Derivatives of 3*H*-1,2,3-Triazolo[4,5-*d*][1,3]thiazine, a New Heterocyclic Nucleus.[1] Some Shifts of a Methylene Group from a Nitrogen to a Sulphur Atom

By **Adrien Albert**, Research School of Chemistry, Australian National University, Canberra, Australia 2600

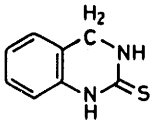
Contrary to expectations, 3-alkyl derivatives of 4-amino-5-aminomethyl-3*H*-1,2,3-triazole (2b and c), when heated with carbon disulphide and a base, did not give a 1,3,6,9-tetrahydro-8-azapurine-2-thione (3b) but a 3-alkyl-3,7-dihydro-1,2,3-triazolo[4,5-*d*][1,3]thiazine-5(4*H*)-thione, *e.g.* (5). This thione (5), the nucleus of which was hitherto unknown, could be methylated on the exocyclic sulphur atom to give the methylthio-derivative (6a), which was readily converted into the amino- and hydrazino-analogues (6b and c). The reaction mechanism that produced the thione (5) depends on the transfer of a 5-methylene group from a nitrogen to a sulphur atom, apparently involving triazol-5-ylmethyldithiocarbamate intermediates [(4) ⟶ (8)]. Two sulphide by-products (9) and (11) were isolated which had also undergone this very unusual N ⟶ S shift. ^{1}H N.m.r., i.r., and mass spectrometric data are presented and discussed.

It has long been known that 2-aminobenzylamine and its derivatives, when heated with carbon disulphide (alone, or with a base) give good yields of 3,4-dihydroquinazoline-2(1*H*)-thione (1) and its derivatives, respectively.[2] Similarly 4-amino-5-aminomethyl-1- (and 2-) methyl-1,2,3-triazole (2a), heated with carbon disulphide and triethylamine in pyridine, give quantitative yields of the corresponding *N*-methyl-1,6-dihydro-8-azapurine-2-thiones (3a).† Hence it was unexpected that the 3-methyl- (2b) and 3-benzyl- (2c) analogues of these triazoles, when treated similarly, should give products differing from the goals (3b) by the loss of one nitrogen atom and gain of one sulphur atom. This was all the more surprising when it was found that less rigorous conditions led to quantitative accumulation of the expected dithiocarbamate intermediate (4). Thus the benzyl diamine (2c) and carbon disulphide, in ethanol at room temperature, furnished the salt (4a) of *N*-(4-amino-3-benzyl-3*H*-1,2,3-triazol-5-ylmethyl)dithiocarbamic acid with the unchanged base (2c); instead, the ammonium salt (4b) was formed if ammonia was initially present.

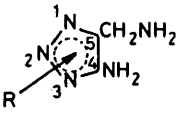
Elemental analysis and mass spectrometry indicated that the product formed by heating the benzyl diamine (2c) with carbon disulphide was the triazolothiazine (5), or an isomer with the nitrogen and sulphur atoms (in the thiazine ring) interchanged. Chemical degradation proved inconclusive, but a single-crystal *X*-ray analysis of the *S*-methyl derivative, in which every hydrogen atom could be located,[3] established the structure as 3-benzyl-5-methylthio-3,7-dihydro-1,2,3-triazolo[4,5-*d*][1,3]thiazine (6a). Hence the parent is the corresponding 5-thione (5). The 3-methyl homologue was made similarly from the appropriate diamine (2b).

These thiones are stable in air, and resistant to boiling with 1N-hydrochloric acid and 1N-sodium hydroxide. The *S*-methyl derivative (6a), in ethanolic ammonia at 110 °C, was converted into the corresponding amine (6b); raising the temperature to 180 °C with a view to replacing the ring-sulphur atom by nitrogen caused gross fragmentation. Hydrazine hydrate in cold methanol converted the methylthio-compound (6a) into the hydrazino-analogue (6c).

