

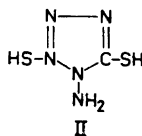
The True Dithio-*p*-urazine and Some Related Sym-tetrazine Derivatives

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Tetrahydro-*sym*-tetrazine-3,6-dithione, or dithio-*p*-urazine, has been prepared by reaction between thiocarbonylhydrazide and the disodium salt of dicarboxymethyl trithiocarbonate. The structure of this potentially tautomeric compound has been investigated by means of infrared and ultraviolet spectra and by nuclear magnetic resonance. The evidence tends to favour the dithione form. By reaction between dithio-*p*-urazine and organic halides in alkaline solution a series of dialkylthio-dihydro-tetrazines has been prepared, from which the corresponding tetrazines have been obtained by oxidation. The dithio-*p*-urazine is rearranged by hot hydrochloric acid to the isomeric 3,5-dimercapto-4-amino-4,1,2-triazole, whereas the dialkylthio-dihydro-tetrazines undergo ring-opening without recyclization under the same conditions. The ultraviolet and infrared spectra of the tetrazines are briefly discussed.

In a previous communication ¹ the compound described by earlier authors as dithio-*p*-urazine (I) has been shown to be 3,5-dimercapto-4-amino-4,1,2-triazole (II). The true dithio-*p*-urazine has now been prepared in 45 % yield by reaction between thiocarbonylhydrazide and the disodium salt of dicarboxymethyl trithiocarbonate in aqueous solution at room temperature. All attempts to increase the yield by varying solvent, pH, or temperature have invariably led to inferior results.



The general structure of dithio-*p*-urazine is demonstrated by its transformation to dihydro-tetrazines and tetrazines as described later. The infrared spectrum shows no bands in the region 2 800—1 550 cm⁻¹, which indicates

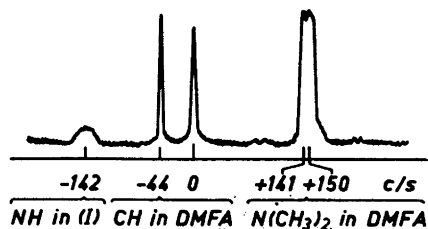
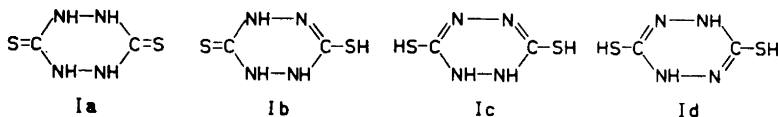


Fig. 1. NMR spectrum of dithio-*p*-urazine in DMFA solution. External standard: benzene.

that primary amino groups are absent. However, within this structural frame four protometric forms (Ia–Id) are possible, and attempts have been made to establish, which of these is the dominating one. Proton magnetic resonance has been recorded in dimethylformamide solution and shows only the broad NH signal and no sign of the sharp SH signal² (Fig. 1). This indicates that the form (Ia) should dominate, at least in dimethylformamide solution. However, Meyer *et al.*³ have found the chemical shift δ -value with respect to the proton resonance in water to be -0.20 for the thiol proton in thiophenol and -0.24 for the methyl protons in dimethylformamide. Therefore, it is possible that the SH signal is not resolved from the CH_3N signal in the present case, and the conclusion must be regarded as tentative. Unfortunately, the low solubility of dithio-*p*-urazine has precluded the use of solvents other than dimethylformamide. Recently Hoffman⁴ and Gronowitz and Hoffman⁵ have employed proton magnetic resonance in order to show that 2-thiouracil exists in the thione form in dimethylsulphoxide solution.

