ON THE CHEMISTRY OF 1,2,4-TRIAZINE I.*

SYNTHESIS OF SUBSTITUTED 1,2,4-TRIAZIN-5-ONES FROM α-KETO ACID AMIDRAZONE DERIVATIVES

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Benzamidrazone reacts with glyoxylic acid or pyruvic acid under the formation of the corresponding amidrazone derivatives *Ia* or *Ib* which are cyclized on refluxing in water or dimethylformamide to 3-phenyl-2,5(4,5)-dihydro-1,2,4-triazin-5-one (*IIa*) and its 6-methyl derivative *IIb*, resp. Analogously, acetamidrazone hydrochloride affords hydrochlorides of glyoxylic acid and pyruvic acid acetamidrazone derivatives *Ic* and *Id*, the free bases of which (liberated by the action of a weak anion exchange resin) cyclize to 3-methyl-2,5(4,5)-dihydro-1,2,4-triazin-5-one (*IIc*) and its 6-methyl derivative *IId*, resp. Infrared and ultraviolet spectra indicate the predominance of the 2,5-dihydro-1,2,4-triazin-5-one tautomeric structure.

The most frequently used synthetic method in the preparation of 1,2,4-triazine derivatives consists in cyclization of α-keto acid semicarbazones or thiosemicarbazones (*A*) in the presence of alkali metal hydroxides or alkoxides[1]. Later on, this reaction was applied to compounds which may be theoretically derived from analogous isosemicarbazones or isothiosemicarbazones (*B*), *cf.* the cyclization of α-keto acid S-alkylisothiosemicarbazones[1-4] (*B*; Y = SR[2]) and guanylhydrazones[5-7] (*B*; Y = NH_2). These compounds, obviously due to a greater nucleophilicity of the terminal nitrogen atom, are cyclized very readily, namely, on refluxing in a suitable solvent or heating above the melting point[5].

* Papers I, II, IX, X, XI, XII, XVI, XVII, XXI, XXIV, XXV, XXXI, XXXVII, XLII, XLIX, LXI, LXV, LXXIII, LXXXII, LXXXIII, and CXXVI of the series "Nucleic acid components and their analogues" also relate to 1,2,4-triazine derivatives as the aza analogues of the naturally occurring pyrimidine derivatives. In these papers, the choice of 1,2,4-triazine derivatives, their reactions, and physico-chemical topics was influenced mainly by biochemical aspects. This original approach led later to a more detailed study on 1,2,4-triazine chemistry, synthetic methods, and preparation of further derivatives along with investigations on their physico-chemical properties. Since the later papers are not concerned with the original biochemical aspect, it was felt advisable to open a new series dealing exclusively with 1,2,4-triazine derivatives.

A similar course of cyclization might be expected with the related amidrazone derivatives of α-keto acids (*B*; Y = R^3). Condensation of amidrazones with α-dicarbonyl compounds represents a convenient method for the preparation of 1,2,4-triazine[8,9] and particularly its alkyl, aryl, and condensed derivatives[10–18]. Reaction of α-keto acids with amidrazones leading to alkyl- and aryl-1,2,4-triazin-5-ones *II* is being object of the present paper.

The benzamidrazone derivatives of glyoxylic acid (*Ia*) and pyruvic acid (*Ib*) were prepared by condensation of these acids with crude benzamidrazone obtained from benzimidoethyl ether and hydrazine. Both compounds are formed in a good yield but their preparation in the pure state is difficult. Because of the ready cyclization at elevated temperature, the crystallisation does not lead to individual products and the melting points are not characteristic. The chromatographic purification of these compounds is difficult because of their polar nature. For this reason, the crude benzamidrazone derivatives *Ia* and *Ib* were directly cyclized on refluxing in water or dimethylformamide under the formation of 3-phenyl-2,5(4,5)-dihydro-1,2,4-triazin-5-one (*IIa*) 6-methyl-3-phenyl-2,5(4,5)-dihydro-1,2,4-triazin-5-one (*IIb*), resp. This cyclization represents simultaneously the proof of structure of the parent compounds.

