1,2,4-Triazines VIII (1). The Synthesis of 1,2,4-Triazino[2,3-*e*]pyrazolo[1,5-*a*]-1,3,5-triazines and 1,2,4-Triazino[4,3-*e*]pyrazolo[1,5-*a*]-1,3,5-triazines

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Substituted 2,5-dihydro-3[3-methyl(or phenyl)-5-aminopyrazolyl]-1,2,4-triazin-5-ones reacted with orthoesters to yield exclusively 1,2,4-triazino[2,3-*e*]pyrazolo[1,5-*a*]-1,3,5-triazin-5-ones. The structure elucidation was supported by independent synthesis of the isomeric 1,2,3-triazino-[4,3-*e*]pyrazolo[1,5-*a*]-1,3,5-triazin-7-one as well as by spectroscopical methods.

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As part of a continuing research program on the chemistry of 1,2,4-triazines (2-4), we now report the synthesis and structure elucidation of two new tricyclic series having a fused 1,2,4-triazine ring system.

3-Hydrazino-1,2,4-triazin-5-ones (**3**) (5,6) used as starting materials for this study, were prepared by the displacement of the methylthio group of the corresponding 3-methylthio-1,2,4-triazin-5-ones (2) by hydrazine. The synthesis of **2** was accomplished by methylation of 6-substituted-2,3,4,5-tetrahydro-1,2,4-triazin-5-one-3-thiones (**1**) which in turn were prepared by interaction of ethyl pyruvate for **1a** (5) or phenylglyoxaldoxime for **1b** (7) and thiosemicarbazide in alkali solutions. The reaction of **3** in acid solutions with 3-iminobutyronitrile (8) afforded high yields of 6-methyl(or phenyl)-3-[3-methyl-5-aminopyrazolyl]-2,5-dihydro-1,2,3-triazin-5-ones (**4a,4b**). Similarly,

Scheme I

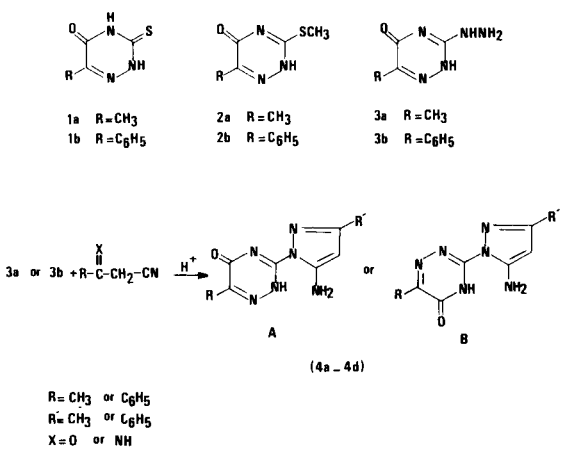
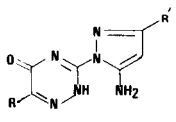


Table I



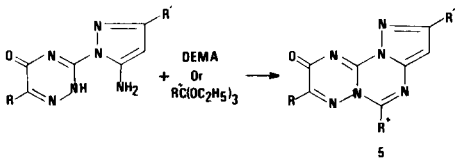
Compound No.	R	R′	Yield %	M.p. °C	Formula	Analyses C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found
4a	CH_3	CH_3	83	274-280	$C_8H_{10}N_6O$	46.60	46.51	4.85	4.79	40.77	40.69
4b	C_6H_5	CH_3	58	205-210	$C_{13}H_{12}N_6O$	58.20	58.25	4.47	4.39	31.34	31.44
4c	CH_3	C_6H_5	69	280-288	$C_{13}H_{12}N_6O$	58.20	58.11	4.47	4.53	31.34	31.29
4d	C_6H_5	C_6H_5	64	219-221	$C_{18}H_{14}N_6O$	65.45	65.51	4.24	4.31	25.45	25.39

α-cyanoacetophenone (9) and **3** in acetic acid medium gave high yields of 6-methyl(or phenyl)-3-[3-methyl-5-aminopyrazolyl]-2,5-dihydro-1,2,4-triazin-5-ones (**4c,4b**) Structure A. Compounds **4** are expected to exist also in the tautomeric 4,5-dihydro form, Structure B. (See Scheme I.)

Compounds **4** that were prepared are reported in Table I.

