.71		
43	63.35	5.67	19.70			63.28	5.61	19.66		
44	59.98	5.37	18.65			60.09	5.35	18.70		
45	59.98	5.37	18.65			59.80	5.30	18.80		
46	51.40	6.71	26.64			51.37	6.71	26.67		
47	48.96	6.16	28.54			48.72	6.10	28.68		
48	46.24	6.21	21.57			46.00	6.48	21.76		
49	64.38	6.26	15.62			64.23	6.31	15.62		

Table IV (Continued)

Compound No.	*Anal.* Calcd. C	H	N	S	Cl	*Anal.* Found C	H	N	S	Cl
50	50.97	6.36	19.81			50.94	6.53	19.94		
51	43.39	6.19	20.24			43.08	6.08	20.22		
52	54.45	5.55	18.14			54.54	5.45	18.09		
53	46.06	6.57			13.59	46.06	6.53			13.20
54	59.45	6.46	20.39			59.30	6.15	20.42		
55	48.08	6.97	20.39			47.95	6.92	20.68		
56	55.69	7.19	19.98			55.40	7.14	20.32		
57	60.73	6.37	17.71			60.50	6.37	17.59		
58	49.90	7.33	19.40			49.93	7.41	19.65		

violet spectra were obtained with a Perkin-Elmer 521 and Perkin-Elmer 350 recording spectrophotometer, respectively. The nuclear magnetic resonance spectra were recorded on a Varian A-60A spectrometer. All spectra were consistent with the proposed structures.

4-Amino-4*H*-1,2,4-triazole-3-thiols.

These intermediates were prepared according to published methods (2,6,7).

2-Halocycloalkanones.

Compounds that were not commercially available were prepared by bromination (cupric bromide) or chlorination (sulfuryl chloride) of the appropriate cycloalkanone. 2-Bromocyclohexane-1,3-dione and 2-bromo-5,5-dimethylcyclohexane-1,3-dione were prepared by the method of Crossley (8,9).

Triazolocycloalkyl- and Triazolobenzocycloalkylthiadiazines.

Method A.

In a typical example, 2-chlorocycloheptanone (Adams Chemical) (15 g., 0.101 mole) and 5-(phenoxymethyl)-4-amino-4*H*-1,2,4-triazole-3-thiol (22.2 g., 0.1 mole) were stirred under reflux in absolute ethanol (350 ml.) for 4 hours. Concentration of the solvent *in vacuo* afforded a yellow solid. Recrystallization from methanol-ethyl acetate afforded 26.1 g. (77%) of **32**, m.p. 155-157° as the hydrochloride salt.

Method B.

In a typical example 2-chlorocyclohexanone (Aldrich) (12 g., 0.09 mole) and 5-tridecyl-4-amino-4*H*-1,2,4-triazole-3-thiol (18 g., 0.06 mole) were stirred at reflux in absolute ethanol (500 ml.), 4 hours and concentrated *in vacuo* to a tan oil. The oil was dissolved in dichloromethane (250 ml.), extracted with 10% sodium hydroxide (2 x 100 ml.), washed with saturated sodium chloride (2 x 100 ml.) and dried (magnesium sulfate). Recrystallization from dichloromethane-pentane afforded 14.9 g. of crude solid. Two more recrystallizations from dichloromethane-pentane yielded 7.2 g. (33.6%) of **18**, m.p. 84-85°.

Method C.

In a typical example, 2-bromodimedone (66 g., 0.3 mole) and 5-methyl-4-amino-4*H*-1,2,4-triazole-3-thiol (39 g., 0.3 mole) were stirred under reflux in absolute ethanol (1450 ml.) for 4 hours. The solvent was removed *in vacuo* and the residue dissolved in 5% sodium hydroxide (800 ml.) filtered and acidified with 5% hydrochloric acid, which precipitated the free base 32.3 g. (43%). Three recrystallizations from ethanol afforded the analytical sample of **5**, m.p. 246-247°.

Triazolocycloalkylhydrothiadiazines.

Method D.

In a typical example, **29** (19.8 g., 0.078 mole) was converted to the free base and dissolved in 2-propanol (300 ml.). To this stirred solution, sodium borohydride (4 g., 0.105 mole) was added and the resulting suspension was heated at reflux for 17 hours; the excess sodium borohydride was then decomposed with methanol (150 ml.). The resulting clear solution was concentrated *in vacuo* to a yellow oily semisolid residue. The residue was dissolved in 5% hydrochloric acid (250 ml.) and the solution was filtered through celite. The filtrate was neutralized with 5% sodium hydroxide and the precipitated yellow oil was extracted with dichloromethane (400 ml.). The dichloromethane was washed with brine, separated, dried (magnesium sulfate) and filtered. The filtrate was saturated with gaseous hydrogen chloride and was then concentrated *in vacuo* to give a yellowish white solid. Recrystallization (methanol-ethyl acetate) gave 6.5 g. (30%) of **58**, m.p. 174-176°.