Some discussion is required about how the methylene group that was bound to a nitrogen atom in the starting material (2c), and also in the presumed intermediate (4),

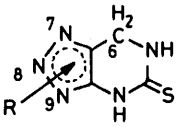


(1)



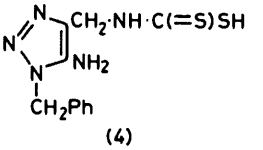
(2)

a; R = 1-Me or 2-Me
b; R = 3-Me
c; R = 3-CH_2Ph



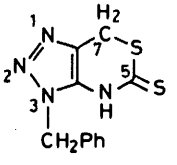
(3)

a; R = 7-Me or 8-Me
b; R = 9-Me or 9-CH_2Ph



(4)

a; salt with base (2c)
b; ammonium salt



(5)

(6)

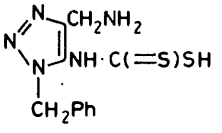
a; R = SMe
b; R = NH_2
c; R = NH·NH_2

has become united to a sulphur atom in the product (5). That the dithiocarbamate salts isolated have the structure (4) and are not salts of the isomer (7) is shown by their non-basic character. Thus lowering the pH of the aqueous solutions to 3 liberated the corresponding acid which did not dissolve on further acidification to pH 1

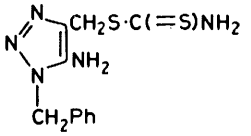
† Unpublished observations to be presented, in context, shortly.

but slowly decomposed to carbon disulphide and the diamine (2c). [This diamine has a highly basic 5-CH_2NH_2 group (pK_a 8.85) and a virtually non-basic 4-NH_2 group (pK_a −0.45), so that it is easy to decide which group is blocked by a substituent.[4]]

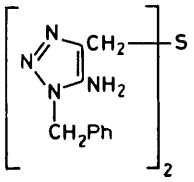
Although it is well established that carbon disulphide attacks *aliphatic* amino-groups preferentially (see review on dithiocarbamates in ref. 5), it cannot be excluded that



(7)



(8)



(9)

the compound (4) is in equilibrium with a little of the isomer (7) at the temperature of the reaction (115 °C). However, postulation of compound (7) as an intermediate became unnecessary after observation of changes in the ^{1}H n.m.r. spectra when an attempt was made to prepare the ammonium salt (4b) in cold water instead of methanol. Whereas crystals prepared in cold methanol gave spectrum (i) (see Table), consonant in every way with formula (4), those prepared in water produced all the peaks listed in both spectra, (i) and (ii), in a 1 : 1 ratio (the exchangeable hydrogen peaks in both spectra were very sharp). All changes seen in passing from spectrum (i) to (ii) are consonant with a shift of the methylene group from nitrogen to sulphur, to yield the non-acidic compound (8). The two most significant of these shifts are (a) the increase in protons in the change from τ 1.70 to 2.01 as −NH− becomes $-NH_2$, and (b) the change from τ 5.42 to 6.00 characteristic of a $-CH_2N \longrightarrow -CH_2S$ shift. For comparison, the CH_2S signal in the sulphide (9) occurs at τ 6.37. Indications of a slow change from spectrum (i) to the mixed spectrum (i) + (ii) could be seen when the ammonium salt (4b) was dissolved in deuterium oxide and attention focused on the peak at τ 6.0 (those at τ 1.7, 2.0, and 5.4 were inaccessible in this solvent). Unfortunately the presumed $-CH_2S$ product (8) decomposed, with evolution of hydrogen sulphide, during all attempts to isolate it.

^{1}H N.m.r. spectra of (i) ammonium 4-amino-3-benzyl-3*H*-1,2,3-triazol-5-ylmethyldithiocarbamate (4b), and (ii) a related product

[τ in $(CD_3)_2SO$]

(i) 1.70 [a] (1 H, NH), 2.78 (5 H, Ph), 4.15 [a] (2 H, 4-NH_2), 4.65 (2 H, CH_2Ph), 5.42 (2 H, d,[b] CH_2NH coupled to NH).

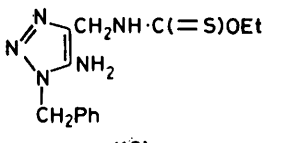
(ii) 2.71 [a] (2 H, SC-NH_2), 2.78 (5 H, Ph), 4.23 [a] (2 H, 4-NH_2), 4.73 (2 H, CH_2Ph), 6.00 (2 H, s, CH_2S).

[a] Vanishes on addition of D_2O. [b] Becomes s on addition of D_2O.

