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THE SYNTHESIS OF *s*-TRIAZOLO[4.3-*a*] 1,3,5-TRIAZINES

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Abstract— *s*-Triazolo[4.3-*a*] 1,3,5-triazines have been synthesized from different hydrazino-1,3,5-triazines. The structures of the products were determined by chemical and spectroscopic methods. Rearrangement of Me groups and the possibility of formation of the isomeric *s*-triazolo[2,3-*a*] 1,3,5-triazines have been investigated.

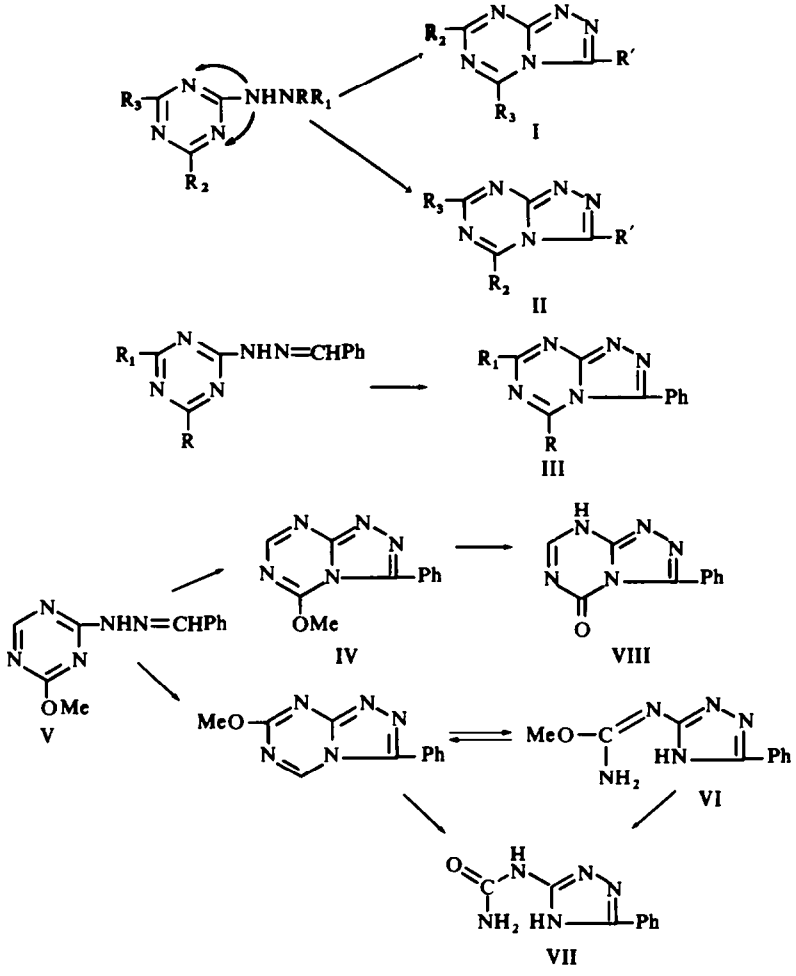
WE WISH to report our investigations on *s*-triazolo-1,3,5-triazines. The known representatives of the *s*-triazolo[4.3-a]1,3,5-triazine ring system were prepared either from *s*-triazoles[1,2] and aliphatic or other precursors,[3,4] or from the corresponding 1,3,5-triazines. This latter approach[5] we have now investigated in greater detail.

As starting material several new hydrazino-1,3,5-triazines have been prepared since the hydrazino or substituted hydrazino group is involved in the formation of the fused *s*-triazolo ring. Whereas with symmetrically 4,6-disubstituted 2-hydrazino-1,3,5-triazines the direction of ring closure is irrelevant, cyclization of unsymmetrical structures can involve one of two neighbouring ring nitrogens and generate thus one or a mixture of two possible isomeric compounds (I, II). There are several factors which may be operative in directing the ring closure, and these will be discussed later.

2-Benzylidenehydrazino-1,3,5-triazines, when submitted to oxidative cyclization with lead tetraacetate in benzene at 20–30°, afforded the corresponding *s*-triazolo-[4.3-*a*] 1,3,5-triazines (III). Under these reaction conditions the eventual isomerization to the *s*-triazolo[2.3-*a*] 1,3,5-triazine system (XVI) is highly improbable (cf similar conversions in the analogous *s*-triazolopyrimidine[6–10] or *s*-triazolopurine series[11]).

With monosubstituted and diversely substituted 2-hydrazino-1,3,5-triazines the orientation of substituents in the triazine part of the bicyclic product(s) is not easily recognized on spectroscopic grounds and therefore chemical evidence was sought. Cyclization of 2-benzylidenehydrazino-4-methoxy-1,3,5-triazine afforded a mixture of two compounds in the ratio of about 2·5 :1. One of them (m.p. 240°), after hydrolysis with hot conc hydrochloric acid, was converted into a compound identified as triazolylurea, VII.[12] On the other hand, hydrolysis with dilute sodium hydroxide or heating with morpholine, transformed the bicyclic product into the corresponding O-methylurea (VI) which could be hydrolyzed further to VII. Moreover, cyclization with diethoxymethyl acetate or triethyl orthoformate reconverted compound VI to the starting triazolotriazine V. The conversion of V into VI or VII could be followed spectrophotometrically and the postulated intermediate hydrated species IX could be detected by rapid neutralization of the hydrated cation.[13]

The 5-methoxyisomer (IV), when treated with a solution of sodium hydroxide,



afforded a product which revealed the presence of a carbonyl group in its IR spectrum and to which structure VIII was assigned. The established different reactivity of V and IV is in accordance with a greater susceptibility of position 5 than 7 towards nucleophilic attack. This is in agreement with the calculated electron densities for the parent system* (Table 1). Moreover, in the case of IV no hydration across the bond 7,8 could be detected. These facts and NMR evidence distinguish between both isomeric methoxy compounds V and IV.