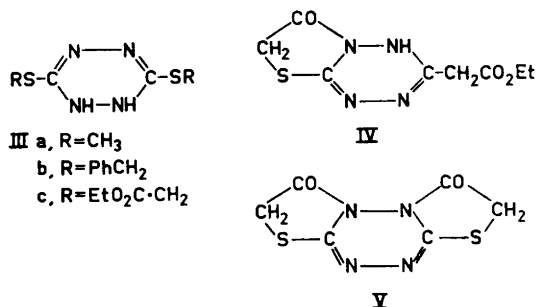


The solid state seems to be composed of the form (Ia), since, as was pointed out above, no absorption bands occur in the region $2800\text{--}1550\text{ cm}^{-1}$, when the infrared spectrum is recorded in a potassium bromide disk. Thus, absorption bands due to S—H stretching vibration around 2500 cm^{-1} , and to C=N stretching vibration, which appear in the spectra of the dihydrotetrazines (III) in the region $1640\text{--}1620\text{ cm}^{-1}$, are absent.

The ultraviolet spectrum of (I) also seems to eliminate the dominance of the dithiol forms (Ic) and (Id) in ethanolic solution. The long-wave length absorption band of (I) appears at 2985 \AA with $\epsilon : 20\,400$, whereas the dihydrotetrazine (IIIa), which ought to have its ring protons in the same positions as the hypothetical dithiol forms of (I), has its main absorption band at 2215 \AA with $\epsilon : 13\,500$.

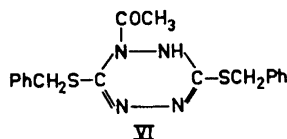
When dithio-*p*-urazine reacts with two equivalents of an organic halide in the presence of two equivalents of alkali, a dialkylthio-dihydrotetrazine (III) is formed. (For dihydrotetrazines, which are readily oxidized to tetrazines,

the 1,2-dihydro structure is generally accepted⁶.) In this way the dimethylthio- and dibenzylthio-dihydrotetrazines have been prepared. When the same reaction is performed with ethyl chloroacetate, complications arise due to secondary reactions between the ethoxycarbonyl groups and the NH groups of the ring. Three compounds have been isolated, *viz.* 3,6-bis-ethoxycarbonylmethylthio-1,2-dihydrotetrazine (IIIc), the bicyclic monolactam (IV), and the tricyclic dilactam (V).



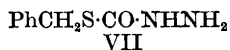
The pure diester (IIIc) is unchanged after boiling in ethanol for one hour. The monolactam (IV) is slowly transformed to the dilactam (V) under the same conditions. In acid solution the transformation is much more rapid. Unexpectedly, the yield of the diester (IIIc) does not increase at the expense of the lactams when the reaction is performed at 0°.

When sodium monochloroacetate and dithio-*p*-urazine react in alkaline medium, and the mixture is acidified, only the dilactam (V) is obtained. This dilactam is very slightly soluble in the common solvents and it does not melt below 300°, so a polymeric structure seems possible. However, the infrared spectrum indicates a monomeric structure. The carbonyl band of the dilactam (V) is found at 1 714 cm⁻¹, whereas that of *N*-acetyl-3,6-dibenzylthio-1,2-dihydrotetrazine (VI) appears at 1 650 cm⁻¹ (potassium bromide disks). Five-membered lactams are known to have their carbonyl frequency near 1 700 cm⁻¹, and in a fused ring system a further increase in carbonyl frequency can be expected⁷.

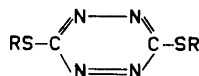


Dihydrotetrazines are known to undergo ring-contraction to the isomeric 4-aminotriazoles at elevated temperatures⁸ and also in hot acid medium^{9,10}. The dithio-*p*-urazine (I) is rearranged by hot dilute hydrochloric acid to dimercapto-aminotriazole (II). The dihydro-tetrazines (III) show a remarkable thermal stability, and the dimethyl derivative (IIIa) sublimes unchanged at 190°. In hot dilute hydrochloric acid the dihydrotetrazines undergo hydrolytic

cleavage, and from the dibenzyl derivative (IIIb) two hydrazides, *viz.* benzylthiocarbonyl-hydrazine (VII), and 1,2-bis-benzylthiocarbonyl-hydrazine (VIII) have been isolated, but no 3,5-dibenzylthio-4-amino-triazole has been



obtained. Dallacker¹¹ has investigated the corresponding reaction of 3,6-dipyridyl-dihydropyridazine and obtained 3,5-dipyridyl-4-amino-triazole together with 1,2-dipyridoylhydrazine.