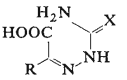
The preparation of α-keto acid acetamidrazone derivatives was performed with the use of acetamidrazone hydrochloride which is stable and may be obtained in the pure state[19]. Its condensation with glyoxylic acid and pyruvic acid led to hydrochlorides of acetamidrazone derivatives *Ic* and *Id*, resp. The free amidrazone derivatives *Ic* and *Id* were liberated by the action of a weak anion exchange resin (Amberlite IR 45 OH^-) and cyclized to 3-methyl-2,5(4,5)-dihydro-1,2,4-triazin-5-one (*IIc*) and its 6-methyl derivative *IId*, resp. In contrast to benzamidrazone derivatives *Ia* and *Ib*, the cyclization of acetamidrazone derivatives *Ic* and *Id* required a longer reaction period and a higher temperature. The noncyclic compounds *Ic* and *Id* may be consequently purified by crystallisation from water.

The above mentioned procedure is suitable for the preparation of 3- or 6-substituted dihydro-1,2,4-triazin-5-ones. Up to the present time, the compounds of this type have been prepared by hydrolysis of the corresponding 5-aminotriazines[20]. The course of cyclization is simultaneously in accordance with our earlier considerations[5].

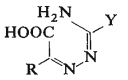
Investigations of the tautomeric structure of the above compounds required 1,2,4-triazinone substituted on the nitrogen atom at position 2 (*III*) or 4 (*IV*) as a model possessing the fixed double bond. The preparation of the 2-substituted triazinone *III* would start from a 2-substituted amidrazone which, however, is obviously inaccessible by the known synthetic procedures[21]. The reverse route, namely, condensation of pyruvic acid 2-methylhydrazone with alkyl iminoacetate was also unsuccessful. On the other hand, the 4-substituted as-triazinones (*e.g.*, *IV*) are readily accessible *via* 3-alkylamidrazones the benzylidene derivatives of which have been recently reported[22]. The benzylidene derivative of 3-methylformamidrazone

(benzaldehyde-methylaminomethylenehydrazone) was converted on refluxing in pyruvic acid to the corresponding 3-methylamidrazone derivative and this directly cyclized in refluxing dimethylformamide to 4,6-dimethyl-4,5-dihydro-1,2,4-triazin-5-one (*IV*).

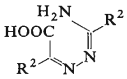
The 1,2,4-triazine derivatives *IIa–IId* may theoretically occurr in three tautomeric forms, namely, in the hydroxytriazine form (*C*) and two triazinone forms possessing the NH group in the *ortho* (*D*) or *para* (*E*) position in respect to the carbonyl group (an *o*-quinonoid or *p*-quinonoid type of conjugation). Determination of the predominant tautomeric form was effected with the use of infrared and ultraviolet spectra of compounds *IIa*, *IIb*, *IIc*, *IId*, and the 4,6-dimethyl derivative *IV* possessing the fixed 4,5-dihydro-1,2,4-triazin-5-one tautomeric form. For infrared spectra in the region of stretching vibrations of NH and C=O groups see Table I; ultraviolet spectra are listed in Table II.

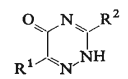


A (X = O, S)

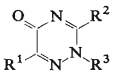


B (Y = SR^2, NH_2, R^3)

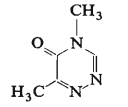




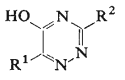
In formulae *I* and *II* *a*: $R^1 = H$, $R^2 = C_6H_5$; *c*: $R^1 = H$, $R^2 = CH_3$; *b*: $R^1 = CH_3$, $R^2 = C_6H_5$; *d*: $R^1 = R^2 = CH_3$.



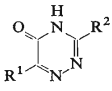
III



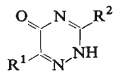
IV



C



D



E

Infrared spectra of chloroform solutions of compounds *IIa–IId* did not exhibit any absorption bands corresponding to ν(OH) vibrations. In all these spectra strong ν(NH) bands at about 3420 cm^{-1} are present. Consequently, the hydroxytriazine form (*C*) cannot predominate. The 3-phenyl derivatives *IIa* and *IIb* exhibit ν(NH)

TABLE I

Infrared Spectra in the ν(NH) and ν(C=O) Region, in Chloroform (cm^{-1})

Compound	ν(NH) bands[a]	ν(C=O) region						
IIa	3 424 s; 3 360 w	1 714 w, sh; 1 706 w;	1 676 w, sh;	1 667 m[b]		1 602 w	1 585 w;	1 546 m[c]
IIb	3 424 s; 3 364 w	1 704 m		1 667 m, sh;	1 656 m[b]	1 609 w, sh; 1 604 m; 1 600 m;	1 589 m;	1 549 s[c]
IIc	3 417 vs; 3 358 m	1 708 m	1 683 w, sh;	1 669 s[b];	1 653 m, sh	1 607 w		1 571 s[c]
IId	3 420 vs; 3 363 m	1 704 w		1 664 m[b]		1 601 w	1 585 w, sh;	1 572 m[c]
IV	—	1 691 vs[c];	1 682 vs, sh;	1 659 m, sh		1 609 w, sh; 1 592 s[b]		1 551 w

[a] Bands were separated on a computer; [b] the 2nd most intensive band in the carbonyl region; [c] the most intensive band in the carbonyl region.