The structure of VIII as an —5(8*H*)one rather than an —5(6*H*)one is substantiated by comparison of UV spectra of the corresponding 6-Me and 8-Me derivatives. Thus the —5(8*H*)one or its 8-Me analog (VIII, XII, R = H) reveals an absorption max at 2400 Å, whereas the corresponding 6-methyl-5(6*H*)one and its 7 Me analog (XI) shows an absorption max at 2540 and 2520 Å, respectively.

The preferential cyclization of 4-substituted 2-benzylidenehydrazino-1,3,5-triazines to 7-substituted *s*-triazolo[4,3-*a*] 1,3,5-triazines can be explained also on electronic

* The general method of calculation was that of the Hückel MO theory.

TABLE 1. CALCULATED ELECTRON DENSITIES FOR *s*-TRIAZOLO[4.3-*a*] 1,3,5-TRIAZINES

Position	1	2	3	4	5	6	7	8	9
Total π-electron density	1·2507	1·2507	0·8928	1·6108	0·7043	1·2610	0·8093	1·3273	0·8928
Frontier electron density	0·0222	0·0222	0·0061	0·0683	0·1422	0·2476	0·0464	0·4387	0·0061

TABLE 2. CALCULATED ELECTRON DENSITIES FOR *s*-TRIAZOLO[2.3-*a*] 1,3,5-TRIAZINES

Position	1	2	3	4	5	6	7	8	9
Total π-electron density	1·2794	0·9285	1·2953	1·5588	0·7478	1·2131	0·8219	1·2261	0·8750
Frontier electron density	0·2317	0·0198	0·3246	0·0015	0·1117	0·0319	0·0903	0·1350	0·0535

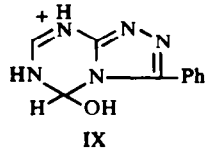
grounds. Conjugative electron donation changes the electronic dissymmetry at N_1, this nitrogen being *para* to the 4-substituent, as compared to N_3 of the triazine ring, which nitrogen is *ortho* to the same substituent. This is of particular importance since the nucleophilicity of a particular nitrogen in the triazine ring is mainly responsible for the direction of ring closure, a circumstance which is operative also within other heterocyclic systems.

Other factors, such as steric effects, are also operative, as envisaged from the cyclization of 2-benzylidenehydrazino-4-methyl-6-methoxy-1,3,5-triazine which afforded mainly the 5-methoxy-7-methyl derivative III (R = OMe, R_1 = Me) and very little of the other isomer III (R = Me, R_1 = OMe). There are several mechanisms proposed for lead tetraacetate oxidations[15,16] and recently nitrileimines [17,18] were detected as intermediates. It is not the aim to discuss these mechanisms, but it should be pointed out that for successful cyclization the benzylidenehydrazino side chain, involved with lead tetraacetate in a transition state, must closely approach the ring nitrogen and at this stage the steric effect becomes important. With the aforementioned triazine the transition state appears to be more hindered by the large Me group if the reaction should proceed towards the formation of the 5-methyl-7-methoxy bicyclic derivative.

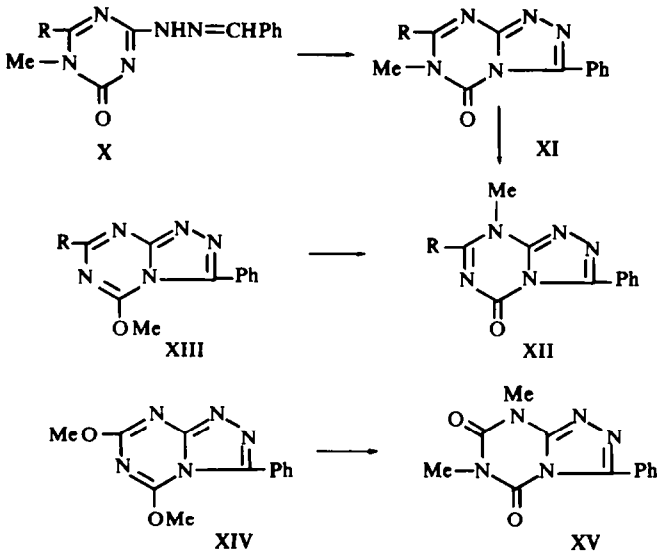
The structure of the aforementioned isomers was established via the reaction of O-methylurea (VI) with triethyl orthoacetate, which yielded III (R = Me, R_1 = OMe). The eventual cyclization which should involve the triazole ring nitrogen at position 2 and which should generate the isomeric 2,3-a-bicyclic system, was excluded by UV spectral evidence and the fact that N_2 is the most basic center only in an alkaline environment.[19]

Another important fact which has to be taken into account is thermal rearrangement of Me groups, a well known feature from the chemistry of alkoxy-pyrimidines, [20]-pyridines, [21]-pyridazines, [22]-1,3,5-triazines[23,24] and related heterocyclic compounds. Recently, for thermal isomerization of 2,4,6-trimethoxy-1,3,5-triazine an intermolecular mechanism has been given.[24]

Whereas the 7-OMe compound (V) when heated at about its m.p. did not rearrange, 5-OMe derivatives, such as IV, were readily rearranged and the Me group migrated to the *para* position of the triazine ring. On the other hand, authentic 6-Me derivatives are obtainable by cyclization of 2-benzylidenehydrazino-5-methyl-1,3,5-triazin-4(5*H*)ones (X) since this process takes place selectively to afford only one product (XI, R = H or Me). Upon heating, again the Me group migrates from position 6 to position 8. The 8-Me isomer (XII, R = H or Me), formed by this rearrangement, is obtainable also by thermal isomerization of XIII. In a similar manner, the 5,7-dimethoxy derivative (XIV) afforded the 6,8-dimethyl isomer (XV), showing again that the driving force for such isomerizations is the greater stability of the amido structures.