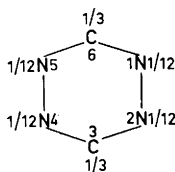
IX

a-c as in III

d, R=CH₂CO₂H

When the dihydropyridazines (III) are oxidized with nitrous acid, bromine, hydrogen peroxide, or ferric chloride, the corresponding tetrazines (IX) are formed in good yields as bright-red solids. When the reaction mixture from sodium monochloroacetate and dithio-*p*-urazine is treated with hydrogen peroxide prior to acidification, a good yield of 3,6-dicarboxymethylthio-tetrazine (IXd) results. The same compound is formed in lower yield when the dilactam (V) is dissolved in hot alkali and treated with hydrogen peroxide and the mixture is acidified.

The ultraviolet absorption spectrum of *sym*-tetrazine has been thoroughly investigated from a theoretical point of view by Liquori and Vaciago¹², and by Mason¹³⁻¹⁵, who have concluded that the maximum at 2 520 Å is due to a $\pi \rightarrow \pi$ transition and the one at 5 420 Å to a $n \rightarrow \pi$ transition (solvent *cyclohexane*). Furthermore, Mason¹³ has tentatively assigned a shoulder at 3 200 Å to a transition from the lowest lone-pair orbital to the second lowest

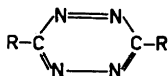


X

unoccupied π orbital. The latter has the form

$$\psi = 1/\sqrt{12} (2\Phi_3 - \Phi_4 - \Phi_5 - 2\Phi_6 - \Phi_1 - \Phi_2)$$

where Φ_i denote atomic orbitals, and when an electron is promoted from a non-bonding orbital to this orbital, its charge is distributed over the ring atoms according to (X). Therefore, the energy of the transition is lowered by electron-attracting substituents in the positions 3 and 6, and raised by electron-donating substituents in the same positions.

Table 1. Spectra of 

R	Solvent	λ_{\max} Å	ϵ	λ_{\max} Å	ϵ	λ_{\max} Å	ϵ
CH ₃ S	Heptane	2 810	23 000	4 100	655	5 380	390
CH ₃ S	Ethanol	2 830	21 500	4 170	615	5 280	360
PhCH ₂ S	Heptane	2 875	31 200	4 125	850	5 385	520
PhCH ₂ S	Ethanol	2 890	28 000	4 160	800	5 300	490
EtOCOCH ₂ S	Ethanol	2 790	25 000	4 060	910	5 230	460
NaOCOCH ₂ S	Water	2 580	15 600	4 130	1 070	5 310	280
H ^a	Cyclohexane	2 520	2 150			5 420	829
H ^a	Water (pH 7)	2 550	2 840			5 100	362
H ₂ N ^b	Dioxane			4 280	1 980	5 280	590
CH ₃ CONH ^b	Ether			3 630	1 800	5 250	520
<i>p</i> -Tosyl-NH ^b	Ether			3 630	1 860	5 270	560

^a From Ref.¹⁴

^b From Ref.¹⁶

The dialkylthio-tetrazines (IX) show the two first-mentioned maxima and in addition one near 4 100 Å (Table 1). In the spectrum of the dimethylthio-tetrazine (IXa) in heptane there is a slight vibrational structure (Fig. 2). The same bands appear in the spectra of 3,6-diamino-tetrazine and some of its derivatives¹⁶. However, the maximum near 4 100 Å cannot be due to a transition like the one proposed by Mason, since the effect of electron-donating substituents is opposite to that expected. When the electron-donating capacity of the amino groups in diamino-tetrazine is diminished by acylation, the absorption is shifted to a shorter wavelength. A similar effect, though smaller, is obtained, when a hydrogen atom in dimethylthio-tetrazine is replaced by an ethoxycarbonyl group.

