691. *The Conversion of Sucrose into Pyridazine Derivatives. Part XII. The Stability of Tetrahydro-6-ketopyridazine and 6-Pyridazone Derivatives towards Acidic Reagents.*

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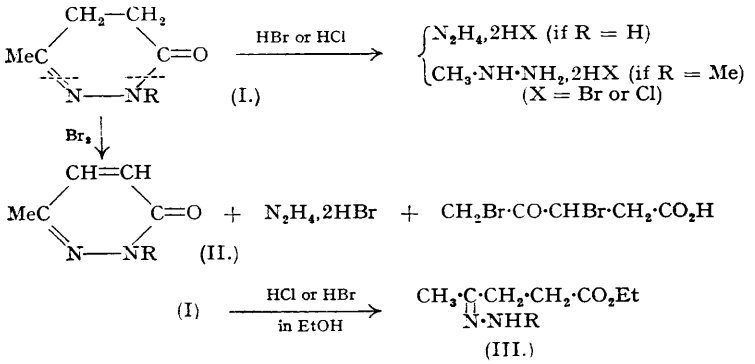
Unlike derivatives of 6-pyridazone which are stable to acids, those of tetrahydro-6-keto-pyridazine are decomposed. The stabilities of some salts of derivatives of 3-methylpyridazine and 3-methyl-6-pyridazone are discussed.

During the preparation of many derivatives of tetrahydro-6-ketopyridazine and 6-pyridazone (Wiggins *et al.*, *J.*, 1947, 239, 549; 1948, 2191, 2195, 2199; 1949, 1248) we have noticed well-defined differences in the behaviour towards acids of these two classes of compound. Curtius (*J. pr. Chem.*, 1894, **50**, 522) and Wolff (*Annalen*, 1912, **394**, 98) have referred to the acid-lability of 1 : 4 : 5 : 6-tetrahydro-6-keto-3-methylpyridazine and von Rothenburg (*J. pr. Chem.*, 1895, **51**, 140) has drawn attention to the difference between pyrazolones and tetrahydropyridazones; the former are stable to acids and the latter unstable. More recently the acid-lability of derivatives of 1 : 4 : 5 : 6-tetrahydro-6-keto-3-methypyridazine substituted at position 5 by alkyl groups has been used to prepare α-alkyl-substituted lævulic acids in good yields (Gault and Salomon, *Ann. Chim.*, 1928, **2**, 133; *Compt. rend.*, 1922, **175**, 274). However, Paal and Koch (*Ber.*, 1904, **37**, 4382) state that pyridazines, when completely reduced, are stable to acids and will form mono-salts.

During the dehydrogenation, with bromine, of 1 : 4 : 5 : 6-tetrahydro-6-keto-3-methyl-pyridazine (I; R = H) to 3-methyl-6-pyridazone (II; R = H) a troublesome side-reaction was encountered owing to the lability of the former to acids. The hydrogen bromide formed during

the reaction resulted in some decomposition of (I), to give hydrazine hydrobromide and lævulic acid brominated in the β- and the δ-position (Overend and Wiggins, *J.*, 1947, 239).



The action of acids on tetrahydro-6-ketopyridazines was therefore further investigated. It was confirmed that treatment of 1 : 4 : 5 : 6-tetrahydro-6-keto-3-methylpyridazine (I; R = H) with hydrogen bromide resulted in the formation of hydrazine hydrobromide, both carbon–nitrogen linkages being broken. Similarly use of hydrogen chloride led to hydrazine hydrochloride. It was shown that in ethyl alcohol solution containing 10%, 5%, or 2% of hydrogen chloride such cleavage of the 1 : 4 : 5 : 6-tetrahydro-6-ketopyridazine ring occurred, but that, if the concentration of hydrogen chloride was reduced to 0·1%, then (I; R = H) could be recovered unchanged. Treatment of (I; R = H) with chlorine also gave hydrazine hydrochloride in good yield, probably because of the hydrogen chloride usually present in commercial chlorine. When 1 : 4 : 5 : 6-tetrahydro-6-keto-1 : 3-dimethylpyridazine (I; R = Me) was treated with hydrogen chloride the reaction followed the same course, both carbon–nitrogen linkages being broken and methylhydrazine hydrochloride formed. However, with either 1 : 4 : 5 : 6-tetrahydro-6-keto-3-methyl-1-phenylpyridazine (I; R = Ph) or 1 : 4 : 5 : 6-tetrahydro-6-keto-3-methyl-1-*p*-nitrophenylpyridazine (I; R = *p*-NO_2·C_6H_4) in ethyl alcohol, only the carbon–nitrogen single bond is cleaved and ethyl lævulate phenylhydrazone (III; R = Ph) and *p*-nitrophenylhydrazone (III; R = *p*-NO_2·C_6H_4) can be isolated. It is interesting that when ethyl lævulate is treated with hydrazine hydrate or a monoalkylhydrazine the corresponding 1 : 4 : 5 : 6-tetrahydro-6-ketopyridazine derivative is formed directly without isolation of an intermediate hydrazone. If phenylhydrazine or a substituted phenylhydrazine is used, the corresponding phenylhydrazone of ethyl lævulate is obtained, and this must be subsequently cyclised in order to give the six-membered cyclic diazine (cf. Overend and Wiggins, *loc. cit.*; *J.*, 1947, 549). In the latter case therefore the carbon–nitrogen linkages in the heterocyclic compound are formed in two stages. Acid treatment of the heterocyclic compounds show that, where these bonds are formed in stages, they can be cleaved likewise, and the last linkage to be made is the first to be broken.