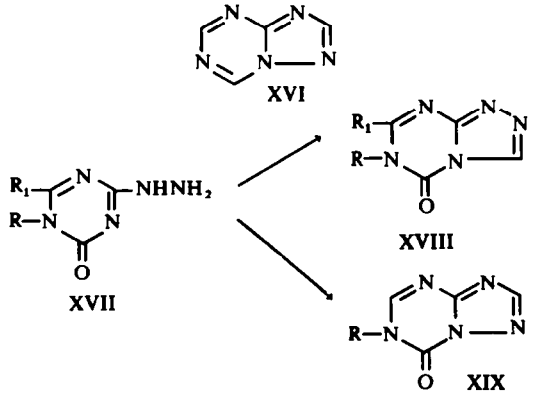


IX



There are some spectroscopic features which correlate with the structural assignments of the aforesaid compounds. Thus, the carbonyl stretching frequencies of *s*-triazolo[4.3-*a*] 1,3,5-triazinones depend on the relative resonance contributions as well as on the inductive effect of the neighbouring group. In accordance with this, the 5-oxo derivatives show absorption bands at higher frequencies (1725–1770 cm^{-1}) than the corresponding *s*-triazolo[4.3-*a*]pyrimidin-5-ones (1700–1705 cm^{-1}) or in particular when compared to *s*-triazolo[4.3-*a*]pyrimidin-7-ones (1685–1695 cm^{-1}).[25]

Valuable data are obtained from NMR spectral correlations. A number of authors have attempted to show that for related nitrogen heterocycles an empirical correlation exists between the chemical shift and electron densities. However, it has been pointed out that the observed chemical shifts are not a very reliable measure of π-electron densities in nitrogen containing heterocyclic compounds. Nevertheless, available spectral evidence from related azoloazines with bridgehead nitrogen[26–32] postulate lower τ-values for protons at position 5. One can also easily distinguish between the OMe and the rearranged N-Me derivatives. The latter, with the Me group bound at N_8 reveal lower τ_{Me}-values than their 6-Me isomers.



In these bicyclic systems, the possibility of isomerization or formation of *s*-triazolo-[2.3-*a*] 1,3,5-triazines (XVI), required authentic representatives of the system* for investigation. As already mentioned, X can cyclize in only one way, 4-hydrazino-1-methyl-1,3,5-triazin-2(1*H*) one or its 6-Me analog (XVII) can afford only the corresponding 5-oxo derivatives (XVIII). To accomplish this cyclization, diethoxymethyl acetate, which has been previously successfully used for the preparation of several *s*-triazoloazines,[33–38] was employed. If these hydrazines (XVII, R = Me, R_1 = H or Me) were allowed to react with diethoxymethyl acetate for a short period and at a moderate temperature, the corresponding bicyclic products of the [4.3-*a*]-series (XVIII, R = Me, R_1 = H or Me) were obtained. However, when XVII (R = R_1 = H) was heated with excess of this reagent under reflux for 10 min the isomeric product belonging to the [2.3-*a*]-system was formed. It was identified as XIX (R = H, 5-azahypoxanthine). This compound and its N-Me derivative (XIX, R = Me) is identical in all respects with the products described previously[39] and synthesized from the appropriate triazole. The formation of both isomeric bicyclic systems parallels the cyclization of 2-hydrazinopyrimidines with triethyl orthoformate where two isomeric *s*-triazolopyrimidines were isolated.[40] Finally, it should be mentioned that treatment of 4,6-dimorpholino-2-hydrazino-1,3,5-triazine with hot formic acid yielded as the only product the formylated derivative.

EXPERIMENTAL

M.ps (Kofler m.p. apparatus) are corrected; IR spectra: Infracord Model 137; NMR spectra: JEOL JNM-C-6OHL spectrometer, TMS as internal standard; UV spectra: Beckman DU Spectrophotometer.

2-Hydrazino-4-methyl-1,3,5-triazine

A soln of 4-methoxy-2-methyl-1,3,5-triazine[41] (0·6 g) in MeOH (1 ml) was treated with hydrazine hydrate (0·3 ml of 80%). After an exothermic reaction, crystals began to separate. The product (0·55 g) was obtained pure after recrystallization from MeOH; m.p. 130–132°. (Found: C, 38·41; H, 5·71; N, 55·64; $C_4H_7N_5$ requires: C, 38·39; H, 5·64; N, 55·97%).

The corresponding benzylidene derivative was prepared in the usual way; m.p. 170–172° (from EtOAc and n-hexane); UV spectrum in EtOH: λ_{max} 2300 and 3080 Å (ε 13,000 and 31,000). (Found: C, 62·08; H, 5·16; N, 32·68; $C_{11}H_{11}N_5$ requires: C, 61·95; H, 5·20; N, 32·85%).

In essentially the same way the following compounds were prepared:

(i) 2-Hydrazino-6-methoxy-4-methyl-1,3,5-triazine was obtained from 2,4-dimethoxy-6-methyl-1,3,5-triazine[41] and had m.p. 157° from MeOH or when sublimed at 130°/5 mm. (Found: C, 38·93; H, 5·77; N, 45·58; $C_5H_9N_5O$ requires: C, 38·70; H, 5·85; N, 45·14%).