Also, the 4 100 Å band undergoes a bathochromic shift (200–400 cm⁻¹) when going from heptane to ethanol as solvent. A $n \rightarrow \pi$ band should give a

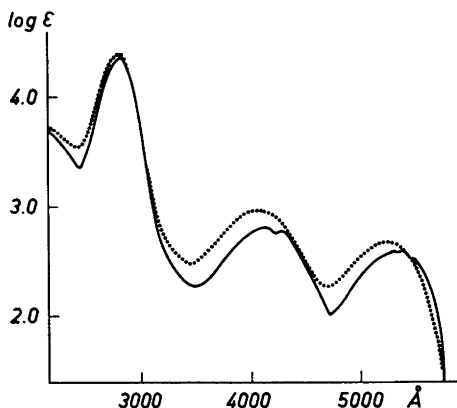


Fig. 2. Ultraviolet-visible spectra of IXa in heptane —, and IXc in ethanol ·····

hypsochromic shift under the same conditions, since it is due to a transition, where the ground state is more stabilized with respect to the excited state in polar and particularly in hydroxylic solvents than in non-polar solvents^{17,18}.

The infrared spectra of diaryltetrazines have been discussed by Wiley *et al.*¹⁹, who report absorption bands in the regions 1 390—1 375 and 925—913 cm^{-1} , which are ascribed to vibrations in the tetrazine ring. Dallacker^{11,20} has prepared dipyridyl-, dithiazolyl-, and some substituted diphenyltetrazines and reports a characteristic absorption band in the region 1 430—1 335 cm^{-1} . However, the dialkylthio-tetrazines (IXa—d) do not all have absorption bands in the regions mentioned above, but all of them show strong bands in the regions 1 253—1 239 and 1 060—1 047 cm^{-1} and weaker bands in the region 980—867 cm^{-1} . The last-mentioned band may be due to a C—S stretching vibration. This vibration is correlated with a band in the region 660—630 cm^{-1} in alkyl sulphides²¹, but on conjugation it is shifted to higher frequencies, 830—710 cm^{-1} in vinyl sulphides²², and 1 000—850 cm^{-1} in thioesters²³. A similar effect must be present in dialkylthio-tetrazines, since the tetrazine ring is highly π -deficient²⁴, and should conjugate strongly with electron-donating substituents.

EXPERIMENTAL

Dithio-*p*-urazine (I)

A solution of dicarboxymethyl trithiocarbonate (22.6 g) in N NaOH (200 ml) was added to a lukewarm solution of thiocarbonylhydrazide (10.6 g) in water (150 ml). The solution was cooled, and within an hour a pale yellow crystalline powder began to separate. After three days the deposition was finished, and the product (6.7 g, 45 % yield) was found to be pure dithio-*p*-urazine (I), m.p. 176° (decomp.). (Found: C 16.1; H 2.82; N 37.4; S 43.2. $\text{C}_2\text{H}_4\text{N}_4\text{S}_2$ (148.20) requires C 16.2; H 2.72; N 37.8; S 43.3).

Dithio-*p*-urazine (0.30 g) was refluxed with N HCl (5 ml) for 3 h. After cooling, colourless rods separated (0.19 g, 63 % yield), m.p. 214—214.5° (decomp.). The infrared spectrum of the product was found to be identical with that of 3,5-dimercapto-4-amino-4,1,2-triazole (II) (m.p.¹ 222°). The product (0.075 g) was dissolved in N NaOH (1.2 ml), and benzyl chloride (0.13 g) in ethanol (2 ml) was added. Colourless flakes separated (0.09 g, 55 % yield), m.p. 148—149°, identified by mixed m.p. and infrared spectrum with 3,5-dibenzylthio-4-amino-4,1,2-triazole¹.