Method E.

Vitride (11.2 ml.) dissolved in dry THF (50 ml.) was added dropwise to a stirred solution of **19** (10.4 g., 0.044 mole) in THF (300 ml.) under a nitrogen atmosphere. The solution was stirred 3 hours at room temperature and the excess vitride was decomposed with water (100 ml.). The solution was extracted with dichloromethane (300 ml.) and then the dichloromethane was extracted with 10% hydrochloric acid. Neutralization of the hydrochloric acid solution gave an oil, 3.9 g. Saturation of an ethyl ether-THF solution of the oil with gaseous hydrogen chloride followed by chilling and recrystallization (THF-ethyl ether) afforded 1.8 g. (15%) of **51**, m.p. 151.5-152.5°.

Propylcarbamic Acid, Ester of 7,8-Dihydro-7,7-dimethyl-3-(trifluoromethyl)-6*H*-*s*-triazolo[3,4-*b*][1,3,4]benzothiadiazin-9-ol (**8**).

Propyl isocyanate (20 ml.) and **7** (7.4 g., 0.024 mole) were heated on a steam bath with occasional stirring for 15 minutes. Chilling the mixture afforded a crystalline mass. Recrystallization from ethyl acetate-hexane followed by recrystallization from carbon tetrachloride yielded **8**, 1.5 g. (16%), m.p. 116-117.5°.

5-*Trans*-Cinnamoyl-3-ethyl-5a,6,7,8,9,9a-hexahydro-5*H*-*s*-triazolo[3,4-*b*][1,3,4]benzothiadiazine (**49**).

A solution of the free base of **48** (2.6 g., 0.011 mole), *trans*-cinnamoyl chloride (2.6 g., 0.016 mole) and pyridine (15 ml.) in dry benzene (40 ml.) was heated and stirred at reflux for 30 minutes. Dilution of the cooled benzene solution with hexane yielded a tan semi-solid, which was recrystallized (methanol-water)

to give yellow needles, 0.45 g. (12%) of **49**, m.p. 140-141°.

N-[3-(Ethyl-5a,6,7,8,9,9a-hexahydro-5*H*-*s*-triazolo[3,4-*b*][1,3,4]-benzothiadiazin-5-yl)carbonylglycine Ethyl Ester (**50**).

Carbethoxymethyl isocyanate (13.0 ml.) and **48** (12.6 g., 0.057 mole) were heated and stirred for 15 minutes on the steam bath. Upon cooling, the solution solidified. The solid was washed with hexane (100 ml.) and then with cold 50% ethanol (100 ml.). The light tan solid (15.8 g.) was dried and recrystallized (ethanol-water) to give 10 g. (50%) of **50**, m.p. 164-165°.

N-[(3-Methyl-5a,6,7,8,9,10,11,11a-octahydro-5*H*-*s*-triazolo[3,4-*b*]-[1,3,4]cycloheptathiazin-5-yl)carbonylaniline (**54**).

A solution of the free base of **53** (6 g., 0.022 mole) and excess phenylisocyanate in dry benzene (200 ml.) was heated and stirred at reflux for 45 minutes. The resulting white precipitate was recrystallized twice (methanol) to yield 2.9 g. (38%) of **54**, m.p. 213-215°.

5-Acetyl-3-ethyl-5,5a,6,7,8,9,10,10a-octahydro-*s*-triazolo[3,4-*b*]-[1,3,4]cycloheptathiadiazine (**56**).

Compound **55** (25 g., 0.09 mole) was converted to the free base and heated at reflux with acetic anhydride (125 ml.) and sodium acetate (10 g.) for 20 hours. Concentration of the resulting suspension *in vacuo* gave a brown semi-solid. The semi-solid was dissolved in a two-phase dichloromethane-water solution and the dichloromethane layer separated, washed with brine and dried (magnesium sulfate). Filtration and concentration of the dichloromethane-heptane) gave brown crystals 12.5 g., m.p. 119-123°. A second recrystallization (ethyl acetate, norit) gave 9.5 g. (38%) of **56**, m.p. 130-131°.

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