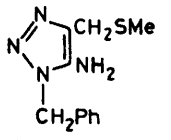
Two further examples of a $-CH_2N$ to $-CH_2S$ shift will now be described. In the first, the dithiocarbamate salts, either (4a) or (4b), when heated under reflux with ethanolic sodium ethoxide (or butanolic sodium butoxide) gave, as sole product, the non-basic symmetrical sulphide (9). Prior addition of carbon disulphide to the butoxide mixture furnished some of the thione (5) as well, but the boiling sodium ethoxide mixture proved to be too cool to sustain this reaction.

The other example arose as follows. Iodomethane converted the ammonium salt (4b) into the corresponding *S*-methyl ester in which the downfield location of the 5-CH_2 group (τ 5.18) confirmed that it was still *N*-linked. However this ester was converted, in boiling ethanolic sodium ethoxide, into the (non-basic) triazoylmethyl methyl sulphide (11) in high yield. Incidentally, attempted recrystallization of the *S*-ester from aqueous ethanol converted it into the monothiocarbamate (10).

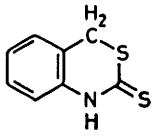
These three shifts of alkyl groups from N to S seem unprecedented, whereas movements in the reverse direction (as in the well-known transformation of alkyl thiocyanates to isothiocyanates) are quite common.



(10)



(11)



(12)

It is likely that in all three cases, an electron-rich carbon-bound sulphur atom attacks the electron-depleted (benzylic) 5-methylene group, simultaneously breaking the CH_2–NH bond, followed by loss of molecular fragments.

A reaction that appears related to the main one described here is the condensation of 2-aminobenzyl alcohol with carbon disulphide, in boiling ethanolic potassium hydroxide, to give 1,4-dihydro-3,1-benzothiazine-2-thione (12),[6] thereas 2-aminobenzylamine forms the quinazoline (1) when treated similarly. It must now be asked why the 3-alkyltriazoles (2b and c) give triazolothiazines, *e.g.* (5), whereas the 1- and 2-alkyltriazoles (2a) furnish 8-azapurines (3a). The answer seems to lie in the difficulty of shedding a proton from the 4-amino-group of the intermediate (4) to give the amine anion that is needed to form a tetrahedral intermediate with the carbon atom of the side chain. This difficulty arises from the propinquity of the electron-releasing alkyl group on N-3. A similar explanation fits the reluctance of 3-alkyl- (as opposed to 1- or 2-alkyl-) derivatives of 4-amino-3*H*-1,2,3-triazole-5-carboxamide

to react with amidines.[7] On the other hand, in the presumed intermediate (8) for producing the triazolothiazine (5), electron acquisition by the 4-amino-group makes it a better leaving group, as in the well-known synthesis of diphenylamine from equimolecular parts of aniline and aniline hydrochloride.[8]

EXPERIMENTAL

^{1}H N.m.r. spectra were obtained with a JEOL Minimar-100 instrument at 30 °C with $SiMe_4$ as internal standard; (*) indicates that the signal disappeared on addition of D_2O. I.r. spectra were recorded with a Perkin-Elmer 257 (grating) instrument calibrated with polystyrene at 1 603 cm^{-1}. Elemental analyses were performed by this University's Analytical Chemistry Services Unit. Purification was monitored by ascending paper chromatography on two Whatman No. 1 papers developed in (*a*) 3% aqueous NH_4Cl and (*b*) butanol–5N-acetic acid (7 : 3 v/v). All alkoxide solutions were prepared from sodium metal and the appropriate alcohol.

Salts of N-(4-*Amino*-3-*benzyl*-3H-1,2,3-*triazol*-5-*ylmethyl*)-*dithiocarbamic Acid* (4).—Carbon disulphide (0.19 g, 0.002 5 mol) in ethanol (2 ml) was dropped into a stirred solution of 4-amino-5-aminomethyl-3-benzyl-3*H*-1,2,3-triazole (2c) [4] (0.20 g, 0.001 mol) in ethanol (3 ml) at 20—25 °C. Stirring was continued for 2 h, and the mixture stored at −5° for 2 h. The fine white precipitate, washed with much ethanol, proved to be the 4-*amino*-5-*aminomethyl*-3-*benzyl*-1,2,3-*triazole salt* (4a) of the title acid (90%), m.p. 141 °C (from methanol) [Found (material dried at 25 °C and 0.01 mmHg): C, 52.4; H, 5.25; N, 29.1; S, 13.3. $C_{11}H_{13}N_5S_2 \cdot C_{10}H_{13}N_5$ requires C, 52.3; H, 5.4; N, 29.0; S, 13.3%]. Carbon disulphide (0.152 g, 0.002 mol) was dropped into a stirred solution of the diamine (2c) (0.40 g, 0.002 mol) in 1N-methanolic ammonia (2.4 ml). Stirring was continued for 2 h, and the solution stored at −5 °C overnight. The large crystals, filtered off, well washed, and dried at 75 °C in air, were the *ammonium salt* (4b) of the title acid (70%) (Found: C, 44.4; H, 5.5; N, 28.3; S, 20.6. $C_{11}H_{13}N_5S_2 \cdot NH_3$ requires C, 44.6; H, 5.4; N, 28.35; S, 21.6%). The evaporated filtrate had the same composition.