Dialkylthio-dihydro-tetrazines (III)

The 3,6-dimethylthio- and 3,6-dibenzylthio-dihydro-tetrazines were prepared by dissolving dithio-*p*-urazine in two equivalents of N NaOH under nitrogen and adding two equivalents of the appropriate organic halide in sufficient ethanol to give a homogeneous solution. The 3,6-dimethylthio-dihydro-tetrazine (IIIa) was obtained in 70 % yield and crystallized from absolute ethanol as pale yellow rods, m.p. 192—193°. (Found: C 27.2; H 4.59; N 32.0; S 36.2. $\text{C}_4\text{H}_8\text{N}_4\text{S}_2$ (176.26) requires C 27.3; H 4.57; N 31.8; S 36.4). The 3,6-dibenzylthio-dihydro-tetrazine (IIIb) was obtained in 65 % yield and crystallized from toluene as pale yellow plates, m.p. 165.5—166°. (Found: C 58.5; H 4.92; N 17.1; S 19.5. $\text{C}_{16}\text{H}_{16}\text{N}_4\text{S}_2$ (328.45) requires C 58.5; H 4.91; N 17.1; S 19.5).

Dithio-*p*-urazine (6.0 g) was dissolved in N NaOH (80 ml) under nitrogen, and a solution of ethyl chloroacetate (15 g) in ethanol (40 ml) was added dropwise with stirring. A colourless precipitate was formed (5.4 g), and when the filtrate was evaporated to about two thirds of the original volume, a further quantity (3.5 g) was obtained. The combined products were extracted with hot chloroform (40 ml). The undissolved material (2.9 g, 32 % yield) consisted of the dilactam (V) to be described later. The chloroform solution was added to carbon tetrachloride (40 ml), and pale yellow, pointed plates separated

(2.0 g, 18 % yield), m.p. 123–124° after recrystallization from ethanol, consisting of the *monolactam* (IV). (Found: C 35.2; H 3.75; N 20.4; S 23.4. $C_8H_{10}N_4O_3S_2$ (274.31) requires C 35.0; H 3.67; N 20.4; S 23.4.) λ_{\max} 2 505 Å with ϵ : 20 000 in absolute ethanol.

Light petroleum (b.p. 40–60°, 80 ml) was added to the chloroform-carbon tetrachloride filtrate from (IV), and colourless, rhombic prisms separated (3.0 g, 23 % yield), m.p. 104–105°, consisting of *3,6-bis-ethoxycarbonylmethylthio-dihydrotetrazine* (IIIc). (Found: C 37.4; H 4.91; N 17.4; S 20.0. $C_{10}H_{16}N_4O_4S_2$ (320.38) requires C 37.5; H 5.03; N 17.5; S 20.0.)

The monolactam (IV, 0.27 g) was refluxed for 24 h in ethanol (5 ml). Only a very small amount of the dilactam (V) had then separated. The same experiment was repeated, but N HCl (1 ml) was added. On heating a precipitate was formed, and after one hour pale yellow prisms were filtered off (0.20 g, 85 % yield). On heating they darkened without melting below 300°, and they were very slightly soluble in the common solvents. In boiling dimethylsulphoxide dissolution occurred, but probably with decomposition, since the solution was dark, and nothing crystallized on cooling. According to analysis the product was the *dilactam* (V). (Found: C 31.5; H 2.01; N 24.4; S 28.0. $C_6H_8N_4O_2S_2$ (228.24) requires: C 31.6; H 1.77; N 24.6; S 28.1.)

Dithio-*p*-urazine (1.5 g) was dissolved in N NaOH (20 ml) under nitrogen, and a solution of monochloroacetic acid (2.5 g) in the equivalent amount of N NaOH was added. On the following day the solution was made acid to Congo red with 5 N HCl, and a precipitate of a pale yellow, microcrystalline powder was obtained (2.05 g, 89 % yield). The product did not melt below 300° and was shown by infrared spectrum to consist of the dilactam (V) just described.