TABLE II

Ultraviolet Spectra

Compound	pH or solvent	Form[a]	λ, nm (log ε)			Compound	pH or solvent	Form[a]	λ, nm (log ε)		
IIa	[b]	N	208 (4·13)	244 (4·43)		*IIc*	9·4	A	227 (4·07)	277 (3·75)	
IIb	[b]	N	208 (4·15)	246 (4·43)		*IId*	[b]	N	—	237 (4·01)	sh 260 (3·78)
IIc	−1·0[c]	C	217 (4·01)	248 (3·63)		*IV*	−1·0[c]	C	228 (3·81)	250 (3·57)	
IIc	4·4	N	—	232 (4·06)	sh 257[d](3·74)	*IV*	6·8	N	221 (3·83)	267 (3·72)	
IIc	[b]	N	—	233 (4·05)	sh 260 (3·65)	*IV*	[b]	N	219 (3·83)	271 (3·72)	

[a] N, neutral form; C, cation; A, anion; [b] ethanol; [c] 5N-H_2SO_4; [d] shoulder.

bands at 3425 cm^{-1}, *i.e.*, according to Mason[23], in the region corresponding to the *p*-quinonoid type of conjugation. The ν(NH) bands of 3-methyl derivatives *IIc* and *IId* are situated at a somewhat lower wave number which does not allow to decide unequivocally between the *p*- and *o*-quinonoid structure. In the carbonyl region, the spectra of compounds *IIa*–*IId* are very similar to each other but differ from that of compound *IV*. The strongest bands in spectra of compounds *IIa*–*IId* in the 1670 to 1655 cm^{-1} and 1575–1545 cm^{-1} region (the latter band is more intensive) indicate an analogous type of conjugation to that of 4-pyridone (1632 cm^{-1}, a = 500; 1516 cm^{-1}, a = 530), *cf.*[24]. Obviously, the ν(C=O) vibration participates in both these absorption bands analogously to 4-pyridone. On the other hand, the most intensive band of 4,6-dimethyl-4,5-dihydro-1,2,4-triazin-5-one (*IV*) corresponding predominantly to ν(C=O) is situated at 1691 cm^{-1} (shoulder at 1682 cm^{-1}).

Analogously, the ultraviolet spectra of 3-methyl derivatives *IIc* and *IId* in ethanol are similar to each other and considerably differ from that of compound *IV*, measured in the same medium (see Table II). On the other hand, ultraviolet spectra of cations *IIc* and *IV* are similar as it may be seen from Fig. 1. Both cations possess obviously the same resonance structure. Measurements of ultraviolet spectra of the 3-methyl derivative *IIc* in buffers of different pH values were used to determine the approximate dissociation constant of the neutral form of compound *IIc*, namely, 7·2. This value may be compared with the pK value (5·94) of 3-methylthio-2,5-dihydro-1,2,4-triazin-5-one[25] which was shown to possess the *p*-quinonoid tautomeric structure[26,27].

In spite of the inaccessibility of 2-methyl-1,2,4-triazin-5-one for a direct spectral proof, the different spectra of compounds *IIa*–*IId* on the one side and the 4-methyl

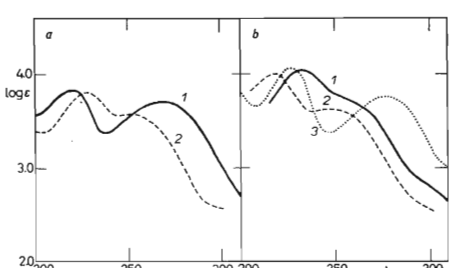


FIG. 1

Ultraviolet Spectra

a) *IV*, ——— neutral form, pH 6·8; — — — cation, H_0 −1; *b*) *IIc*, ——— neutral form, pH 4·5; — — — cation, H_0 −1; ... anion, pH 9·5.

derivative *IV* on the other as well as the absolute ν(NH) and ν(C=O) wave number values clearly favour the *p*-quinonoid, *i.e.*, 2,5-dihydro-1,2,4-triazin-5-one structure as the predominant tautomeric form of 1,2,4-triazin-5-one 3-methyl and 3-phenyl derivatives in chloroform, ethanolic, and aqueous media. The occurrence of the *p*-quinonoid form was shown also in the case of 3-amino-1,2,4-triazin-5-one[27] (6-azaisocytosine) and (*vide supra*) 3-methylthio-1,2,4-triazin-5-one[26,27]. The *p*-quinonoid structure obviously represents the energetically most advantageous form of the 1,2,4-triazin-5-one system.