Compounds **4** were allowed to react with diethoxymethyl acetate (DEMA) (10) or orthoesters, and found to afford tricyclic compounds. The elemental analyses and mass spectra of the compounds obtained corresponded to either substituted 1,2,4-triazino[2,3-*e*]pyrazolo[1,5-*a*]-1,3,5-triazin-9-ones (**5**) or 1,2,4-triazino[4,3-*e*]pyrazolo-[1,5-*a*]-1,3,5-triazin-7-ones (**6**). Ring formation between the amino group of pyrazole and N_2 or N_4 of the triazine ring would afford compounds **5** or **6**, respectively. The

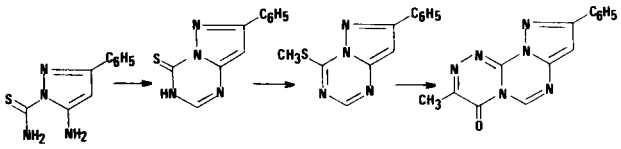
Scheme II



5

5a R=R′=CH_3, R″=H
5b R=R′=R″=CH_3
5c R=CH_3, R′=C_6H_5, R″=H
5d R=CH_3, R′=C_6H_5, R″=CH_3
5e R=C_6H_5, R′=CH_3, R″=H
5f R=C_6H_5, R′=CH_3, R″=CH_3
5g R=C_6H_5, R′=C_6H_5, R″=H
5h R=C_6H_5, R′=C_6H_5, R″=CH_3

Scheme III



6

tricyclic compound obtained in each case was subjected to tlc in different solvent systems and found to consist of one isomer.

Identification of the structure of tricyclic compounds prepared was achieved by independent synthesis of 8-methyl-2-phenyl-7*H*-1,2,4-triazino[4,3-*e*]pyrazolo[1,5-*a*]-1,3,5-triazin-7-one (**6**) synthesized by interaction of 4-hydrazino-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazin-7-one (11) and ethyl pyruvate in the presence of sodium methoxide; see Schemes II and III.

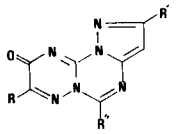
In addition to being the expected reaction product based on the intermediate used, the uv spectra of the isomeric 6-methyl-2-phenyl-1,2,4-triazino[4,3-*e*]pyrazolo-[1,5-*a*]-1,3,5-triazin-7-one (**6**) is consistent with the structure. The latter compound has two maxima at 280 (log ϵ 3.56) and 310 nm (log ϵ 3.61) as a result of a homoanular conjugated dienone type structure in the 1,2,4-triazine moiety.

The isomeric 9-one, compound **5**, absorbs at 270 nm (log 4.40) which is in good agreement with a cross conjugate structure type in the 1,2,4-triazinone.

On the basis of these observations it is concluded that N_2 of the 1,2,4-triazine rather than N_4 was the site of ring closure to afford exclusively compounds **5**.

Compounds **5** that were prepared are summarized in Table II.

Table II



Compound No.	R	R′	R″	Yield %	M.p. °C	Formula	Analyses C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found
5a	CH_3	CH_3	H	38	245-250	$C_9H_8N_6O$	50.00	49.89	3.70	3.66	38.88	38.93
5b	CH_3	CH_3	CH_3	49	240-242	$C_{10}H_{10}N_6O$	52.17	52.23	4.34	4.41	36.52	36.64
5c	CH_3	C_6H_5	H	61	320-324	$C_{14}H_{10}N_6O$	60.43	60.66	3.59	3.49	30.21	30.18
5d	CH_3	C_6H_5	CH_3	48	320-323	$C_{15}H_{12}N_6O$	61.46	61.40	4.10	4.11	28.76	28.86
5e	C_6H_5	CH_3	H	37	290-298	$C_{14}H_{10}N_6O$	60.43	60.61	3.59	3.67	30.21	30.11
5f	C_6H_5	CH_3	CH_3	56	265-270	$C_{15}H_{12}N_6O$	61.64	61.77	4.10	4.06	28.76	28.50
5g	C_6H_5	C_6H_5	H	71	270-278	$C_{19}H_{12}N_6O$	67.05	66.88	3.52	3.60	24.70	24.60
5h	C_6H_5	C_6H_5	CH_3	64	316-319	$C_{20}H_{14}N_6O$	67.79	67.69	3.95	3.80	23.72	23.63

EXPERIMENTAL

Melting points were taken on a Kofler hot stage microscope and are uncorrected. The ir spectra were obtained on a Leitz Model III spectrograph. Nmr spectra were determined using a Varian T-60 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian MAT CH-5 spectrometer at 70 eV.