The corresponding benzylidene derivative had m.p. 188–190° (from EtOAc and n-hexane); UV spectrum in EtOH: λ_{max} 2240 and 3060 Å (ε 17,120 and 35,500). (Found: C, 59·06; H, 5·29; N, 28·88; $C_{12}H_{13}N_5O$ requires: C, 59·25; H, 5·39; N, 28·79%).

(ii) 2-Hydrazino-1,3,5-triazine was prepared from 2-phenoxy-1,3,5-triazine[42] and was purified by sublimation; m.p. 180–182° (Lit.[43] gives m.p. 178–179°).

Its benzylidene derivative had m.p. 235°; UV in EtOH; λ_{max} 2300 and 3080 Å (ε 13,050 and 30,300). (Found: C, 60·20; H, 4·94; N, 35·08; $C_{10}H_9N_5$ requires: C, 60·29; H, 4·55; N, 35·16%).

2-Hydrazino-4-methylthio-1,3,5-triazine

A methanolic soln (6 ml) of 2,4-bis(methylthio) 1,3,5-triazine[41] (0·8 g) was treated with hydrazine hydrate (0·3 ml of 80%) and the mixture was stirred at room temp for 2 hr. The separated product was recrystallized from MeOH to afford the pure compound (62%), m.p. 152–153°. (Found: C, 30·62; H, 4·55; $C_4H_7N_5S$ requires: C, 30·57; H, 4·49%).

The benzylidene derivative had m.p. 173–175° (from EtOH); UV spectrum in EtOH: λ_{max} 2320, 2560

* The calculated electron densities[14] for the parent system are presented in Table 2.

and 3100 Å (ε 16,090, 15,490 and 36,400). (Found: C, 53·97; H, 4·52; N, 28·80; S, 13·00; $C_{11}H_{11}N_5S$ requires: C, 53·87; H, 4·52; N, 28·56; S, 13·05%).

2-Hydrazino-4,6-bis(methylthio)-1,3,5-triazine

A soln of 2,4,6-tris(methylthio) 1,3,5-triazine [44] (2·19 g) in hot dioxan (30 ml) was treated with hydrazine hydrate (0·65 g of 80%) and the mixture was then heated under reflux for 8 hr. After evaporation to dryness the residue was recrystallized from dioxan; m.p. 200°. (Found: C, 29·66; H, 4·62; $C_5H_9N_5S_2$ requires: C, 29·56; H, 4·47%).

Its benzylidene derivative had m.p. 223–225° from EtOH. (Found: C, 49·77; H, 4·64; N, 23·75; S, 21·65; $C_{12}H_{13}N_5S_2$ requires: C, 49·48; H, 4·50; N, 24·05; S, 21·97%).

2-Hydrazino-4-methoxy-1,3,5-triazine

2,4-Dimethoxy-1,3,5-triazine[12] (0·45 g) was dissolved in the minimum amount of MeOH at room temp and hydrazine hydrate (0·2 g of 80%) was added. The reaction mixture was left overnight and the product (0·3 g, 67%) purified by sublimation at 120°/10 mm or by recrystallization from aqueous MeOH; m.p. 132–135°. (Found: N, 49·76; $C_4H_7N_5O$ requires: N, 49·63%).

The corresponding benzylidene derivative melted at 208–210°, from EtOH; UV spectrum in EtOH: λ_{max} 2220 and 3060 Å (ε 18,400 and 34,300). (Found: C, 57·31; H, 4·59; N, 30·60; $C_{11}H_{11}N_5O$ requires: C, 57·63; H, 4·84; N, 30·55%).

4-Hydrazino-1-methyl-1,3,5-triazin-2(1H)one

A soln of 4-methoxy-1-methyl-1,3,5-triazin-2(1*H*)one[45] (0·45 g) in MeOH (10 ml) was treated with hydrazine hydrate (0·2 ml of 80%). The mixture was stirred at room temp for 30 min and then left overnight. The product was collected and recrystallized from MeOH (0·4 g, 90%); m.p. 230° (dec). (Found: C, 34·25; H, 5·26; N, 49·79; $C_4H_7N_5O$ requires: C, 34·04; H, 5·00; N, 49·63%).

Its benzylidene derivative had m.p. 250°. (Found: C, 57·22; H, 4·86; N, 30·71; $C_{11}H_{11}N_5O$ requires: C, 57·63; H, 4·84; N, 30·55%).

In a similar manner 4-hydrazino-1,3,5-triazin-2(1*H*)one was obtained from 4-methoxy-1,3,5-triazin-2(1*H*)one;[45] m.p. 215° from aqueous EtOH. (Found: C, 27·94; H, 3·50; N, 55·03; $C_3H_5N_5O$ requires: C, 28·35; H, 3·97; N, 55·10%). The corresponding benzylidene derivative was obtained as a monohydrate, m.p. 243–245° from N,N-dimethylformamide and toluene. For analysis it was dehydrated at 140°. (Found: C, 55·70; H, 4·22; N, 32·34; $C_{10}H_9N_5O$ requires: C, 55·81; H, 4·22; N, 32·54%).

1,6-Dimethyl-4-hydrazino-1,3,5-triazin-2(1H)one

A mixture of 1,6-dimethyl-4-methoxy-1,3,5-triazin-2(1*H*)-one[45] (0·77 g), MeOH (2 ml) and hydrazine hydrate (0·31 g of 80%) was left at room temp for 2 hr. The product can be purified either by sublimation at 180°/5 mm or by recrystallization from MeOH (yield 0·7 g, 82%; m.p. 205–207°. (Found: C, 38·66; H, 5·67; N, 45·28; $C_5H_9N_5O$ requires: C, 38·70; H, 5·85; N, 45·14%).