Infrared spectra of compounds *IIa*–*IId* (in chloroform as solvent) exhibit also weaker ν(NH) bands at 3360 cm^{-1} and ν(C=O) bands at about 1705 cm^{-1} which probably correspond to a lesser amount of the *o*-quinonoid tautomeric form in the equilibrium mixture. Thus, *e.g.*, 4-pyrimidinone predominating in the *o*-quinonoid form[23] exhibits in the monomeric state in chloroform a ν(NH) band at 3380 cm^{-1} and ν(C=O) band at 1704 cm^{-1} (*cf.*[28]). Under the assumption of an equal absorptivity and half intensity band width of ν(NH) bands of the *p*-quinonoid and *o*-quinonoid form, the ratio of integrated absorption intensities of both bands, separated on the computer, indicates for compounds *IIa*–*IId* in chloroform solution constants K_T of the tautomeric equilibrium 4(H) $\rightleftarrows$ 2 (H) in the range of 2·6 to 4·6. The proportion of the *o*-quinonoid form with compounds *IIa*–*IId* is thus considerably higher than with 3-dimethylamino-2,5-dihydro-1,2,4-triazin-5-one the K_T value of which in aqueous solutions was estimated[27] to be within the order of magnitude of 100.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). Unless stated otherwise, the analytical samples were dried at room temperature for 8 hours at 0.1 Torr.

Spectroscopic Measurements

Infrared spectra. Because of the considerably low solubility of compounds *IIa*–*IId* in chloroform, the measurements were performed with saturated solutions ($c < 5 \cdot 10^{-3}$M) in 4 cm (the ν(NH) region) and 2·6 mm (the ν(C=O) region) cells. The spectra were measured on a Perkin-Elmer 621 apparatus. Separation of ν(NH) bands and calculation of integrated absorption intensities was effected by the modified method of Meiron[29] using damped least squares[30] on an Elliott 503 computer.*

Ultraviolet spectra. Measurements were performed on a single-beam Optica Milano CF 4 spectrophotometer.

Glyoxylic Acid Benzamidrazone Derivative (*Ia*)

A 5M solution of sodium hydroxide (6 ml) was covered with ether (25 ml) and treated with benzimidoethyl ether hydrochloride (3·72 g; 20 mmol). The mixture was shaken until the solid

* Vitek A.: Program FA 450. Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague 1969.

dissolved. The ethereal layer was separated and the aqueous layer extracted with three 25 ml portions of ether. The ethereal solutions were combined, dried over anhydrous magnesium sulfate, and concentrated to the volume of 50 ml. Methanolic hydrazine (0·605 g; 20 mmol) was then added to the concentrate, the mixture allowed to stand at 3°C for 12 hours, and evaporated to dryness under diminished pressure. The residue was diluted with ethanol (20 ml) and a solution of glyoxylic acid monohydrate (1·84 g; 20 mmol) in ethanol (6 ml) was added. The mixture was allowed to stand at 3°C for 12 hours and then precipitated portionwise with ether (total 150 ml) to afford the first crop of the crude derivative *Ia* (2·6 g; 68%). Mother liquors were evaporated to give the second crop which was directly cyclized to the triazinone *IIa* (yield, 0·5 g; *vide infra*). Total yield of compound *Ia* 3·4 g (88%; referred to crude *Ia* and recalculated from the triazinone *IIa*).

Pyruvic Acid Benzamidrazone Derivative (*Ib*)

The procedure was analogous to the preparation of compound *Ia*. Thus, 3·7 g (20 mmol) of ethyl iminobenzoate hydrochloride, 0·605 g (20 mmol) of hydrazine, and 1·76 g (20 mmol) of pyruvic acid afforded 1·8 g (43%) of the crude amidrazone derivative *Ib* and 0·9 g of the triazinone *IIb*. Total yield, 2·9 g (70%) of the derivative *Ib* (calculated as above).

