Formation of 4-Hydroxy-3-(α-hydroxybenzyl)-4-phenyl-2-pyrazolin-5-one from the Interaction of 3,6-Bis-(α-hydroxybenzyl)-*s*-tetrazine with Potassium Hydroxide in Methanol

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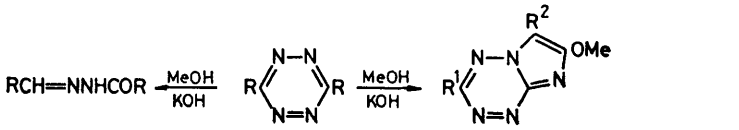
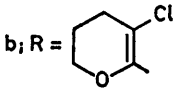
4-Hydroxy-3-(α-hydroxybenzyl)-4-phenyl-2-pyrazolin-5-one has been obtained from the reaction of methanolic potassium hydroxide with 3,6-bis-(α-hydroxybenzyl)-*s*-tetrazine and its structure proved by an alternative synthetic route. The mechanism of the rearrangement has been shown to involve a hydride transfer to a further tetrazine molecule which undergoes reduction to the dihydro-derivative.

In a recent paper [1] we reported the formation of the 3-benzyl-7-methoxy-6-phenylimidazo[1,2-*b*]-*s*-tetrazines (2a) and (2b) from the interaction of the 3,6-dibenzyl-*s*-tetrazines (1c) and (1d) and potassium hydroxide in methanol. Prior work by Pinner,[2] confirmed by us,[1] suggested that 3,6-diphenyl-*s*-tetrazine (1a) gave benzaldehyde benzoylhydrazone (3a) under similar conditions, while Riobé [3] obtained the analogous product (3b) from 3,6-bis-(2,3-dihydro-5-chloropyran-6-yl)-*s*-tetrazine (1b). We have now studied the action of methanolic potassium hydroxide on 3,6-bis-(α-hydroxybenzyl)-*s*-tetrazine (1e) and found that this reaction takes a completely different pathway from either of the others [*i.e.* (1) ⟶ (2) or (1) ⟶ (3)] previously reported.



(3) (1) (2)

a; R = Ph

b; R = 

c; R = $PhCH_2$

d; R = p-$ClC_6H_4CH_2$

e; R = PhCHOH

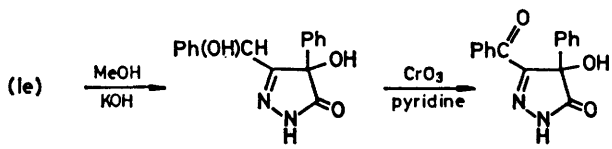
a; $R^1 = PhCH_2$, $R^2 = Ph$

b; $R^1 = p$-$ClC_6H_4CH_2$, $R^2 = p$-ClC_6H_4

The tetrazine (1e) was prepared in the usual way by the action [4] of hydrazine hydrate on ethyl mandelimidate hydrochloride [5] with subsequent oxidation of the intermediate dihydrotetrazine with nitrous acid. This preparation gives a mixture of the diastereoisomeric tetrazines which could not be separated by crystallisation or chromatographic techniques, although Yates and his co-workers [6] reported the isolation of one pure stereoisomer of compound (1e). This, however, was obtained in small quantities by hand-picking different crystal types [7] and does not represent a viable route to useful quantities of material.

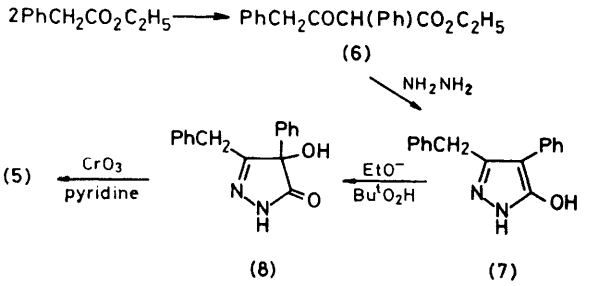
Treatment of the tetrazine (1e) with a methanolic solution of potassium hydroxide resulted in loss of the characteristic red colour of the tetrazine and evolution of nitrogen. After partial removal of solvent and addition of water, extraction with ether yielded only benzaldehyde and an unidentified oil, with no trace of any compound of type (2). Acidification of the aqueous residues gave, on work-up, a white solid which spectral evidence (see Experimental section) suggested was 4-hydroxy-3-(α-hydroxybenzyl)-4-phenyl-2-pyrazolin-5-one (4). Compound (4) was oxidised to its benzoyl derivative (5) to simplify identification by removing the possibility that species (4) was a mixture of different diastereoisomers. Structural proof, by synthesis of the novel compound (5), is shown in Scheme 1.