6-Methyl-3-[3-methyl-5-aminopyrazolyl]-2,5-dihydro-1,2,4-triazin-5-one (**4a**).

To a solution of 1.82 g. (0.01 mole) of 3-hydrazino-6-methyl-1,5-dihydro-2,4-triazin-5-one (**3a**) (5) in 20 ml. of ethanol and 10 ml. of acetic acid, 2.9 g. (0.01 mole) of α-cyanoacetophenone (9) was added. The mixture was refluxed for 5 hours. After cooling, the precipitate was separated and recrystallized from ethanol-acetic acid to give 1.66 g. (83%) of **4a**, m.p. 274-280°. Molecular weight by mass spectroscopy m/e 206 (M^+); nmr (trifluoroacetic acid): 2.73 (s, 3H, CH_3), 6.33 (s, 1H, CH) and 7.35-7.91 (m, 5H, C_6H_5); ir max (potassium bromide): 1660, 1615, 1582, 1531, 1505, 1448, 1390, 1323, 1237, 1067, 961, 782, 750, 741, and 690 cm^{-1}.

Compounds **4b-4d** reported in Table I were prepared similarly.

8-Methyl-2-phenyl-9*H*-1,2,4-triazino[2,3-*e*]pyrazolo[1,5-*a*]-1,3,5-triazin-9-one (**5c**).

Method A.

A suspension of 536 mg. (2 mmoles) of **4c** in 5 ml. of triethyl orthoformate was refluxed for 10 hours. The excess of triethyl orthoformate was then removed under reduced pressure and the residue was recrystallized from alcohol-acetic acid to give 340 mg. (61%) of **5c**, m.p. 320-324°; mass spectroscopy: m/e 278 (M^+), 237 (M-CH_3CN), 175 (M-C_6H_5CN), 103, 85 and 77; nmr (trifluoroacetic acid): 1.99 (s, 3H, CH_3), 6.62 (s, 1H, C_3H), 6.99-7.30 (m, 5H, C_6H_5) and 8.14 (s, 1H, C_5H); ir max (potassium bromide): 1670, 1625, 1608, 1538, 1460, 1400, 1258, 1145, 943, 885, 803, 775, and 678 cm^{-1}.

Method B.

Identical results were obtained when the reaction was conducted in diethoxymethyl acetate (DEMA) (10) instead of triethyl orthoformate. The refluxing time was reduced to 30 minutes.

Compounds **5a**, **5c**, **5e**, and **5g** were prepared using method A and B and are reported in Table II.

5,8-Dimethyl-2-phenyl-9*H*-1,2,4-triazino[2,3-*e*]pyrazolo[1,5-*a*]-triazin-9-one (**5d**).

Method A for preparation of **5c** was followed except that triethyl orthoacetate was used as condensing agent, m.p. 320-323°; mass spectroscopy: m/e 294 (M^+), 251 M-CH_3CN, 189 M-C_6H_5CN, 148 M-(C_6H_5CN, CH_3CN), 120 M-(C_6H_5CN, CO), and 77; nmr (trifluoroacetic acid): 1.80 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 6.41 (s, 1H, CH).

Compounds **5**, **5f** and **5h** were prepared similarly (see Table II).

8-Methyl-2-phenyl-7*H*-1,2,4-triazino[4,3-*e*]pyrazolo[1,5-*a*]-1,3,5-triazin-7-one (**6**).

4-Hydrazino-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**7**) (10), 2.26 g. (0.01 mole), and 1.74 g. (0.015 mole) of ethyl pyruvate were dissolved in 25 ml. of ethanol. To the boiling solution, 0.54 g. (0.01 mole) of sodium methoxide was added. After 5 hours refluxing, the mixture was evaporated to dryness. The residue was washed with ether and recrystallized from ethanol-acetic acid to give 0.83 g. (30%) of **6**, m.p. 295-300°; molecular weight by mass spectroscopy: m/e 278 (M^+); nmr (trifluoroacetic acid): 2.05 (s, 3H, CH_3), 6.59 (s, 1H, C_3H), 6.91-7.36 (m, 5H, C_6H_5) and 8.23 (s, 1H, C_5H); ir max (potassium bromide): 1672, 1620, 1583, 1560, 1538, 1469, 1436, 1330, 941, 805, 761, and 684 cm^{-1}.

Anal. Calcd. for $C_{14}H_{10}N_6O$: C, 60.43; H, 3.59; N, 30.21. Found: C, 60.29; H, 3.68; N, 30.49.

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