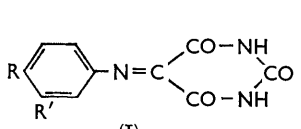
1035. *Reactions of Alloxan with Aromatic Amines: Dioxindole-3-carboxyureides and Oxindole-3-spiro-5′-oxazolidine-2′,4′-diones*

By J. W. Clark-Lewis and J. A. Edgar

Reaction of anhydrous alloxan with *p*-substituted aromatic amines in acetic acid gives highly coloured anils initially, and finally yields dioxindole-3-carboxyureides. The ureides cyclise in aqueous base to oxindole-spiro-oxazolidinediones. 5-(3,4-Dimethylphenylamino)-5-hydroxybarbituric acid is formed as an unstable adduct from anhydrous alloxan and 3,4-dimethylaniline in diglyme. This structure was previously assigned to the isomeric 5,6-dimethyldioxindole-3-carboxyureide by Berezovskii, Rodionova, and Gurko.

Anhydrous alloxan reacts with *p*-toluidine in acetic acid to give the deeply coloured anil (I; R = Me, R′ = H), and by further reaction yields 5-methyldioxindole-3-carboxyureide (II; R = Me, R′ = H) as the stable end-product. The initial product formed from anhydrous alloxan and *p*-toluidine is presumably the adduct (III; R = Me, R′ = R″ = H) which, although stabilised by the inductive effects of the neighbouring carboxyamide groups that account for the stability of alloxan monohydrate, can nevertheless lose water

to form the anil. This dehydration is facilitated in acid media, but by adding 3,4-dimethylaniline to anhydrous alloxan in dry diglyme the adduct (III; R = R′ = Me, R″ = H) was isolated (see below).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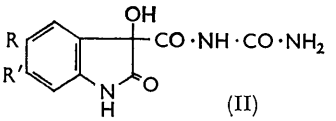
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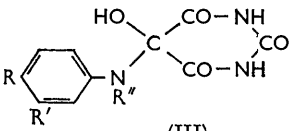
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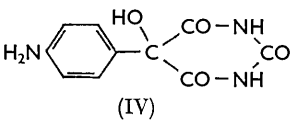
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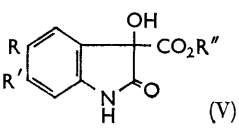
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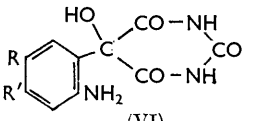

(VI)

Aromatic amines with a free *p*-position have been known for 75 years to yield 5-*p*-aminophenyl-5-hydroxybarbituric (IV) and its analogues by reaction with alloxan.[1] Substitution by alloxan *ortho* to an amino-group in an aromatic nucleus appears not to have been recorded previously, although condensation of mesoxalic ester with *p*-substituted aromatic amines yields dioxindoles (V)[2] analogous to the ureides (II). Formation of dioxindole-3-carboxyureides (II) is aided by substituents (R′) which activate the position *ortho* to the amino-group towards electrophilic substitution, and presumably proceeds *via* the 5-*o*-aminophenyl-5-hydroxybarbituric acids (VI) which then undergo transamidation to give the ureides (II). Similar fission of the alloxan ring occurs in the formation of quinoxalonecarboxyureides from *o*-phenylenediamines and alloxan under neutral conditions.[3] 5-Methyl- (II; R = Me, R′ = H), 5,6-dimethyl- (II; R = R′ = Me), and 5,6-dimethoxy-dioxindole-3-carboxyureide (II; R = R′ = OMe) were thus obtained from *p*-toluidine (31%), 3,4-dimethylaniline (68%), and 3,4-dimethoxyaniline (92%). Reactions leading to the adducts (III) and the anils (I) are reversible, so that ureides (II) are the stable end-products from the reaction of alloxan with *p*-substituted anilines in acetic acid.

The structures of the dioxindole-3-carboxyureides were inferred from the infrared spectra of the compounds, which showed the dioxindole carbonyl absorption at 5·8 μ (lit.,[4] 5·79—5·83 μ) and also a broad band at 5·9—5·95 μ attributed to the ureide side-chain. The intact pyrimidine ring (*e.g.*, in VII; R = H)[5] is stable towards acids but ureide side-chains are readily hydrolysed by dilute acids.[3] Hydrolysis of the dioxindoles (II) gave the carboxylic acids (V; R″ = H) which were identified by aeration of the basified solutions and isolation of the corresponding isatins (VIII; R = Me and OMe). Addition of 50% aqueous potassium hydroxide to the dioxindolecarboxyureides caused liberation of ammonia and separation of crystalline dipotassium salts of the spiroindoles (IX) which were liberated by acidification of solutions of the salts. The n.m.r. spectrum of the potassium salt of the spiroindole (IX; R = R′ = OMe) confirmed the aromatic substituted pattern, and hence the orientation of the parent ureide (II; R = R′ = OMe) which, like the other ureides, was too sparingly soluble for n.m.r. measurements. The oxindole spiro-oxazolidinediones showed N–H stretching absorption at 3·1 μ and three carbonyl

[1] G. Pellizzari, *Gazzetta*, 1887, **17**, 409; 1888, **18**, 340; 1889, **19**, 397; 1911, **41**, 21; cf. F. E. King and J. W. Clark-Lewis, *J.*, 1951, 3077.