3-Phenyl-2,5(4,5)-dihydro-1,2,4-triazin-5-one (*IIa*)

The benzamidrazone derivative *Ia* (0·191 g; 1 mmol) was refluxed in dimethylformamide (3 ml) for 15 minutes, the solution evaporated to dryness under diminished pressure, and the residue crystallised from water (active charcoal) to afford 0·124 g (71%) of compound *IIa*, m.p. 249 to 250°C (reported[20], m.p. 245°C). For $C_9H_7N_3O$ (173·2) calculated: 62·42% C, 4·07% H, 24·26% N; found: 62·47% C, 4·33% H, 24·24% N.

3-Phenyl-6-methyl-2,5(4,5)-dihydro-1,2,4-triazin-5-one (*IIb*)

The procedure was analogous to the preparation of compound *IIa*. Thus, 0·205 g (1 mmol) of the amidrazone derivative *Ib* afforded 0·166 g (89%) of compound *IIb*, m.p. 245—247°C (no melting point value is given in the literature[20]). For $C_{10}H_9N_3O$ (187·2) calculated: 64·16% C, 4·85% H, 22·45% N; found: 64·05% C, 4·64% H, 22·51% N.

Glyoxylic Acid Acetamidrazone Derivative (*Ic*)

Glyoxylic acid monohydrate (0·92 g; 10 mmol) was added to a solution of acetamidrazone hydrochloride[19] (1·09 g; 10 mmol) in water (6 ml), the reaction mixture allowed to stand at room temperature for 30 minutes, and then passed through a column (10 ml) of Amberlite IR 45 (OH^-) ion exchange resin. The column was eluted with water and the eluate evaporated to dryness under diminished pressure. Crystallisation of the residue from water afforded 0·99 g (63%) of the hydrate of the amidrazone derivative *Ic*. For $C_4H_7N_3O_2 . 1\frac{1}{2} H_2O$ (156·1) calculated: 30·77% C, 6·46% H, 26·91% N; found: 31·02% C, 6·89% H, 26·13% N.

Pyruvic Acid Acetamidrazone Derivative (*Id*)

The procedure was analogous to the preparation of compound *Ic*. Thus, 0·55 g (5 mmol) of acetamidrazone hydrochloride and 0·44 g (5 mmol) of pyruvic acid afforded 0·46 g (64%) of compound *Id*. For $C_5H_9N_3O_2$ (143·1) calculated: 41·95% C, 6·34% H, 29·35% N; found: 42·19% C, 6·09% H, 29·32% N.

3-Methyl-2,5(4,5)-dihydro-1,2,4-triazin-5-one (*IIc*)

A solution of the acetamidrazone derivative *Ic* (0·313 g; 2 mmol) in dimethylformamide (3 ml) was refluxed for 30 minutes, evaporated to dryness under diminished pressure, and the residue recrystallised from ethanol to afford 0·147 g (66%) of compound *IIc*, m.p. 203—205°C. For $C_4H_5N_3O$ (111·1) calculated: 43·24% C, 4·54% H, 37·87% N; found: 43·42% C, 4·86% H, 37·72% N.

3,6-Dimethyl-2,5(4,5)-dihydro-1,2,4-triazin-5-one (*IId*)

A solution of the acetamidrazone derivative *Id* (0·143 g; 1 mmol) in dimethylformamide (3 ml) was refluxed for 1 hour, evaporated to dryness under diminished pressure, and the residue crystallised from ethanol to afford 0·107 g (85%) of compound *IId*, m.p. 275—276°C. For $C_5H_7N_3O$ (125·1) calculated: 47·99% C, 5·64% H, 33·58% N; found: 47·97% C, 5·74% H, 33·61% N.

4,6-Dimethyl-4,5-dihydro-1,2,4-triazin-5-one (*IV*)

Pyruvic acid (0·44 g; 5 mmol) was added to a suspension of benzaldehyde-methylaminomethylenehydrazone monohydrate[22] (0·89 g; 5 mmol) in water (30 ml) and the mixture distilled to remove benzaldehyde. The residual solution was evaporated to dryness under diminished pressure and the residue refluxed in dimethylformamide (6 ml) for one hour. The solution was evaporated to dryness under diminished pressure and the residue purified by chromatography on a column of silica gel (20 g) according to Pitra and Štěrba[31] in ethyl acetate to afford 0·335 g (53%) of compound *IV*, m.p. 105—108°C. For $C_5H_7N_3O$ (125·1) calculated: 47·99% C, 5·64% H, 33·58% N; found: 48·41% C, 5·93% H, 33·34% N.

Elemental analyses were performed in the Analytical Department (Dr J. Horáček, Head) of our Institute.

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