3-Benzyl-4-phenyl-2-pyrazolin-5-one (7) (shown as the enol) was synthesised from the β-oxo-ester (6) and hydrazine. Veibel and Linholt [8] have shown that 4-substituted pyrazolin-5-ones having a hydrogen at C(4) are susceptible to oxidation with t-butyl hydroperoxide in a base and yield the 4-hydroxy-derivatives. Compound (7) proved no exception and was readily converted into 3-benzyl-4-hydroxy-4-phenyl-2-pyrazolin-5-one (8), the benzyl group of which, on treatment with chromium trioxide in pyridine, was oxidised yielding compound (5) identical with that obtained from the tetrazine (1e).



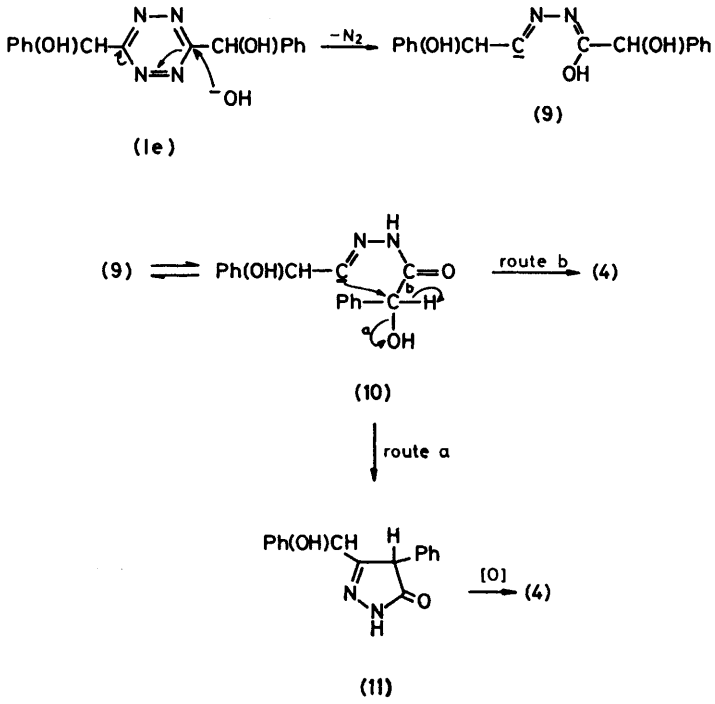
(4) (5)

Two mechanisms for the rearrangement of the tetrazine (1e) to the pyrazolin-5-one (5), might appear feasible in the light of the above work; these are illustrated in Scheme 2. In both, the initial hydroxide-ion attack



SCHEME 1

at a tetrazine-ring carbon with resultant loss of nitrogen gives an intermediate (9) [or its tautomer (10)]. This intermediate (10) can ring-close to a 2-pyrazolin-5-one by anion attack at the remote benzylic centre with loss of either (*a*) a hydroxide ion to give compound (11) which could then undergo oxidation at C(4) to give the isolated product (4) (route **a**), or (*b*) loss of a hydride ion to give the product (4) directly (route **b**).



