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Aminolysis of 1,2,3-Benzotriazin-4(3*H*)-thione

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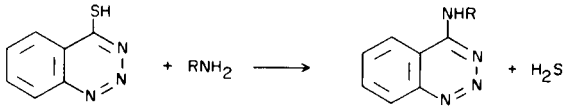
A series of 4-*N*-substituted 1,2,3-benzotriazin-4(3*H*)-imines was prepared by aminolysis of 1,2,3-benzotriazine-4(3*H*)-thione and its 6-chloro derivative with primary aliphatic amines. The reaction was shown to be sensitive to amine structure and to reaction conditions. Frequently observed tar formation is attributed to instability resulting from the cryptodiazonium character of the triazine ring. Spectral data substantiate the thiono and imino structures of the starting compounds and products, respectively, in the solid state.

A series of *N*-substituted 4-aminobenzo-1,2,3-triazines (IIa) was desired for testing as potential antimalarials. A promising approach to the preparation of such compounds appeared to involve aminolysis of 1,2,3-benzotriazine-4-thiol (Ia):

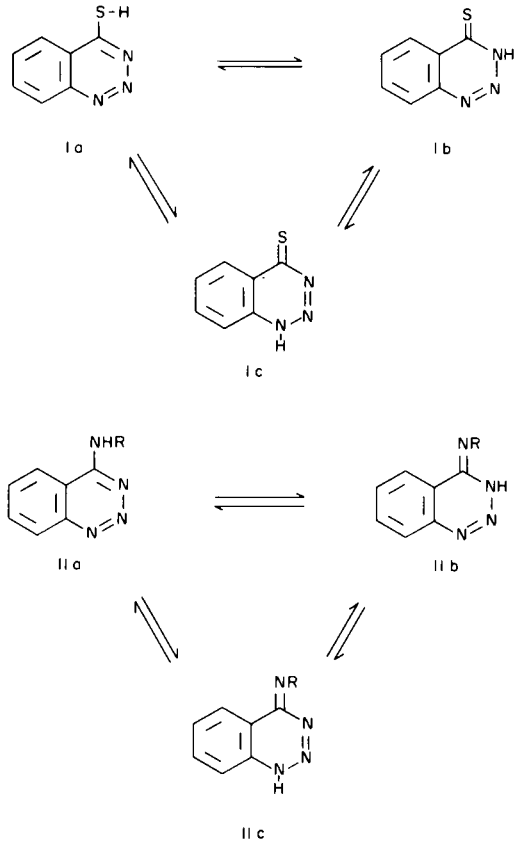


Ia IIa

Although this specific reaction is unknown, one stated to be of this general type was reported by Grundmann and Ulrich (2) using hydrazine with the 7-chloro analog of Ia. However, for unexplained reasons they employed the methyl thioether of Ia when preparing the unchlorinated analogs by reaction with hydrazine or ammonia. Presumably this was done because the aminolysis of some heterocyclic methyl thioethers, for example those derived from thiohydantoins (3), proceeds more easily than that of the parent thiols. We have found, however, that the reaction occurs directly with Ia, and that the extra methylation step is therefore unnecessary. Leonard and Curtin (4) similarly prepared *N*-substituted 4-amino quiazolines by aminolysis of 4-mercaptoquinazoline.

Although Ia reacts with hydrazine in refluxing ethanol (*ca.* 78°), efforts to employ this procedure with *n*-butylamine were without success. The use of a higher reaction temperature (refluxing 1-butanol, *ca.* 118°), however, did give the desired product. Compounds prepared by this method are listed in Table I.

Compound Ia and those of type II are capable of tautomerism as follows:



Structures Ia and IIa, rather than the tautomeric forms, have in the past been tacitly assumed to be correct without