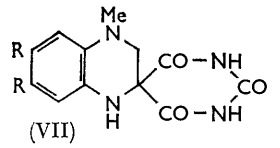
[2] W. C. Sumpter and F. M. Miller, in "Heterocyclic Compounds with Indole and Carbazole Systems," "Chemistry of Heterocyclic Compounds," ed. A. Weissberger, Interscience, New York, 1954, pp. 112, 149.

[3] F. E. King and J. W. Clark-Lewis, *J.*, 1951, 3379.

[4] E. Wenkert, A. K. Bose, and T. L. Reid, *J. Amer. Chem. Soc.*, 1953, **75**, 5514; J. W. Clark-Lewis and G. F. Katekar, *J.*, 1959, 2825.

[5] F. E. King and J. W. Clark-Lewis, *J.*, 1951, 3080; J. W. Clark-Lewis, J. A. Edgar, J. S. Shannon, and M. J. Thompson, *Austral. J. Chem.*, 1964, **17**, 877.

peaks at 5·5, 5·7, and 5·8 μ. Absorption at 5·5 and 5·7 μ is characteristic of oxazolidine-2,4-diones [6] and the oxindole carbonyl absorption occurred at 5·8 μ. Methylation of the oxindolespiro-oxazolidinediones (or the dioxindolecarboxyureides) with methyl iodide–acetone–potassium carbonate gave the corresponding *NN'*-dimethyl derivatives with infrared absorption similar to that of the spiro-oxazolidinediones (IX) except for the absence of N–H absorption.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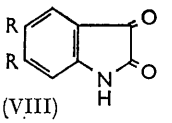
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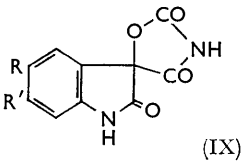
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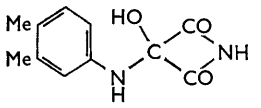
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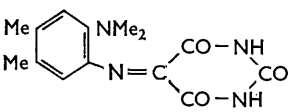
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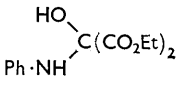
(XII)

Berezovskii, Rodionova, and Gurko [7] recently assigned structure (III; R = R' = Me; R'' = H) to the product obtained from 3,4-dimethylaniline and alloxan in ethanol–acetic acid mixture, and a similar structure (III; R = R' = Me; R'' = D-ribityl) to the analogous product from 3,4-dimethyl-*N*-D-ribitylaniline. The evidence quoted was clearly compatible with dioxindolecarboxyureide structures, and direct comparison of the ureide (II; R = R' = Me) with the compound prepared from 3,4-dimethylaniline as described by the Russian authors established the identity of the two products. Alkaline degradation of the ureide (II; R = R' = Me) gave the spiroindole (IX; R = R' = Me), as already mentioned, and the tartronimide (X) reported by the Russian workers was not obtained in the present work. The product obtained from 3,4-dimethyl-*N*-D-ribitylaniline is presumably the analogous 1-D-ribityl derivative of the carboxyureide (II; R = R' = Me). The incorrect formulation (III; R = R' = Me, R'' = H) for the dioxindolecarboxyureide (II; R = R' = Me) was based [7] on elemental analysis, the absence of a primary aromatic amino-group, and exclusion of an anil structure from comparison of light-absorption data. The Russian workers [7] unfortunately chose the condensation product (VII; R = Me) from alloxan and 4,5-dimethyl-2-dimethylaminoaniline as the reference "anil," apparently unaware that Rudy and Cramer's erroneous anil structure (XI) [8] had been revised in 1951 to the spiran (VII; R = Me).[5]

Anhydrous alloxan and 3,4-dimethylaniline in dry diglyme gave an unstable crystalline product with properties indicative of the structure (III; R = R' = Me, R'' = H). It differed from the isomeric ureide (II; R = R' = Me) in melting point, infrared absorption, solubility, and stability. The 5-arylamino-5-hydroxybarbituric acid (III; R = R' =Me, R'' = H) dissolved readily in warm aqueous ethanol to form, initially, a deep red solution (possibly due to anil formation), but the compound decomposed in boiling ethanol and recrystallisation could not be achieved. The isomeric ureide (II; R = R' = Me) was sparingly soluble in aqueous ethanol and stable in the boiling solvent. The ureide melted at 204°, whereas the hydroxyuramil (III; R = R' = Me, R'' = H) became purple at *ca.* 140°, presumably through dehydration to the anil, and finally decomposed with evolution of gas at 226°. The 5-arylamino-5-hydroxybarbituric acid (III; R = R' = Me, R'' = H) decomposed in boiling ethanol to a mixture of salts of 3,4-dimethylaniline with alloxanic acid and 5-(3,4-dimethylphenylamino)barbituric acid (see succeeding Paper).