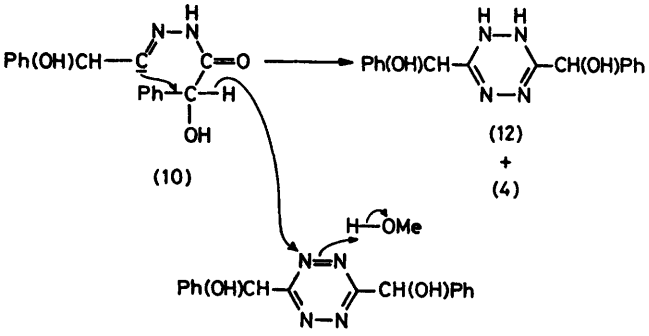
SCHEME 2

It is known that 4-substituted pyrazolin-5-ones having a hydrogen as substituent at C(4) are susceptible to oxidation in basic conditions [9] (see above), hence route a could be feasible; the loss of a hydride ion in basic conditions (route **b**) might at first sight appear less acceptable. It was decided that an investigation of the action of methanolic potassium hydroxide on the tetrazine (1e) under nitrogen could help elucidate this problem, as intermediate (11) might then be isolated if route **a** was, in fact, the appropriate one. When the reaction was carried out under nitrogen, however, a new product emerged; this was shown by n.m.r. to be a complex of two molecules of compound (4) with one molecule of a dihydro-derivative * of the tetrazine (1e). In addition a small amount of free dihydrotetrazine was also isolated. It would thus appear that the easily reduced tetrazine system is acting, under nitrogen, as a hydride acceptor (Scheme 3); the reduction of the tetrazine to its dihydro-derivative being completed by transfer of a proton from the solvent. The conclusion that the product was a 2 : 1 complex, rather than a mixture, arises because it had a melting point higher than either of its component parts. All attempts to make this complex, however, by co-crystallisation of compound (4) and the dihydro-derivative of the tetrazine (1e) failed. The complex could be recrystallised unchanged from a variety of solvents, but on preparative t.l.c. plates the dihydro-tetrazine slowly oxidised to the tetrazine (1e) which could then be separated from the pyrazolinone (4) chromatographically. One further example has been found in the literature [11] which supports this idea that tetrazines can act as hydride acceptors for reactions other than direct reductions; the tetrahydrotetrazine (13), on

* There is considerable confusion in the literature and no real certainty as to whether these dihydro-compounds are the 1,2- or 1,4-dihydro-*s*-tetrazines. Conflicting evidence has been presented for both substitution patterns and the position is further complicated by the 'isomeric' 4-amino-1,2,4-triazoles, which often simultaneously occur in preparations, being mistaken in earlier work for the dihydro-tetrazines. See ref. 10 for an up-to-date review.

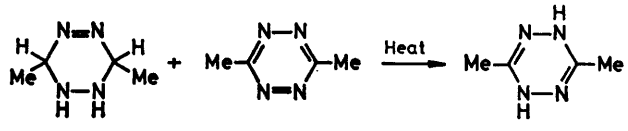
heating with its parent (14), yields the dihydrotetrazine (15) (claimed to be a 1,4-dihydro-arrangement, *cf.* footnote *).

The fact that no dihydrotetrazine, or complex containing it, was isolated in the experiment open to the air is explicable on the basis that dihydrotetrazines are



SCHEME 3

readily oxidised to tetrazines, especially when impure; *e.g.* most preparations of dihydrotetrazines from the action of hydrazine on a suitable precursor (*e.g.* an imidate salt [12]) give rise to tetrazines in addition to the expected dihydro-derivatives. Tetrazine (1a) reformed by oxidation in this way could thus undergo attack by alkali and yield the pyrazolinone (4).



(13) (14) (15)

Attempts to confirm the structure of compound (4) by *X*-ray diffraction were defeated by the fact that its lath-like crystals underwent plastic deformation on cleavage.

EXPERIMENTAL

The n.m.r. spectra were run on a Varian EM 360 (60 MHz) instrument.

Preparation of Ethyl Mandelimidate Hydrochloride.—Mandelonitrile, prepared from benzaldehyde [13] (71 g), was used in the standard Pinner synthesis [4] to obtain ethyl mandelimidate hydrochloride (76.9 g), m.p. 119—121 °C.