Its benzylidene derivative had m.p. 237–240° from EtOH. (Found: C, 59·18; H, 5·63; N, 28·62; $C_{12}H_{13}N_5O$ requires: C, 59·25; H, 5·35; N, 28·79%); UV spectrum (in ethanol): λ_{max} 2220 and 3100 Å (ε 18,200 and 34,000).

2,4-Dimorpholino-6-formylhydrazino-1,3,5-triazine

2,4-Dimorpholino-6-hydrazino-1,3,5-triazine[46] (1 g) when heated with formic acid (96%) under reflux for 4 hr formed the formylated product; m.p. 239–240° from EtOH. (Found: C, 46·44; H, 6·24; N. 31·98; $C_{12}H_{19}N_7O_3$ requires: C, 46·59; H, 6·19; N, 31·70%).

5-Methoxy-3-phenyl-s-triazolo[4·3-a]1,3,5-*triazine* (IV) and *7-methoxy-3-phenyl-s-triazolo*[4·3-a]1,3,5-*triazine* (V)

(i) 2-Benzylidenehydrazino-4-methoxy-1,3,5-triazine (6·87 g), lead tetraacetate (13·3 g) and benzene (150 ml) were stirred for 3 hr, the mixture was then heated to boil and filtered hot. Upon cooling the product was filtered off and had m.p. 240°. The residue from the first filtration of the hot benzene soln was treated with iced water and another 4 g of the product were obtained (total yield 65%). The 7-OMe isomer can be purified by recrystallization from AcOH or from EtOAc and n-hexane; m.p. 240°; UV spectrum: in EtOH: λ_{max} 2380 Å (22,000 = ε); in water: 2360 Å (ε 11,100); NMR spectrum: CD_3SOCD_3: τ = 0·19 (s, H_5), 5·89 (s, 7-CH_3O), 1·77 and 2·42 (two multiplets, Ph). (Found: C, 58·32; H, 4·23; N, 30·82; $C_{11}H_9N_5O$ requires: C, 58·14; H, 3·99; N, 30·82%).

(ii) The above benzene filtrate was evaporated to dryness and triturated with a small quantity of benzene, yielding 2·2 g of the isomeric 5-OMe compound (IV) which started melting at about 120°, crystallized from the melt in needles and these melted at about 300° (yield 29%). For analysis the compound was crystallized twice from benzene; UV spectrum in ethanol; λ_{max} 2400 Å (ε 31,400); 0·1 NHCl: 2380 Å (ε 24,850); NMR spectrum: CD_3SOCD_3: τ = 1·25 (s, H_7), 5·63 (s, 5-CH_3O), two multiplets centered at 1·76 and 2·43 (Ph). (Found: C, 58·13; H, 4·16; N, 30·83; $C_{11}H_9N_5O$ requires: C, 58·14; H, 3·99; N, 30·82%).

The insoluble portion from the crystallization from benzene was recrystallized from aqueous EtOH and a small amount of a compound with m.p. 300° was obtained and identified by IR spectra as VIII.

(iii) Compound VI (0·1 g) was dissolved in diethoxymethyl acetate (0·5 ml) by gentle warming. After a while a compound separated and was found identical in all respects V, prepared as described under (i). In another procedure, the same urea derivative was heated under reflux with triethyl orthoformate for 2 days and the same product (V) was isolated and identified.

O-*Methyl*-N-(5-*phenyl*-1,2,4-*triazolyl*-3)-*urea* (VI)

(i) A suspension of V (0·5 g) in 0·5 N NaOH (5 ml) was stirred at room temp for 6 hr. After standing on ice a product (0·3 g) with m.p. 205° was obtained and found identical with the compound prepared as described under (ii).

(ii) The same bicyclic compound V (0·25 g) was heated with morpholine (0·105 g) and EtOH (5 ml) under reflux for 3 hr. The soln was evaporated to dryness and the residue was crystallized from EtOAc and n-hexane; m.p. 203–205°; UV spectrum in ethanol: λ_{max} 2380 Å (ε 18,700); water: 2360 Å (ε 12,710); 0·1N NaOH: 2690 Å (ε 10740). (Found: C, 55·36; H, 5·23; N, 32·26; $C_{10}H_{11}N_5O$ requires: C, 55·29; H, 5·10; N, 32·24%).

N-(5-*Phenyl*-1,2,4-*triazolyl*-3)*urea* (VII)

(i) Compound V (1 g) was heated to boiling with conc HCl (3 ml). From the resulting soln a product separated and was recrystallized from 2-methoxy-ethanol and water; m.p. 236–240°, mixed m.p. with an authentic specimen prepared according to Kaiser and Peters[12] was undepressed. (Found: C, 53·10; H, 4·90; $C_9H_9N_5O$ requires: C, 53·19; H, 4·46%).

(ii) The same compound VII could be obtained if VI (0·1 g) was heated with conc HCl (0·3 ml), m.p. 236–240° and mixed m.p. with the compound prepared as described under (i) was undepressed.

3-*Phenyl*-s-*triazolo*[4,3-a]1,3,5-*triazin*-5(8H)*one* (VIII)

Compound IV (0·15 g) was dissolved in 0·5 N NaOH (5 ml). After standing at room temp for 30 min, the soln was cooled to 0° and neutralized with HCl to pH 3. The ppt was recrystallized from aqueous EtOH, yield 0·1 g, m.p. 300°; IR spectrum: 1770 cm^{-1} (CO); UV spectrum in EtOH: λ_{max} 2400 Å (ε 27,600); 0·1N HCl or 0·1N NaOH: 2400 Å (ε 25,200). (Found: C, 56·55; H, 3·51; N, 32·43; $C_{10}H_7N_5O$ requires: C, 56·33; H, 3·31; N, 32·85%).