[6] J. W. Clark-Lewis, *Chem. Rev.*, 1958, **58**, 91; M. Pianka and D. J. Polton, *J.*, 1960, 983.
[7] V. M. Berezovskii, E. P. Rodinova, and L. N. Gurko, *Zhur. obshchei Khim.*, 1962, **32**, 3368.
[8] H. Rudy and K. Cramer, *Ber.*, 1938, **71**, 1234.

Formation of the 5-phenylamino-5-hydroxybarbituric acid from anhydrous alloxan is analogous to the formation of anilinotartronic esters, *e.g.*, (XII), from aromatic amines and anhydrous diethyl oxomalonate in dry ether.[9]

Experimental

Microanalyses were performed by the Australian Microanalytical Service, Melbourne. Infrared spectra were recorded on an Infracord instrument, for Nujol mulls unless otherwise stated, and ultraviolet spectra for solutions in 95% ethanol. The n.m.r. spectrum of the potassium salt 5,6-dimethoxyoxindole-3-spiro-5′-oxazolidinedione in D_2O was recorded with a Varian DP60 instrument at 60 Mc./sec. and calibrated with side-bands generated from the proton signal of HDO. Chemical shifts are given as τ-values.

5-p-*Methylphenyliminobarbituric Acid* (I; R = Me, R′ = H).—A mixture of anhydrous alloxan (0·4 g.) and *p*-toluidine (0·26 g.) in acetic acid (10 ml.) was boiled under reflux for 10 min. The anil (0·3 g., 46%) was rapidly deposited as dark red prisms from the dark red solution, and crystallisation from acetone–light petroleum (b. p. 60—80°) gave 5-p-*methylphenyliminobarbituric acid* as almost black prisms, m. p. 256° (Found: C, 57·4; H, 4·0; N, 18·6. $C_{11}H_9N_3O_3$ requires C, 57·1; H, 3·9; N, 18·2%). Carbonyl absorption occurred at 5·7, 5·85, and 5·9 μ, and absorption also occurred at 3·1 and 3·2 μ; $\lambda_{max.}$ 231 (ε 13,500) and 485 mμ (ε 1500); $\lambda_{min.}$ 395 mμ (ε 250); the colour of the solutions faded and light-absorption measurements were therefore made soon after preparation of the solution.

5-(3,4-*Dimethylphenylamino*)-5-*hydroxybarbituric Acid* (III; R = R′ = Me, R″ = H).—Anhydrous alloxan (1·4 g.) in dry diglyme (10 ml.) at room temperature was added to a solution of 3,4-dimethylaniline (1·21 g.) in diglyme (5 ml.) and the mixture was kept at 2—3° overnight. 5-(3,4-*Dimethylphenylamino*)-5-*hydroxybarbituric acid* crystallised from the reaction mixture in colourless prisms (2·0 g., 76%), m. p. 226° (decomp.) (Found: C, 54·5; H, 4·9; N, 15·8. $C_{12}H_{13}N_3O_4$ requires C, 54·7; H, 5·0; N, 16·0%). Infrared absorptions were observed near 3·1, 5·8, and 5·95 μ (with a weak band at 5·7 μ). When boiled with aqueous ethanol the compound was converted into the 3,4-dimethylaniline salts of 3,4-dimethylphenylaminobarbituric acid and of alloxanic acid, and treatment of the 5-arylamino-5-hydroxybarbituric acid with 10% aqueous barium hydroxide gave 3,4-dimethylaniline and barium alloxanate.

5-*Methyldioxindole*-3-*carboxyureide* (II; R = Me, R′ = H).—A solution of anhydrous alloxan (1·43 g.) and *p*-toluidine (1·07 g.) in acetic acid (20 ml.) was set aside for 3 days with occasional warming to dissolve any precipitated anil. The initially red reaction mixture became yellow during this period, and the colourless product which separated was collected and washed free from anil with water. 5-*Methyldioxindole*-3-*carboxyureide* crystallised from water as colourless needles (0·8 g., 31%), m. p. 200° (Found: C, 51·7; H, 4·5; N, 16·0. $C_{11}H_{11}N_3O_4,\frac{1}{2}H_2O$ requires C, 51·2; H, 4·7; N, 16·3%). Carbonyl absorptions occurred near 5·8 and 5·95 μ, and N–H and O–H stretching absorptions at 2·95, 3·0, and 3·1 μ.