TABLE I

4-*N*-Substituted 1,2,3-Benzotriazin-4(3*H*)imines

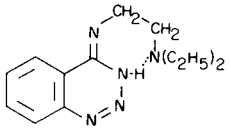
Compound	R (a)	Percent Yield (b)	M.P., °C	Molecular Formula	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
III	*n*-C_4H_9-	55	153-155	$C_{11}H_{14}N_4$	65.3	6.9	27.7	65.1	7.0	27.4
IV	*n*-C_4H_9- (c)	40	198	$C_{11}H_{13}ClN_4$	55.7	5.5	---	55.5	5.8	---
V	$(C_2H_5)_2N(CH_2)_2$-	63	130-132	$C_{13}H_{19}N_5$	63.7	7.8	28.5	63.4	7.5	28.5
VI	$(C_2H_5)_2N(CH_2)_2$- (c)	35	181-182	$C_{13}H_{18}ClN_5$	55.8	6.5	---	56.0	6.7	---
VII	$C_2H_5O(CH_2)_3$-	48	112-114	$C_{12}H_{16}N_4O$	62.0	7.0	---	62.0	7.1	---
VIII	1-*n*-$C_6H_{13}O(CH_2)_3$-	40	95-97	$C_{16}H_{24}N_4O$	66.6	8.3	19.4	66.9	8.5	19.1
IX	$C_6H_5CH_2$-	32	204-205	$C_{14}H_{12}N_4$	71.2	5.1	---	70.9	5.3	---
X	$C_6H_5CH_2$- (c)	30	201-204	$C_{14}H_{11}ClN_4$	62.1	4.1	---	62.3	4.3	---
XI	4-$CH_3OC_6H_4CH_2$-	46	205-207	$C_{15}H_{14}N_4O$	67.7	5.3	21.1	67.9	5.6	21.2
XII	4-$ClC_6H_4CH_2$-	45	213-214	$C_{14}H_{11}ClN_4$	62.1	4.1	---	62.2	4.3	---
XIII	$C_6H_5(CH_2)_2$-	50	200-202	$C_{15}H_{14}N_4$	72.0	5.6	22.4	71.6	5.5	22.4
XIV	$C_6H_5(CH_2)_3$-	60	145-147	$C_{16}H_{16}N_4$	---	--	21.2	---	--	21.1

(a) R as in Formula II b or c, except as indicated. (b) Expressed as mole percent basis of I used. (c) 6-Chloro derivatives.

any experimental basis (5, 6, 7). We have found, however, that the solid state infrared spectrum of I, as well as of its 6- and 7-chloro derivatives, shows absorption at 3100 cm^{-1}, corresponding to prior assignments for ring -NH-. The thiono structure Ib or Ic is therefore preferred to the thiol form Ia; it is not possible to differentiate between Ib and Ic. The thione form is in fact currently favored in many ring compounds of this general type (7). The more acidic form Ia would, of course, predominate in solution in the presence of an amine.

The oxygen analog of I gave a similar spectrum and is therefore concluded to exist in the keto rather than the enol form. The complex band system at 1690 cm^{-1} also points to the amide structure.

In the case of II (R=H), solid state infrared bands were noted at 3320 and 3100 cm^{-1}. The former suggests the presence of =NH, and the latter is in the range found for NH modes in indazole derivatives, which contain the -NHN= moiety. These observations are consistent with imino structure IIb or IIc, but do not differentiate between them. On the other hand, amino structure IIa would require two absorption bands above 3300 cm^{-1} separated by 60 to 80 cm^{-1}, which were not observed. Compounds III, V and XII gave similar solid state infrared spectra, and therefore are concluded to have the imino form. The solid state spectrum of compound XI, on the other hand, indicates that it has the amino configuration IIa, since the -NH- stretch appears at 3345 cm^{-1}. The solution infrared spectrum of V shows a band at 3370 cm^{-1} with a width at half-peak height of 60 cm^{-1}, suggesting strong intramolecular hydrogen bonding as in structure Va.



V a

Solution UV spectra of all five of the above compounds have the same pattern. The spectra are nearly identical, except for that of II (R=H), in which the maxima are shifted 50 to 100 Å to shorter wavelengths. These spectra show that all of these compounds have the same structure in solution, but they do not distinguish between the amino and imino configurations.

It will be noted that preparation of all of the derivatives listed in Table I involves the use of primary aliphatic or aralkyl amines. Extensive but unsuccessful efforts were made to extend the reaction to other amines, as follows. Primary diamines (ethylenediamine, 1,6-diaminohexane, and *N,N'*-bis(3-aminopropyl)piperazine) appeared to react as usual in refluxing 1-butanol; normal hydrogen sulfide evolution was observed, and no tar formation was noted. However, the products appeared to comprise a mixture of unreacted starting material, "mono" and "di" derivatives,

and other unknown compounds which could not be separated by crystallization procedures.

Branched-chain primary amines (*sec*-butylamine, cyclohexylamine) did not react in refluxing butanol, but hydrogen sulfide evolution was noted in refluxing 2-ethoxyethanol (*ca.* 135°). However, the reaction products comprised intractable tars from which nothing definite could be isolated. Secondary amines (di(*n*-butyl)amine, piperidine) similarly reacted only in 2-ethoxyethanol, again with complete decomposition. Use of acetonitrile as the reaction solvent gave no improvement. Since the methylthio ethers of some heterocyclic compounds undergo aminolysis more easily than the parent thiols (3), an attempt was made to obtain the cyclohexylamino derivative by this procedure. No improvement was noted, however.