3-*Benzyl*-3,7-*dihydro*-1,2,3-*triazolo*[4,5-d][1,3]*thiazine*-5(4H)-*thione* (5).—The diamine (3c) (3.00 g, 0.015 mol), dry pyridine (60 ml), triethylamine (3.00 g, 2 mol equiv.), and carbon disulphide (5.70 g, 5 mol equiv.) were heated under reflux in a bath (115 °C) for 6 h. The volatile components were removed at 90 °C and 25 mmHg. The residue was shaken with 1N-potassium hydroxide (37.5 ml), the residual tar rejected, and the solution acidified to pH 3.5 with formic acid. Another cycle of dissolution and precipitation, followed by washing with ethanol–water (1 : 1 v/v), then with ether, yielded large yellow *crystals* (63%), m.p. 190 °C (effervescence) [from ethanol–water (1 : 1 v/v)] [Found (material dried at 80 °C in air): C, 50.6; H, 3.95; N, 21.3; S, 24.7. $C_{11}H_{10}N_4S_2$ requires C, 50.35; H, 3.8; N, 21.35; S, 24.4%], M^+ 262 [other prominent peaks at *m/e* 233, 201, 157, 131, and 91 (benzyl)], τ [$(CD_3)_2SO$] (nothing between −2 and 0), 2.81 (5 H, m, Ph), 4.40 (2 H, PhCH_2), and 5.75 (2 H, CH_2S).

3-*Methyl*-3,7-*dihydro*-1,2,3-*triazolo*[4,5-d][1,3]*thiazine*-5-*thione*.—The diamine (2b) (as 1.125 g of 1 : 1 phosphate,[4] 0.005 mol), dried pyridine (20 ml), triethylamine (2.00 g), and carbon disulphide (1.90 g, 5 mol equiv.) were heated under reflux in a bath (115 °C) for 3 h. The volatile components were removed as before, and the residue dissolved in 1N-potassium hydroxide (7.5 ml), clarified, and acidified to pH 3.5. The solid, filtered off and washed with ethanol–water (1 : 1 v/v), and then with ether, and finally recrystallized from ethanol gave large yellow *crystals* (53%), m.p. 194 °C (effervesces) [Found (for material dried at 110 °C in air): C, 32.5; H, 3.5; N, 30.2; S, 34.2. $C_5H_6N_4S_2$ requires C, 32.2; H, 3.3; N, 30.1; S, 34.4%], τ [$(CD_3)_2SO$] (nothing between −2 and 0) 5.75 (2 H, CH_2) and 6.03 (3 H, Me).

3-*Benzyl*-5-*methylthio*-3,7-*dihydro*-1,2,3-*triazolo*[4,5-d]-[1,3]*thiazine* (6a).—The thione (5) (0.524 g, 0.002 mol) in 1N-sodium hydroxide (2.4 ml, 1.2 mol equiv.) was stirred in a mortar with iodomethane (0.34 g, 1.2 mol equiv.) for 15 min. After filtration, the solid, recrystallized from cyclohexane (2 crops), gave the *methylthio-compound* (6a), m.p. 127 °C (90%) [Found (material dried at 80 °C in air): C, 52.3; H, 4.4; N, 20.3; S, 23.2. $C_{12}H_{12}N_4S_2$ requires C, 52.15; H, 4.4; N, 20.3; S, 23.2%], $\nu_{max.}$ (Nujol mull) 1 565m, 1 315m, 1 270s, 1 175m, 955s, 760m, and 700m cm^{-1}, τ [$(CD_3)_2SO$] 2.69 (5 H, Ph), 4.28 (2 H, CH_2Ph), 5.60 (2 H, SCH_2), and 7.42 (3 H, Me).