3-*Phenyl*-s-*triazolo*[4.3-a]1,3,5-*triazine* (III, R = R_1 = H)

2-Benzylidenehydrazino-1,3,5-triazine (1 g) and lead tetraacetate (2·2 g) were stirred in benzene (30 ml) for 2 hr. Thereafter the mixture was heated to boiling and filtered hot. From the filtrate a product (0·3 g, 30%) separated and was recrystallized from EtOAc and n-hexane; m.p. 233°; UV spectrum in ethanol: λ_{max} 2380 Å (ε 18,150); dioxan λ_{max} 2400 Å (ε 23,800); water: λ_{max} 2380 Å (ε 16,600); NMR spectrum: CD_3SOCD_3: τ = + 0·05 (s, H_4), 0·97 (s, H_7) and two multiplets centered at 1·74 and 2·46 (Ph). (Found: C, 60·54; H, 3·76; N, 35·41; $C_{10}H_7N_5$ requires: C, 60·90; H, 3·58; N, 35·52%).

7-*Methyl*-3-*phenyl*-s-*triazolo*[4.3-a]1,3,5-*triazine* (III, R = H, R_1 = Me)

2-Benzylidenehydrazino-4-methyl-1,3,5-triazine (1·15 g), lead tetraacetate (2·6 g) and benzene (20 ml) were stirred at room temp for 45 min. Since heat was evolved, external cooling with water was applied. The solid was filtered off and crystallized from benzene. From the filtrate after evaporation an additional quantity of the product could be obtained (total yield 49%); m.p. 190°; UV spectrum in ethanol λ_{max} 2400 Å (ε 20,600); NMR spectrum: CD_3SOCD_3: τ = 0·04 (s, H_5), 7·26 (s, 7-CH_3), and two multiplets centred at 1·77 and 2·42 (Ph). (Found: C, 62·62; H, 4·31; N, 33·18; $C_{11}H_9N_5$ requires: C, 62·55; H, 4·30; N, 33·16%).

7-*Methylthio*-3-*phenyl*-s-*triazolo*[4·3-a]1,3,5-*triazine* (III, R = H, R_1 = SCH_3)

2-Benzylidenehydrazino-4-methylthio-1,3,5-triazine (0.4 g), lead tetraacetate (725 mg) and benzene (10

ml) were stirred at room temp for 3 hr. The solid was filtered off and treated with iced water (4 ml). Crystallization of the crude product from benzene yielded 38%; m.p. 238–240°; UV spectrum in EtOH; λ_{max} 2400 Å (ε 20,250); NMR spectrum: CD_3SOCD_3: τ = 0·25 (s, H_5), 7·34 (s, 7-CH_3S), and two multiplets centred at 1·77 and 2·43 (Ph). (Found: C, 54,12; H, 4·05; N, 28·99; S, 13·09; $C_{11}H_9N_5S$ requires: C, 54·32; H, 3·73; N, 28·80; S, 13·16%).

The benzene filtrate was evaporated to dryness and 1 ml of benzene were added, yielding 0·1 g of a compound with an IR spectrum not identical with the above product and m.p. of 120–200°. TLC on silicagel-G and using CCl_4 and EtOAc, 1:1, as the mobile phase, the presence of two compounds was detected with R_f values of 0·22 and 0·8 (the pure above 7-methyltio derivative showed R_f value 0·8). There was not enough of the second isomer to be isolated pure and fully characterized, but most probably this is the 5-methylthio isomer.

7-*Morpholino*-3-*phenyl*-s-*triazolo*[4.3-a]1,3,5-*triazine* (III, R = H, R_1 = morpholino) *and* 5-*morpholino*-3-*phenyl*-s-*triazolo*[4.3-a]1,3,5-*triazine* (III, R_1 = H, R = *morpholino*)

To a suspension of 2-benzylidenehydrazino-4-morpholino-1,3,5-triazine[47] (0·5 g) in glacial AcOH (15 ml) lead tetraacetate (0·78 g) was added portionwise. The reaction mixture spontaneously warmed up to 30° and after addition was complete it was heated at 50° for 5 min. Thereafter the mixture was stirred at room temp for 1 hr and then poured into iced water (100 ml). The product (0·3 g) was washed with 5% Na_2CO_3 aq and was recrystallized from EtOAc (yield 60%); m.p. 233–235. In spite of the rather sharp m.p. the NMR spectrum revealed the presence of a mixture of the 7- and 5-morpholino isomers in the ratio of 2:3. NMR spectrum: CD_3SOCD_3: τ = 0·44 (s, H_5), 1·56 (s, H_7), 6·72 (m, 5-morpholino), 6·21 (m, 7-morpholino).

In a similar manner, oxidative cyclization with Br_2 afforded a product, composed of both isomers.

5,7-*Dimethoxy*-3-*phenyl*-s-*triazolo*[4.3-a]1,3,5-*triazine* (III, R = R_1 = OCH_3)

2-Benzylidenehydrazino-4,6-dimethoxy-1,3,5-triazine[5] (1 g) was dissolved in minimum amount of AcOH and lead tetraacetate (2·2 g) was added portionwise at room temp. The mixture was left overnight and then poured into iced water (200 ml). The product (0·6 g, 60%) was recrystallized twice from EtOAc and n-hexane; m.p. 138–140°, from the melt new crystals separated and these melted then at about 200°; NMR spectrum: CD_3SOCD_3: τ = 5·85 (s, 5-CH_3O), 5·96 (s, 7-OCH_3), and two multiplets centred at 1·85 and 2·47 (Ph). (Found: C, 55·93; H, 4·50; N, 27·05; $C_{12}H_{11}N_5O_2$ requires: C, 56·02; H, 4·31; N, 27·23%).