Curtius (*J. pr. Chem.*, 1894, **50**, 3212) claimed that treatment of 1 : 4 : 5 : 6-tetrahydro-6-keto-3-methylpyridazine with nitrous acid and concentrated sulphuric acid yielded 1 : 4 : 5 : 6-tetrahydro-6-keto-3-methyl-5-oximinopyridazine, but reported neither the melting point nor analytical data for the compound. Exact repetition of this experiment gave a product agreeing with Curtius's description, but shown to be hydrazine sulphate. Clearly the acidic treatment had resulted, as expected, in scission of both the carbon–nitrogen linkages in the diazine ring.

Although derivatives of 1 : 4 : 5 : 6-tetrahydro-6-ketopyridazine are unstable to acidic reagents those of its dehydrogenated product, 6-pyridazone, are stable and in general form salts. However, the stability of these salts varies with the nature of the substituents in the heterocyclic ring. The preparation of salts of this type has been described already, usually when the synthesis of the parent base was outlined (Wiggins *et al.*, *loc. cit.*), but we now report a systematic summary of their properties.

The hydrochloride of 3-methylpyridazine underwent decomposition on long storage, whereas 3-methyl-6-pyridazone formed a fairly stable mono-hydrochloride and -hydrobromide (Overend and Wiggins, *J.*, 1947, 239) although these are hydrolysed in aqueous solution. Contrary to reports by Poppenberg (*Ber.*, 1901, **34**, 3264) it was shown that 3-chloro-6-methylpyridazine forms a stable mono-hydrochloride and -hydrobromide and also a platinichloride

(Overend and Wiggins, *loc. cit.*); these are highly coloured. Both 3-amino-6-methylpyridazine and its acetyl derivative form only mono-salts; those of the former are stable in aqueous solution, but the hydrochloride and hydrobromide of the latter are easily hydrolysed. It might be expected that 3-amino-6-methylpyridazine would form a di-salt. However, it is probable that the resonating pyridazine nucleus reduces the basicity of the amino-group to such an extent that it does not form stable salts. 1 : 3-Dimethyl- and 1-ethyl-3-methyl-6-pyridazone and 3-methoxy-6-methylpyridazine each form a monohydrochloride and a monohydrobromide (Overend, Turton, and Wiggins, *J.*, 1950, 3505), none of them stable on prolonged exposure to the atmosphere. The presence of an electron-attracting group in the molecule tends to suppress salt formation. For example, whereas 3-methyl-6-pyridazone forms a stable salt, 3-methyl-1-phenyl-6-pyridazone forms an unstable monohydrochloride, and neither 5-chloro-3-methyl-1-phenyl-6-pyridazone nor 3-methyl-1-*p*-nitrophenyl-6-pyridazone forms salts. This is further exemplified by the case of 4-amino-6-methyl-2-phenyl-3-pyridazone and the 1-*p*-nitrophenyl analogue : the former forms a salt whereas the latter does not.

From this account it is clear that pyridazine and 6-pyridazone derivatives are mono-acid bases (cf. Gabriel and Colman, *Ber.*, 1899, **32**, 395) (this is so even for a symmetrical structure, since Paal and Koch, *Ber.*, 1904, **37**, 4382, state that 3 : 6-dimethylpyridazine forms only mono-salts) unless salt-formation is inhibited by a strongly electron-attracting group. These facts are in agreement with recent work on benzodiazines.

Experimental.

Treatment of 1 : 4 : 5 : 6-*Tetrahydro*-6-*keto*-3-*methylpyridazine with Hydrogen Halides.*—(a) *Hydrogen bromide.* The anhydrous ketone (0·1 g.) in ethyl alcohol (5 c.c.) was cooled to 0°. Dry hydrogen bromide was passed through the solution, which became warm. Hydrazine hydrobromide which separated crystallised from glacial acetic acid as a fine white powder which was water-soluble but insoluble in ether and had m. p. 202° (Found : N, 14·2; Br, 82·0. Calc. for $N_2H_4,2HBr$: N, 14·4; Br, 82·4%). Curtius (*Ber.*, 1887, **20**, 1632) gives m. p. 195°.