Acetylation of 3,6-dibenzylthio-dihydrotetrazine

Dibenzylthio-dihydrotetrazine (IIIb, 0.66 g) and acetic anhydride (5 ml) were refluxed for 15 minutes. Then the acetic anhydride and acetic acid were removed *in vacuo*, and the residue crystallized from toluene as colourless rods, m.p. 141.5–142.5°, of 1-acetyl-3,6-dibenzylthio-dihydrotetrazine (VI). (Found: C 58.5; H 5.04; N 15.2; S 17.3. $C_{18}H_{18}N_4OS_2$ (370.47) requires C 58.3; H 4.90; N 15.1; S 17.3.)

Hydrolysis of 3,6-dibenzylthio-dihydrotetrazine

Dibenzylthio-dihydrotetrazine (IIIb, 1.64 g) was refluxed with ethanol (50 ml) and conc. hydrochloric acid (5 ml) until after 10 h no red colour appeared when a drop of the solution was mixed with a drop of sodium nitrite solution. The solution was then evaporated to dryness on the water bath, and the residue was ground with water (20 ml) and filtered. Crystalline sodium acetate (1.5 g) was added to the aqueous extract, and a precipitate was formed, which crystallized from 50 % aqueous ethanol as colourless plates, m.p. 116–117°, of *benzylthiocarbonyl-hydrazine* (VII). (Found: C 52.9; H 5.35; N 15.2; S 17.7. $C_8H_{10}N_2OS$ (182.24) requires C 52.7; H 5.54; N 15.4; S 17.6.)

The water-insoluble material (1.25 g) crystallized from ethanol (5 ml) as colourless plates (0.85 g), m.p. 155.5–156°, of *1,2-bis-benzylthiocarbonyl-hydrazine* (VIII). (Found: C 57.5; H 4.70; N 8.50; S 19.1. $C_{16}H_{16}N_2O_2S_2$ (332.43) requires C 57.8; H 4.85; N 8.42; S 19.3.)

The ethanolic mother liquor was evaporated to dryness, the semicrystalline residue was dissolved in chloroform, and the infrared spectrum was recorded. It was not very well resolved, but it showed no bands at 3 380 and 1 620 cm^{-1} , where 3,5-dibenzylthio-4-amino-4,1,2-triazole has characteristic absorption bands.

Dialkylthio-tetrazines

The dihydrotetrazines (IIIa–c) can be oxidized to tetrazines in a variety of ways. The following method was found convenient in all cases because of its rapidity. The dihydrotetrazine was dissolved in ethanol, and the calculated amount of 2 N ferric chloride was added. Water was added to precipitate all tetrazine, which came out in an almost pure state. The *3,6-dimethylthio-1,2,4,5-tetrazine* (IXa) crystallized from light petroleum

(80–100°) as bright-red rods, m.p. 83.5–84°. (Found: C 27.6; H 3.52; N 32.4; S 36.5. $C_4H_6N_4S_2$ (174.24) requires C 27.6; H 3.47; N 32.2; S 36.8).

The 3,6-dibenzylthio-1,2,4,5-tetrazine (IXb) crystallized from ethanol as bright-red rods, m.p. 139–140°. (Found: C 58.8; H 4.42; N 17.0; S 19.5. $C_{16}H_{14}N_4S_2$ (326.43) requires C 58.9; H 4.32; N 17.2; S 19.6).

The 3,6-bis-ethoxycarbonylmethylthio-1,2,4,5-tetrazine (IXc) crystallized from benzene-heptane as bright-red rods, m.p. 84–85°. (Found: C 37.6; H 4.38; N 17.6; S 20.1. $C_{10}H_{14}N_4O_4S_2$ (318.36) requires C 37.7; H 4.43; N 17.6; S 20.1).