Preparation of 3,6-*Bis*-(α-*hydroxybenzyl*)-s-*tetrazine* (1e).—Ethyl mandelimidate hydrochloride (32.4 g) was added in portions during 15 min to a stirred, aqueous solution of hydrazine hydrate (85%; 98 ml) at 0 °C. Stirring was continued for 3 h at 0 °C and the crude dihydrotetrazine which precipitated was filtered off and added, without delay, to sodium nitrite (20 g) in water (48 ml) at 0 °C. Glacial acetic acid (120 ml) was added in drops during 30 min to the cooled, stirred mixture which was then kept for 2 h at 0 °C, when further portions of sodium nitrite (3 g) and glacial acetic acid (23 ml) were added.[6] After stirring for 1 h at room temperature the crude tetrazine was filtered, washed with a little water, and recrystallised from methanol; yield 6.2 g, m.p. 158—168 °C (lit.,[6] 174—175 °C). The diastereoisomers could not be separated by recrystallisation or chromatography; the literature m.p. refers to a hand-picked crystal sample.[7]

Isolation of 3,6-*Bis*-(α-*hydroxybenzyl*)-1,2-*dihydro*-s-*tetrazine* (1e).—The crude dihydrotetrazine (12), prepared as above, was washed with a little water and then dissolved in ethyl acetate. After drying, the solution was evaporated to small bulk under reduced pressure, when the dihydrotetrazine precipitated. This was filtered off and recrystallised from ethyl acetate. The product was white and free from any pink tinge, m.p. 181—186 °C (lit.,[4] 193 °C).

Action of Methanolic Potassium Hydroxide on the Tetrazine (1e).—(a) *In air.* The tetrazine (1e) (2 g) was stirred in methanol (20 ml) at 35—40 °C (bath temperature), and potassium hydroxide (0.75 g) in methanol (10 ml) was added in drops during 15 min, during which time gas (N_2) was evolved. Stirring was continued at the same temperature for 1 h and the flask was then sealed and left overnight at room temperature. The reaction mixture was then evaporated to small bulk under reduced pressure, water was added, and the solution extracted with ether and ethyl acetate. Evaporation of these solvents, after drying, yielded benzaldehyde and unidentified oils. The aqueous residue was then acidified with hydrochloric acid (5M) and extracted with ether and ethyl acetate. Evaporation of these solvents, after drying, yielded 4-*hydroxy*-3-(α-*hydroxybenzyl*)-4-*phenyl*-2-*pyrazolin*-5-*one* (4) (0.52 g), m.p. 182—183 °C (on recrystallisation from chloroform containing a little ethanol) (Found: C, 67.7; H, 5.0; N, 9.7. $C_{16}H_{14}N_2O_3$ requires: C, 68.1; H, 5.0; N, 9.9%); ^{1}H n.m.r. (CD_3COCD_3) δ 4.9 (1 H, d, CHO*H*), 5.4 (1 H, d, C*H*OH), 5.7 (1 H, s, CPhO*H*), 7.2 (5 H, s, Ph), 7.3 (5 H, s, Ph), and 10.2 (1 H, s br, NH). The i.r. spectrum (Nujol mull) showed aromatic bands and in addition a broad band with peaks at 3 350, 3 300, and 3 230 cm^{-1} (O–H and N–H) and strong absorptions at 1 780 and 1 730 cm^{-1} (C=O, C=N).