5-*Amino*-3-*benzyl*-3,7-*dihydro*-1,2,3-*triazolo*[4,5-d][1,3]-*thiazine* (6b).—The methylthio-compound (6a) (0.18 g, 0.000 65 mol) and 3N-ethanolic ammonia (8 ml) were heated in an autoclave at 110 °C for 10 h. The resultant solution was taken to dryness and the residue, recrystallized from benzene, yielded the *amine* (6b) (75%), m.p. 137 °C (labile form) or 165 °C [Found (material dried at 80 °C in air): C, 53.8; H, 4.6; N, 28.5; S, 31.1. $C_{11}H_{11}N_5S$ requires C, 53.9; H, 4.5; N, 28.55; S, 13.1%], τ [$(CD_3)_2SO$] 2.33* (2 H, NH_2), 2.65 (5 H, Ph), 4.62 (2 H, CH_2Ph), and 5.70 (2 H, 7-CH_2).

3-*Benzyl*-5-*hydrazino*-3,7-*dihydro*-1,2,3-*triazolo*[4,5-d][1,3]-*thiazine* (6c).—The methylthio-compound (6a) (0.414 g, 0.001 5 mol) was dissolved in boiling methanol (4.5 ml). Hydrazine hydrate (0.55 g, 7.5 mol equiv.) was added to the warm solution. The mixture was set aside at 20 °C overnight, then chilled at −5 °C giving colourless crystals (65%) of the *hydrazine* (6c), m.p. 159 °C (from methanol) [Found (material dried at 80 °C in air): C, 50.8; H, 4.7; N, 32.5; S, 12.2. $C_{11}H_{12}N_6S$ requires C, 50.75; H, 4.65; N, 32.3; S, 12.3%], $\nu_{max.}$ (KBr disc) 3 240 + 2 920m (NH), 1 570s, 1 535s, 1 485m, 1 205m, 1 190m, 1 125m, and 830 cm^{-1}.

Bis-(4-*amino*-3-*benzyl*-3H-1,2,3-*triazol*-5-*ylmethyl*) *Sulphide* (9).—The dithiocarbamate salt (4a) (0.723 g, 0.001 5 mol) and 0.5N-ethanolic sodium ethoxide (6 ml) were heated under reflux for 2 h, then taken to dryness at 50 °C and 25 mmHg. Water (3 ml) was added to the residue, and the mixture refrigerated and filtered, giving the *sulphide* (9) (37%), m.p. 173 °C [from ethanol–water (1 : 1 v/v)] [Found (materials dried at 110 °C in air): C, 59.2; H, 5.6; N, 27.85; S, 7.8. $C_{20}H_{22}N_8S$ requires C, 59.1; H, 5.4; N, 27.6; S, 7.9%], M^+ (230 °C and 1 × 10^{-6} Torr) 406 [other prominent peaks at *m/e* 372, 358, 354, 300, 298, 266, 220, 188, 187, 159, 132, 106, and 91 (benzyl)], τ [$(CD_3)_2SO$] 2.73 (2 × 5 H, Ph), 4.25* (2 × 2 H, NH_2), 4.66 (2 × 2 H, CH_2Ph), and 6.37 (2 × 2 H, CH_2S).

S-*Methyl* N-(4-*Amino*-3-*benzyl*-3H-1,2,3-*triazol*-5-*ylmethyl*)*dithiocarbamate*.—Aqueous ammonia (17N; 0.24 ml, 0.004 mol) and carbon disulphide (0.167 g, 0.002 2 mol) were added in turn to a stirred solution of 4-amino-5-aminomethyl-3-benzyl-3*H*-1,2,3-triazole (2c) (0.40 g, 0.002 mol) in methanol (4 ml). The mixture was stirred at 20 °C for 1 h,