Dithio-*p*-urazine and monochloroacetic acid were dissolved and mixed as above, and after one hour Perhydrol (1 ml) was added. On the following day a small amount of the dilactam (V) was removed by filtration, and the filtrate was made acid to Congo red with 5 N HCl. A precipitate of fernleaf-like, red prisms was obtained (2.1 g, 80 % yield). The product was purified by dissolution in N sodium bicarbonate solution, filtration and precipitation with 5 N HCl, and was shown by analysis to consist of 3,6-dicarboxymethylthio-1,2,4,5-tetrazine (IXd), m.p. 255° (decomp.). (Found: C 27.6; H 2.40; N 21.2; S 24.3. $C_6H_4N_4O_4S_2$ (262.26) requires C 27.5; H 2.31; N 21.4; S 24.4.)

The same product was obtained in 25–30 % yield, when the dilactam (V) was dissolved in hot N NaOH, treated with Perhydrol, and then acidified as above.

The nuclear magnetic resonance spectrum (Fig. 1) was obtained with a Varian Associates model V-4 300-B high resolution NMR spectrometer operating at 40 Mc/s, and a flux stabilized 12" electromagnet from the same company. The magnet sweep was calibrated by the modulation side band technique. The infrared spectra have been recorded with a Perkin-Elmer model 221 prism-grating instrument, and the ultraviolet spectra with a Beckman DU spectrophotometer.

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REFERENCES

1. Sandström, J. *Acta Chem. Scand.* **15** (1961) 1295.
2. Abraham, R. J., Pople, J. A. and Bernstein, H. J. *Can. J. Chem.* **36** (1958) 1302.
3. Meyer, L. H., Saika, A. and Gutowsky, H. S. *J. Am. Chem. Soc.* **75** (1953) 4567.
4. Hoffman, R. A. *Svensk Kem. Tidskr.* **72** (1960) 610.
5. Gronowitz, S. and Hoffman, R. A. *Arkiv Kemi* **16** (1961) 459.
6. Wiley, P. F. in Weissberger, *The chemistry of heterocyclic compounds: The 1,2,3- and 1,2,4-triazines, tetrazines and pentazines*. Interscience Publishers, New York 1956, p. 179.
7. *The chemistry of penicillin*. Princeton University Press 1949, p. 390.
8. Curtius, Th., Darapsky, A. and Müller, E. *Ber.* **48** (1915) 1624.
9. Pinner, A. *Ber.* **30** (1897) 1871.
10. Bülow, C. and Weber, F. *Ber.* **42** (1909) 1990.
11. Dallacker, F. *Monatsh.* **91** (1960) 294.
12. Liquori, A. M. and Vaciago, A. *Gazz. chim. ital.* **86** (1956) 769.
13. Mason, S. F. *J. Chem. Soc.* **1959** 1240.
14. Mason, S. F. *J. Chem. Soc.* **1959** 1247.
15. Mason, S. F. *J. Chem. Soc.* **1959** 1263.
16. Lin, C.-H., Lieber, E. and Horwitz, J. P. *J. Am. Chem. Soc.* **76** (1954) 427.
17. Bayliss, N. S. and McRae, E. G. *J. Phys. Chem.* **58** (1954) 1002.
18. Pimentel, G. C. *J. Am. Chem. Soc.* **79** (1957) 3323.
19. Wiley, R. H., Jarboe, Jr., C.H. and Hayes, F.N. *J. Org. Chem.* **22** (1957) 835.
20. Lipp, M., Dallacker, F. and Thoma, J. *Monatsh.* **91** (1960) 595.
21. Sheppard, N. *Trans. Faraday Soc.* **46** (1950) 429.
22. Boonstra, H. J. and Rinzema, L. C. *Rec. trav. chim.* **79** (1960) 962.
23. Baker, A. W. and Harris, G. H. *J. Am. Chem. Soc.* **82** (1960) 1923.
24. Albert, A. *Heterocyclic Chemistry*. Essential Books, Fair Lawn 1959, p. 39.

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