Aniline failed to react even at 135° in refluxing 2-ethoxyethanol, since no evolution of hydrogen sulfide was observed. The somewhat more basic aromatic amine, 4-anisidine, behaved likewise. Apparently the even more strongly basic aliphatic amines are required for decomposition to occur at this temperature.

Hydrazine, both in our hands and as reported in the literature (2), reacts easily with I in refluxing ethanol forming the desired product in good yield. Attempts to prepare analogous compounds from methylhydrazine, 1,1-dimethylhydrazine or phenylhydrazine were, however, unsuccessful, both in ethanol and in 1-butanol.

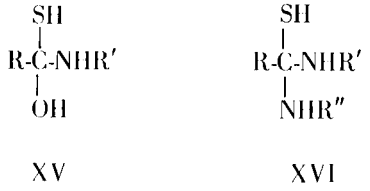
Our results appear consistent with those noted by Leonard and Curtin in their study of the aminolysis of 4-mercaptoquinazoline (4). They obtained 70-80% yields with primary aliphatic amines, and 0-27% with secondary. Our lower yields from primary amines, and our failure to obtain any product from secondary amines, may reflect the instability of the 1,2,3-benzotriazine ring compared with quinazoline. On the other hand, we noted no reaction with aniline under conditions found by Leonard and Curtin to give the desired product, albeit in poor yield.

As indicated in Table I, three derivatives of 6-chloro-1,2,3-benzotriazine-4(3*H*)-thione were prepared. The 7-chloro analog also appeared to react normally with *n*-butylamine and with 2-(diethylamino)ethylamine. However, the products could not be obtained analytically pure, although the spectral and analytical data suggest that the desired materials were in fact formed.

The results obtained show that aminolysis of I is quite sensitive to reaction conditions and to the structure of the amine used. This will be discussed in turn.

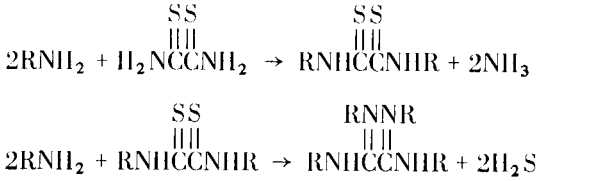
Previous work has shown that the 1,2,3-benzotriazines as a class are fairly unstable and in fact are more correctly regarded as cryptodiazonium compounds (5, 6, 8). The triazine ring opens under acid or alkaline conditions, with the side chain carbon atom often generating a nitrile, amide or an acid group. The appearance of a nitrile band at 2220 cm^{-1} in our tarry reaction mixture indicates this type of decomposition.

The failure of branched-chain primary amines to react suggests that steric hindrance may be involved. There are several reported instances of steric interference with nucleophilic attack of the positive thiono carbon atom of thioamides. Such has been noted both with open-chain thioamides, and with compounds in which that group is part of a heterocyclic ring. The 4-thiono group in 5,5-dimethyl-2,4-dithiohydantoin can be hydrolyzed to a carbonyl group, but the diethyl and cyclopentamethylene analogs are unreactive (9). *N*-Alkyl monothionsuccimides give hydrolysis rate data which "are in agreement with the general prediction which would be anticipated by Newman's "rule of six" and can readily be explained in terms of steric effects where the alkyl substituent shows nucleophilic attack by water in the rate-determining step" (10). The transition state in these examples has the tetrahedral configuration XV.



XV XVI

More directly analogous to our reaction is the aminolysis of dithiooxamide, studied by Hurd and coworkers (11):



Both steps in this reaction, as well as that studied by us, involve transition states of the structure XVI, which is even more sterically demanding than XV. The results obtained by Hurd and coworkers are similar to those noted by us. They also found that their reaction proceeded with primary aliphatic amines, but that aromatic and secondary aliphatic amines were inoperative. Although we found cyclohexylamine unreactive, Hurd and coworkers noted that it did react, but more slowly and only over an extended period of time. They suggested that "steric hindrance of the nucleophilic attack of the amine at the thionyl carbon atom may be the explanation", but did not discuss this conclusion in any further detail. We experienced no difficulty, however, in constructing Fischer-Taylor-Hirschfelder models of the transition state of type XVI, as well as the final product, when starting with I

and isobutylamine. The reason for the selectivity of this reaction is therefore not immediately obvious.

EXPERIMENTAL

Methods.