5,7-*Bis*(*methylthio*)3-*phenyl*-s-*triazolo*[4.3-a]1,3,5-*triazine* (III, R = R_1 = SCH_3)

A suspension of 2-benzylidenehydrazino-4,6-bis-(methylthio)-1,3,5-triazine (0·5 g) in glacial AcOH (25 ml) was cooled to 15° and during stirring lead tetraacetate (0·9 g) was added in such a manner that the reaction temp could be kept between 15 and 18°. After the addition was complete, the mixture was stirred 1 hr at room temp, filtered, the filtrate diluted with iced water (200 ml) and the product was immediately filtered off and crystallized from EtOAc (yield 78%); m.p. 192–193°; UV spectrum in EtOH: λ_{max} 2640 Å (ε 33,500); NMR spectrum: CD_3SOCD_3: τ = 7·37 (s, 5-CH_3S), 7·45 (s, 7-CH_3S), 2,35 (s, Ph). (Found: C, 49·91; H, 3·83; N, 24·35; $C_{12}H_{11}N_5S_2$ requires: C, 49·83; H, 3·83; N, 24·21%).

7-*Methoxy*-5-*methyl*-3-*phenyl*-s-*triazolo*[4.3-a]1,3,5-*triazine* (III, R = CH_3, R_1 = OCH_3)

A mixture of VI (1 g) and triethyl orthoacetate (20 ml) was heated under reflux for 6 hr in an atmosphere of dry N_2. The reaction mixture was then left overnight at − 15° and the product (0·65 g, 59%) was recrystallized from EtOAc and n-hexane; m.p. 194°; UV spectrum in EtOH: λ_{max} 2340 and 2780 Å (ε 28,200 and 11,210); NMR spectrum: CD_3SOCD_3: τ = 7·13 (s, 5-CH_3), 5·95 (s, 7-CH_3O), and two multiplets centered at 1·78 and 2·44 (Ph). (Found: C, 59·99; H, 4·34; N, 28·98; $C_{12}H_{11}N_5O$ requires: C, 59·74; H, 4·60; N, 29·03%).

5-*Methoxy*-7-*methyl*-3-*phenyl*-s-*triazolo*[4.3-a]1,3,5-*triazine* (III, R = OCH_3, R_1 = CH_3)

A mixture of 2-benzylidenehydrazino-6-methoxy-4-methyl-1,3,5-triazine (1·2 g), lead tetraacetate (2·22 g) and benzene (40 ml) was stirred at room temp for 5 hr. After filtration, the filtrate was evaporated to dryness and the residual oil was treated with diethyl ether. The solid product (0·8 g, 67%) was recrystallized for analysis from benzene and n-hexane, m.p. 123–125°, after resolidification the needles had m.p. 280°; UV

spectrum in EtOH: λ 2380 Å (ε 21,900); NMR spectrum: CD_3SOCD_3 τ = 5·91 (s, 5-CH_3O), 7·43 (s, 7-CH_3), and two multiplets centered at 1·82 and 2·40 (Ph). (Found: C, 59·87; H, 4·89; N, 28·88; $C_{12}H_{11}N_5O$ requires: C, 59·74; H, 4·60; N, 29·03%).

6-*Methyl*-3-*phenyl*-s-*triazolo*[4.3-a]1,3,5-*triazin*-5(6H)*one* (XI, R = H)

A mixture of X (R = H; 0·75 g), lead tetraacetate (1·7 g) and benzene (50 ml) was stirred at room temp for 5 hr, then heated to boiling and filtered hot. The product was triturated with iced water (15 ml), filtered and washed with 5 ml water. The pure compound was obtained after recrystallization from EtOAc (0·4 g, 53%), m.p. 200–220°, from the melt needles were formed and they melted at 280°; UV spectrum in EtOH: λ 2680 Å (ε 13,850); IR spectrum: KBr: 1755 cm^{-1} (CO); NMR spectrum at 75°: CD_3SOCD_3: τ = 1·63 (s, H_7), 6·52 (s, 6-CH_3), and two multiplets centered at 2·19 and 2·47 (Ph). (Found: C, 57·90; H, 4·08; N, 30·90; $C_{11}H_9N_5O$ requires: C, 58·14; H, 3·99; N, 30·82%).

8-*Methyl*-3-*phenyl*-s-*triazolo*[4.3-a]1,3,5-*triazin*-5(8H)*one* (XII, R = H)

(i) Compound XI (R = H) when sublimed at 210–220° was transformed into another compound with m.p. over 280° and with an IR spectrum identical with the product obtained as described under (ii).

(ii) When compound XIII (R = H) was heated above its m.p. at 130–150° for 5 min or when it was sublimed at 200°, it was transformed into XII (R = H); m.p. 300–320°; UV spectrum in EtOH: λ 2400 Å (ε 26,400); IR spectrum: KBr: 1760 cm^{-1} (CO); NMR spectrum at 75°: CD_3SOCD_3: τ = 1·46 (s, H_7), 6·40 (s, 8-CH_3), and two multiplets centered at 1·80 and 2·45 (Ph). (Found: C, 57·94; H, 4·18; N, 30·57; $C_{11}H_9N_5O$ requires: C, 58·14; H, 3·99; N, 30·82%).