then iodomethane (0.312 g, 0.002 2 mol) added. Stirring was continued for 3 h. The solution, set aside at −5 °C overnight, deposited the *title compound* (84% in two crops), m.p. 154 °C (from benzene) [Found (for material dried at 80 °C in air): C, 49.4; H, 5.2; N, 23.7; S, 21.8. $C_{12}H_{15}N_5S_2$ requires C, 49.1; H, 5.15; N, 23.4; S, 21.9%], $\nu_{max.}$ 3 390 + 3 280 + 3 150 (NH), 1 615, 1 550, 1 295, 1 210, 1 070, and 915 (all m) cm^{-1}, τ [$(CD_3)_2SO$] −0.35* (1 H, NH), 2.35 (5 H, Ph), 4.25* (2 H, NH_2), 4.52 (2 H, CH_2Ph), 5.18 (2 H, d, 5-CH_2 coupled to NHCS, D_2O changes d to s), and 7.42 (3 H, Me). Attempted recrystallization from ethanol–water (1 : 1 v/v) converted it into O-*ethyl* N-(4-*amino*-3-*benzyl*-3H-1,2,3-*triazol*-5-*ylmethyl*) *monothiocarbamate* (10) (with loss of methanethiol), m.p. 145 °C (from benzene) [Found: C, 53.6; H, 5.8; N, 24.1; S, 11.2. $C_{13}H_{17}N_5OS$ requires C, 53.6; H, 5.9; N, 24.0; S, 11.0%], $\nu_{max.}$ 3 370 + 3 290 + 3 180m (NH), 1 625s, 1 540br m, 1 408m, 1 305m, 1 245m, 1 230s, and 1 190m cm^{-1}, τ [$(CD_3)_2SO$] 0.54* (1 H, NH), 2.62 (5 H, Ph), 4.37* (2 H, NH_2), 4.58 (2 H, CH_2Ph), 5.5 (4 H, m, CH_2 of Et + 5-CH_2 coupled to N*H*CS, multiplet simplified by addition of D_2O), and 8.70 (3 H, t, Me of Et).

4-*Amino*-3-*benzyl*-3H-1,2,3-*triazol*-5-*ylmethyl Methyl Sulphide* (11).—The *S*-methyl ester (0.22 g, 0.000 75 mol) and ethanolic 0.5M-sodium ethoxide (3 ml) were heated under reflux for 18 h. The solution was taken to dryness *in vacuo* (60 °C). Water (1 ml) was added and the solid, filtered off and recrystallized from cyclohexane–benzene (1 : 1 v/v), gave the *sulphide* (11) (76%), m.p. 95 °C [Found: C, 56.4; H, 6.0; N, 23.9; S, 13.4. $C_{11}H_{14}N_4S$ requires C, 56.4; H, 6.0; N, 23.9; S, 13.7%], M^+ 234 [other prominent peaks at *m/e* 189, 187, 159, 132, and 91 (benzyl)], τ [$(CD_3)_2SO$] 2.79 (5 H, Ph), 4.50* (2 H, NH_2), 4.70 (2 H, CH_2Ph), 6.37 (2 H, CH_2S), and 8.01 (3 H, Me).

I thank Professor E. Campaigne, Dr. D. J. Brown, Mr. R. Rickards, Dr. R. Bramley, and Dr. A. Dunand for discussion, and Mrs. L.-E. Hogie for skilled experimental assistance.

[9/1616 *Received*, 11*th October*, 1979]

REFERENCES

[1] Earlier communications on ring-systems containing both nitrogen and sulphur atoms: A. Albert and K. Tratt, *J. Chem. Soc.* (*C*), 1969, 152; A. Albert and C. J. Lin, *J.C.S. Perkin I*, 1977, 210.

[2] M. Busch, *Ber.*, 1892, **25**, 2853; *J. prakt. Chem.*, 1895, **51**, 128; W. L. F. Armarego, ' The Quinazolines,' Wiley–Interscience, New York, 1967, p. 276.

[3] A. Albert and A. Dunand, *Angew. Chem.*, 1980, **92**, 319.

[4] A. Albert *J.C.S. Perkin I*, 1973, 1634.

[5] M. Bogemann, S. Petersen, O.-E. Schultz, and H. Söll in Houben-Weyl's ' Methoden der Organische Chemie,' Georg Thieme Verlag, Stuttgart, 4th edn., 1955, vol. 9, p. 824.

[6] C. Paal and O. Commerell, *Ber.*, 1894, **27**, 2427.

[7] A. Albert and A. M. Trotter, *J.C.S. Perkin I*, 1979, 922.

[8] M. de Laire, J. Girard, and C. Chapotaut, *C.r. Acad. Sci.*, 1866, **63**, 92.