Melting points were taken in capillary tubes on a Mel-Temp block and are uncorrected. Infrared spectra were determined in potassium bromide pellets with a Perkin-Elmer Model 521 spectrophotometer and in some cases in Nujol mulls with a Perkin-Elmer Infracord 137. Ultraviolet spectra were determined in absolute ethanol with a Cary Model 14 spectrophotometer.

1,2,3-Benzotriazin-4(3*H*)-thione (I).

The procedure of Grundmann and Ulrich (2), involving diazotization of 2-aminobenzothioamide gave the product in similar yields and with the same melting point; ir (potassium bromide), 3100, 2970-2800 (NH resonance in -N=N-NH- ⇌ -NH-N=N-), 1275, 1220, 1180, 1135, 905 cm^{-1} (five most intense bands 1700-700 cm^{-1}). The published procedure for preparing 2-aminobenzothioamide (12), involving the addition of hydrogen sulfide to 2-aminobenzonitrile over 10 hours, followed by a workup requiring several days, was considerably improved by employing a method developed at this laboratory (13), as follows: 2-aminobenzonitrile (Aldrich Chemical Co., 100 g., 0.85 mole), 500 ml. of dimethylformamide, and 1.2 ml. of diethylamine catalyst were mixed in a laboratory reaction flask and the mixture was heated to 50-60°. Sixty-six g. (1.9 moles) of hydrogen sulfide was bubbled into the reaction mixture over 2 hours with stirring, after which the mixture was stirred at that temperature for 1 hour. The solvent was largely removed in a rotary vacuum drier, and the 157 g. of residue was added to several volumes of water. Filtration, washing and drying gave 115 g. (89%), m.p. 115-120° (lit. (12) 121.5°); ir (Nujol) 3450, 3250, 3100 (NH stretches), 1650, 1620, 1590 (NH_2 deformations), 1410 (C=S (probable)), 906, 758 cm^{-1} (other strong bands).

6-Chloro-1,2,3-benzotriazine-4(3*H*)-thione.

This compound was prepared in a manner similar to I by diazotization of 2-amino-5-chlorobenzothioamide, m.p. 207° dec.; ir (potassium bromide) 3100, 2960 (NH stretches), 1585, 1550 (ring modes), 1445 (C=S (probable)), 1180, 1120 cm^{-1} (other strong bands).

Anal. Calcd. for $C_7H_4ClN_3S$: C, 42.5; H, 2.0. Found: C, 42.8; H, 2.2.

2-Amino-5-chlorobenzothioamide.

This compound was prepared in 80% crude yield by the reaction of hydrogen sulfide with 2-amino-5-chlorobenzonitrile (14) using pyridine as the solvent and triethylamine as the catalyst (2). It had m.p. 142-143.5°; ir (potassium bromide), 3100, 3000 (NH stretches), 1650, 1600, 1550 (NH_2 deformations), 1465 or 1420 (C=S (probable)), 1145, 920 cm^{-1} (other strong bands).

Anal. Calcd. for $C_7H_7ClN_2S$: C, 45.0; H, 3.8. Found: C, 44.9; H, 3.9.

7-Chloro-1,2,3-benzotriazine-4(3*H*)-thione.

This compound was prepared by the published procedure (2) in the yield given. Our best m.p. (205°) was, however, lower than that reported (215°). The required intermediate, 2-amino-4-chlorobenzothioamide, was prepared in 84% crude yield by reaction of the corresponding nitrile with hydrogen sulfide using pyridine as solvent and triethylamine as the catalyst (2). The yield was only 50% employing dimethylformamide and diethylamine, as used above for preparation of the unchlorinated thioamide.

4-(*n*-Butylimino)-(3*H*)-1,2,3-benzotriazine (III).

Into a 100 ml. reaction flask was placed 6.5 g. (0.04 mole) I, 75 ml. 1-butanol and 3.3 g. (0.045 mole) of *n*-butylamine. The mixture was heated to reflux. Rapid evolution of hydrogen sulfide was noted at first; after 5 hours this was very slight and heating was discontinued. The solvent was removed *in vacuo* at 100°. The solid residue was recrystallized from 200 ml. of benzene. The yield was 4.6 g. (55%), m.p. and analytical data are cited in Table I; ir (potassium bromide) 3220, 3110 (NH stretches), 2945, 2920, 2850 (CH stretches), 1610, 1585 (ring modes), 1160, 1125, 760 cm^{-1} (other strong bands).

The other compounds listed in Table I were prepared similarly, with reaction times varying from 0.5 to 8 hours, depending upon the rate of evolution of hydrogen sulfide.

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