6,7-*Dimethyl*-3-*phenyl*-s-*triazolo*[4.3-a]1,3,5-*triazin*-5(6H)*one* (XI, R = CH_3)

A mixture of X (R = Me; 0·4 g), lead tetraacetate (0·73 g) and benzene (7 ml) was stirred at room temp for 3 hr. The product was treated with water (5 ml) and the insoluble part (0·2 g) was recrystallized from benzene. From the filtrates an additional 75 mg of the product could be obtained after evaporation (total yield 69%), m.p. 197–200°, from the melt needles were formed and these melted at 315°; UV spectrum in EtOH: λ 2680 Å (ε 8,210); IR spectrum: KBr: 1725 cm^{-1} (CO); NMR spectrum: CD_3SOCD_3: τ = 6·52 (s, 6-CH_3), 7·42 (s, 7-CH_3), and two multiplets centered at 2·22 and 2·47 (Ph). (Found: C, 59·67; H, 4·62; $C_{12}H_{11}N_5O$ requires: C, 59·74; H, 4·60%).

7,8-*Dimethyl*-3-*phenyl*-s-*triazolo*[4.3-a]1,3,5-*triazin*-5(8H)-*one* XII (R = CH_3)

This compound could be obtained either by sublimation of XI (R = CH_3) or XIII (R = CH_3) at 240°. The product had m.p. 300–305° and IR spectra of both isomerized products were identical; UV spectrum in EtOH: λ 2400 Å (ε 25,700); IR spectrum: KBr: 1735 cm^{-1} (CO); NMR spectrum: CD_3SOCD_3: τ = 7·37 (s, 7-CH_3), 6·39 (s, 8-CH_3), and two multiplets centered at 1·86 and 2·48 (Ph), (Found: C, 59·67; H, 4·57– N, 28·82; $C_{12}H_{11}N_5O$ requires: C, 59·75; H, 4·60; N, 29·03%).

6,8-*Dimethyl*-3-*phenyl*-s-*triazolo*[4.3-a]1,3,5-*triazine*-5(6H),7(8H)*dione* (XV)

Compound XIV, when sublimed at 200°, was transformed into another compound with m.p. 222–225° (XV); UV spectrum in EtOH λ_{max} 2320 and 2580 Å (ε 24,750 and 12,910); IR spectrum: KBr: 1775 and 1700 cm^{-1} (CO); NMR spectrum: CD_3SOCD_3: τ = 6·66 (s, 6-CH_3), 6·42 (s, 8-CH_3), and two multiplets centered at 1·90 and 2·48 (Ph). (Found: C, 55·81; H, 4·21; N, 27·11; $C_{12}H_{11}N_5O_2$ requires: C, 56·02; H, 4·31; N, 27·23%).

6-*Methyl*-s-*triazolo*[4.3-a]1,3,5-*triazin*-5(6H)*one* (XVIII, R = CH_3, R_1 = H)

When XVII (R = CH_3, R_1 = H; 423 mg) was mixed with diethoxymethyl acetate (0·6 g) heat was evolved and from the initially formed soln crystals separated. The product (0·38 g, 84%) was recrystallized from dioxan; m.p. 165–167°; UV spectrum in EtOH: λ 2520 Å (ε 6600); IR spectrum: KBr: 1755 cm^{-1} (CO); NMR spectrum: CD_3SOCD_3: τ = 0·88 (s, H_3); 1·59 (s, H_7), 6·48 (s, 6-CH_3). (Found: C, 39·78; H, 3·58; N, 46·78; $C_5H_5N_5O$ requires: C, 39·73; H, 3·33; N, 46·34%).

6,7-*Dimethyl*-s-*triazolo*[4.3-a]1,3,5-*triazin*-5(6H)*one* (XVIII, R = R_1 = CH_3)

A mixture of XVII (R = R_1 = CH_3; 0·6 g) and diethoxymethyl acetate (0·8 g) was heated to 70°. From the resulting soln crystals separated and the product (0·6 g) was recrystallized from dioxan; m.p. 209–211; UV spectrum in EtOH: 2540 Å (ε 7700); 0·1N HCl: 2540 Å (ε 7820); IR spectrum: KBr: 1750 cm^{-1} (CO); NMR spectrum: CD_3SOCD_3: τ = 0·87 (s, H_3), 6·48 (s, 6-CH_3), 7·42 (s, 7-CH_3). (Found: C, 43·91; H, 4·46; N, 42·24; $C_6H_7N_5O$ requires: C, 43·63; H, 4·27; N, 42·41%).

s-Triazolo[2.3-a]1,3,5-*triazin*-5(6H)*one* (5-*azahypoxanthine*) (XIX, R = H)

Compound XVII (R = R_1 = H; 0·63 g) and diethoxymethyl acetate (2g) were heated under reflux for 10 min. After cooling, the product was filtered off (0·5 g) and recrystallized from dioxan; m.p. 265°, Lit.[39] gives m.p. 271°. (Found: C, 35·02; H, 2·43; N, 51·24; $C_4H_3N_5O$ requires: C, 35·04; H, 2·21; N, 51·09%); UV spectrum in EtOH: 2620 Å (ε 6620); 0·1N HCl: 2480 Å (ε 4980); 0·1 N NaOH: 2570 Å (ε 5950).

6-*Methyl-s-triazolo*[2.3-a]1,3,5-*triazin*-5(6H)*one* (XIX, R = CH_3)

The above XIX R = H; 0·2 g) was stirred in an ethereal soln of diazomethane at 0° for 3 hr. The oily product was crystallized from dioxan; m.p. 220°, Lit[39] gives m.p. 220°; UV spectrum in EtOH 2580 Å (ε 5940); 0·1 N HCl: 2540 (ε 6060); IR spectrum: 1750 cm^{-1} (CO). (Found: C, 39·54; H, 3·67; N, 46·75; $C_5H_5N_5O$ requires: C, 39·73; H, 3·33; N, 46·34%).

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