(b) *Under nitrogen.* The reaction was repeated under nitrogen at atmospheric pressure. Provision was made for evaporating the reaction mix to small bulk under reduced pressure without introducing air and after the reintroduction of nitrogen at atmospheric pressure dilute hydrochloric acid was stirred into the liquors to effect neutralisation before air was admitted. Thereafter the aqueous mixture was extracted with ether and ethyl acetate. Evaporation of these solvents, after drying, gave an oil which, on triturating with a little chloroform, yielded a pinkish white solid (0.80 g), m.p. 210—218 °C (after recrystallisation from chloroform with a little ethanol; recrystallisation from acetone and from aqueous ethanol gave an unchanged m.p.). The mass spectrum showed peaks at *m/e* 296 [the dihydrotetrazine (12)] and 282 [the pyrazolinone (4)], but no peaks at higher mass. The chloroform used for trituration yielded, on evaporation, 3,6-bis-(α-hydroxybenzyl)-1,2-dihydro-*s*-tetrazine (12) (0.09 g), m.p. 189—190 °C (after recrystallisation from chloroform with a little ethanol) (lit.,[4] 193 °C). A mixed melt with authentic dihydrotetrazine (see above) and comparison of i.r. spectra confirmed this structure. The ^{1}H n.m.r. spectrum of the pinkish white solid exhibited peaks which corresponded to a 2 : 1 ratio of (4) and (12) and repeated elution by ether on a preparative t.l.c. plate (silica) yielded (4) and 3,6-bis-(α-hydroxybenzyl)-*s*-tetrazine (1e) (both confirmed by i.r. spectra which were identical with authentic samples). Attempts to produce the high-melting ' complex ' by mixing the components [(4) and the dihydro-derivative of compound (1e)], with or without recrystallis-

ation, failed, however; the product always exhibited the normal depression of the melting point associated with a simple mixture.

Oxidation of 4-Hydroxy-3-(α-hydroxybenzyl)-4-phenyl-2-pyrazolin-5-one (4).—Chromic oxide (0.5 g) was added in portions, with stirring, to dry pyridine (5 ml) at 15—20 °C. To the resulting slurry was added the pyrazolinone (4) (0.12 g) in pyridine (1 ml) with stirring. The mixture was left overnight, at room temperature in a stoppered vessel, after which it was dispersed in water (100 ml) and extracted with ethyl acetate. Drying and repeated evaporation under reduced pressure with aliquots of toluene gave *3-benzoyl-4-hydroxy-4-phenyl-2-pyrazolin-5-one* (5) (0.02 g), m.p. 213—214 °C (from toluene) (Found: C, 66.6; H, 4.4; N, 9.8%; M^+, 280.083 98. $C_{16}H_{12}N_2O_3 \cdot \frac{1}{2}H_2O$ requires C, 66.4; H, 4.5; N, 9.7%; M^+, for $C_{16}H_{12}N_2O_3$, 280.084 77); ^{1}H n.m.r. (CD_3COCD_3) δ 5.8 (1 H, s, OH), 7.3—8.1 (10 H, m, Ph), and 11.2 (1 H, s br, NH); i.r. ν (Nujol mull) 3 230br (O–H), 1 740 s br, (C=O), and 1 640 s cm^{-1} (C=N).

Synthesis of 3-Benzoyl-4-hydroxy-4-phenyl-2-pyrazolin-5-one (5).—(a) *Cyclisation.* Ethyl 3-oxo-2,4-diphenylbutanoate (6) (prepared [14] from ethyl phenylacetate by the action of isopropylmagnesium bromide) was treated with hydrazine hydrate [15] to yield 3-benzyl-4-phenyl-2-pyrazolin-5-one (7), m.p. 145 °C. The i.r. spectrum of compound (7) exhibited a broad band at 2 600 cm^{-1} and a strong split absorption at 1 600 and 1 585 cm^{-1}, but no absorptions in the carbonyl or enolic hydroxy group regions. Heating for 8 h at 125 °C gave the substance (7), m.p. 171—172 °C (lit.,[15] 172.5—173 °C) and the i.r. spectrum showed a sharp absorption at 3 400 (enolic OH) and 2 sets of triple absorptions at 1 600—1 560 and 1 510—1 480 cm^{-1} (C=N) (Found: C, 76.8; H, 5.6; N, 11.3%; M^+, 250.111 17. $C_{16}H_{14}N_2O$ requires C, 76.8; H, 5.6; N, 11.2%; M^+, 250.110 60).