(b) *Hydrogen chloride.* A similar experiment was carried out replacing hydrogen bromide by dry hydrogen chloride. The solid which separated recrystallised from aqueous alcohol in white prisms, m. p. 203—203·5°, alone or on admixture with hydrazine hydrochloride (Curtius, *loc. cit.*, reports m. p. 198°).

(c) Anhydrous 1 : 4 : 5 : 6-tetrahydro-6-keto-3-methylpyridazine (2·0 g.) was dissolved in alcohol (20 c.c.) containing 10% of hydrogen chloride. A white solid slowly separated. It was collected and shown to be hydrazine hydrochloride, m. p. 203°. The experiment was repeated with alcohol containing 5%, 2%, and 0·1% of hydrogen chloride severally. Except in the last case, when 1 : 4 : 5 : 6-tetrahydro-6-keto-3-methylpyridazine was recovered unchanged (m. p. 82° after recrystallisation from water), hydrazine hydrochloride was obtained.

Treatment of 1 : 4 : 5 : 6-*Tetrahydro*-6-*keto*-3-*methylpyridazine with Commercial Chlorine.*—(*a*) Commercial chlorine was bubbled through a solution of 1 : 4 : 5 : 6-tetrahydro-6-keto-3-methylpyridazine monohydrate (1·14 g.) in acetic acid (10 c.c.) until 1·24 g. had been absorbed. The mixture became hot and assumed a transient pink colour. On cooling, a solid separated and was collected. After being washed with hot acetic acid, this solid (0·51 g., 56%) had m. p. 201—203°, alone or on admixture with hydrazine hydrochloride (Found : Cl, 67·2. Calc. for $N_2H_4,2HCl$: Cl, 67·6%). Concentration of the filtrate gave a syrup which decomposed on attempted distillation.

(*b*) The ketone monohydrate (7 g.) was dehydrated at 120°/12 mm. for 1·5 hours and then dissolved in glacial acetic acid (50 c.c.). The solution was cooled to 0° and dry commercial chlorine (3·8 g.) was passed into it. After the addition of ether and storage, a white crystalline solid separated and was collected. Recrystallisation from alcohol–ether gave hydrazine hydrochloride (4·1 g., 73%), m. p. 203°.

Treatment of 1 : 4 : 5 : 6-*Tetrahydro*-6-*keto*-3-*methylpyridazine with Sulphuric Acid* (cf. Curtius, *J. pr. Chem.*, 1894, **50**, 3213).—Nitrous anhydride was bubbled through a solution of the ketone (1·99 g.) in water (10 c.c.), to form nitrous acid *in situ*. No material separated, and so concentrated sulphuric acid (5 drops) was added. Next morning a solid which had separated was collected. Recrystallisation from aqueous alcohol gave shining white plates (0·74 g., 32·2%) of hydrazine sulphate, m. p. 263°, alone or on admixture with an authentic specimen.

Treatment of 1 : 4 : 5 : 6-*Tetrahydro*-6-*keto*-1 : 3-*dimethylpyridazine with Hydrogen Chloride.*—Dry hydrogen chloride was bubbled through a solution of the ketone (0·1 g.) in alcohol (2 c.c.). Methylhydrazine hydrochloride which separated recrystallised from alcohol as colourless needles, m. p. 139°, alone or on admixture with an authentic sample (Found : C, 10·1; H, 6·9. Calc. for $CH_6N_2,2HCl$: C, 10·1; H, 6·7%).

Treatment of 1 : 4 : 5 : 6-*Tetrahydro*-6-*keto*-3-*methyl*-1-*phenylpyridazine with Hydrogen Chloride.*—The ketone (0·1 g.) in absolute alcohol (5 c.c.) was treated with dry hydrogen chloride. No solid separated even after addition of ether. The solvent was evaporated and an oily solid remained. This was separated by crystallisation from aqueous alcohol into unchanged ketone, m. p. 107°, and ethyl lævulate phenylhydrazone, m. p. 103°. In addition an unidentified oil was isolated.

Treatment of 1 : 4 : 5 : 6-*Tetrahydro*-6-*keto*-3-*methyl*-1-p-*nitrophenylpyridazine with Hydrogen Chloride.*—The ketone (0·1 g.) in alcohol (5 c.c.) was treated with hydrogen chloride. The solution was then evaporated to dryness. The residue, recrystallised from aqueous alcohol, formed orange needles, m. p. 157°, alone or on admixture with ethyl lævulate *p*-nitrophenylhydrazone, prepared as follows :

A mixture of *p*-nitrophenylhydrazine (0·15 g.) in alcohol (5 c.c.) and an alcoholic solution (5 c.c.) of ethyl lævulate (0·1 g.) was warmed and on cooling deposited *ethyl lævulate* p-*nitrophenylhydrazone* (quantitative yield), orange needles (from aqueous alcohol), m. p. 157° (Found : C, 55·9; H, 6·4; N, 14·6. $C_{13}H_{17}O_4N_3$ requires C, 55·9; H, 6·1; N, 15·0%).

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