(b) *Oxidation of the ring carbon.* The pyrazolinone (7) (5.0 g) was dissolved in a mixture of sodium ethoxide in ethanol (2M; 12 ml) and t-butyl alcohol (30 ml) under dry conditions.[8] t-Butyl hydroperoxide (6 ml) was added; the solution heated at 70 °C (bath temperature) for 20 min, with stirring, under a drying tube, and then left overnight at room temperature. The sodium salt of 3-benzyl-4-hydroxy-4-phenyl-2-pyrazolin-5-one (8) (4.15 g) which separated was filtered off and dried at room temperature in a vacuum desiccator before being dispersed in water (500 ml) at *ca.* 50 °C. Neutralisation with hydrochloric acid (5M) precipitated the free pyrazolinone (8) (3.9 g) which was filtered off, taken up in ethyl acetate, and dried. Evaporation of the solvent and recrystallisation from ethanol gave *compound* (8), m.p. 173—174 °C (Found: C, 70.4; H, 5.1; N, 10.2%; M^+, 266.104 81. $C_{16}H_{14}N_2O_2 \cdot \frac{1}{2}H_2O$ requires C, 69.8; H, 5.4; N, 10.2%. $C_{16}H_{14}N_2O_2$ requires M^+, 266.105 51); $\nu_{max.}$ (Nujol mull) 1 710s (C=O) and 3 200br cm^{-1} (OH); ^{1}H n.m.r. ([$^2H_6$]DMSO) δ 3.6 (2 H, m, CH_2), 7.1 (1 H, s, OH), 7.3 (5 H, s, C_6H_5), 7.4 (5 H, s, C_6H_5), and 11.2 (1 H, s br, NH).

(c) *Oxidation of the benzylic side-chain.* To the chromium trioxide–pyridine complex prepared as above (from 3 g CrO_3), was added, with stirring, a solution of (8) (0.6 g) in dry pyridine (6 ml) at room temperature. After leaving overnight in a sealed flask the mixture was dispersed in water (500 ml) and extracted with ethyl acetate. After drying and repeated evaporation under reduced pressure with aliquots of toluene, the product (0.20 g) was purified by dry column chromatography [silica eluted with ether–petroleum (b.p. 40—60 °C) (1 : 1)] and, after recrystallisation from toluene, was shown to be 3-benzoyl-4-hydroxy-4-phenyl-2-pyrazolin-5-one, identical with (5) above by mixed m.p. and i.r. spectra (Found: M^+, 280.083 71. $C_{16}H_{12}N_2O_3$ equires M^+, 280.084 77).

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REFERENCES

[1] D. G. Neilson, K. M. Watson, and T. J. R. Weakley, *J. Chem. Soc., Perkin Trans. 1,* 1979, 333.
[2] A. Pinner, *Ber.,* 1894, **27**, 984.
[3] O. Riobé, *C. R. Acad. Sci., Ser. C.,* 1972, **274**, 1462.
[4] A. Pinner, *Ber.,* 1897, **30**, 1890.
[5] D. G. Neilson in ' The Chemistry of Amidines and Imidates,, ed. S. Patai, Wiley, New York, 1975, p. 391.
[6] P. Yates, O. Meresz, and H. Morrison, *Tetrahedron Lett.,* 1967, 77.
[7] P. Yates, personal communication.
[8] S. Veibel and S. C. Linholt, *Act. Chem. Scand.,* 1954, **8**, 1383.
[9] S. Veibel and S. C. Linholt, *Act. Chem. Scand.,* 1955, **9**, 970.
[10] P. F. Wiley in ' The Chemistry of Heterocyclic Compounds, The 1,2,3-Triazines and 1,2,4-Triazines, Tetrazines, and Pentazines,' eds. A. Weissberger and E. C. Taylor, Wiley, New York, 1978, p. 1112.
[11] W. Skorianetz and E. sz. Kovats, *Helv. Chim. Acta,* 1972, **55**, 1404.
[12] D. G. Neilson in ' The Chemistry of Amidines and Imidates,' ed. S. Patai, Wiley, New York, 1975, p. 433.
[13] B. B. Corson, ' Organic Syntheses, Collective Vol. 1,' ed. H. Gilman, Wiley, New York, 1932, p. 329.
[14] J. B. Conant and A. H. Blatt, *J. Am. Chem. Soc.,* 1929, **51**, 1227.
[15] V. M. Rodionov and N. M. Suvarov, *J. Gen. Chem. USSR,* 1950, **20**, 1273.