5,6-*Dimethyldioxindole*-3-*carboxyureide* (II; R = R′ = Me).—The ureide was prepared by warming a solution of 3,4-xylidine (1·21 g.) and anhydrous alloxan (1·43 g.) in acetic acid (10 ml.) until the initial red colour had disappeared. Dilution with water precipitated 5,6-*dimethyldioxindole*-3-*carboxyureide* (1·8 g., 68%) which, after being washed with ethanol and ether, crystallised from a large volume of water or ethanol in plates or needles, m. p. 204° (Found: C, 54·7; H, 5·1; N, 15·5. $C_{12}H_{13}N_3O_4$ requires C, 54·7; H, 5·0; N, 16·0%). Carbonyl absorption occurred near 5·8 and 5·9 μ, and N–H and O–H stretching absorptions near 2·95 and 3·9 μ. The compound was also prepared as described by Berezovskii, Rodionova, and Gurko [7] who reported it as the isomeric 5-(3,4-dimethylphenylamino)-5-hydroxybarbituric acid.

5,6-*Dimethoxydioxindole*-3-*carboxyureide* (II; R = R′ = OMe).—3,4-Dimethoxynitrobenzene, m. p. 98° (lit.,[10] 96°), was prepared by nitration of 1,2-dimethoxybenzene [11] and reduced with sodium sulphide [12] to 3,4-dimethoxyaniline, m. p. 88°, b. p. 180°/25 mm. (lit.,[13] m. p. 87·5—88°, b. p. 174—176°/22 mm.). A solution of 3,4-dimethoxyaniline (1·53 g.) and alloxan

[9] R. S. Curtiss and F. G. C. Spencer, *J. Amer. Chem. Soc.*, 1909, **31**, 1053; R. S. Curtiss, H. S. Hill, and R. H. Lewis, *ibid.*, 1911, **33**, 400; R. S. Curtiss and F. G. C. Spencer, *ibid.*, p. 985.
[10] K. U. Matsmoto, *Ber.*, 1878, **11**, 131.
[11] D. Cardwell and R. Robinson, *J.*, 1915, **107**, 255.
[12] R. G. Fargher, *J.*, 1920, **117**, 865.
[13] J. S. Buck and W. S. Ide, *Org. Synth.*, 1936, **16**, 4.

monohydrate (1·6 g.) in 50% aqueous acetic acid (25 ml.) was boiled under reflux. The red reaction mixture quickly became yellow and the reaction was complete in 5 min. The solvent was evaporated under reduced pressure and the residue was washed with ethanol. 5,6-*Dimethoxydioxindole-3-carboxyureide* crystallised from ethanol or water as colourless needles (2·8 g., 95%), m. p. 198° (Found: C, 48·8; H, 5·0; N, 13·9; O, 32·6. $C_{12}H_{13}N_3O_6$ requires C, 48·8; H, 4·4; N, 14·2; O, 32·5%). The yield was only slightly less when reactants were condensed in aqueous ethanol. Carbonyl absorption occurred near 5·8 and 5·95 μ, and N–H and O–H stretching absorptions near 2·9 and 3·05 μ.

5-*Methyloxindole-3-spiro-5′-oxazolidine-2′,4′-dione* (IX; R = Me, R′ = H).—Addition of 50% aqueous potassium hydroxide (10 ml.) to 5-methyldioxindole-3-carboxyureide (1·3 g.) liberated ammonia and caused separation of the potassium salt of the spiran as plates. Acidification of an aqueous solution of the potassium salt gave 5-*methyloxindole-3-spiro-5′-oxazolidine-2′,4′-dione* which crystallised from water as needles (0·9 g., 77%), m. p. 287° (Found: C, 57·3; H, 3·6; N, 12·1. $C_{11}H_8N_2O_4$ requires C, 56·9; H, 3·5; N, 12·1%). Carbonyl absorptions occurred near 5·5, 5·65 and 5·85 μ, and N–H stretching near 3·1 μ.

5,6-*Dimethyloxindole-3-spiro-5′-oxazolidine-2′,4′-dione* (IX; R = R′ = Me).—Addition of 50% aqueous potassium hydroxide (7 ml.) to 5,6-dimethyldioxindole-3-carboxyureide (1·3 g.) gave the dipotassium salt of the spiran (1·4 g., 87%). Acidification of an aqueous solution of the potassium salt (1·4 g.) with dilute sulphuric acid gave 5,6-*dimethyloxindole-3-spiro-5′-oxazolidine-2′,4′-dione* (1·0 g., 80% from the ureide) which crystallised from water as prisms, m. p. 99—100° (Found: C, 57·9; H, 4·2; N, 11·2. $C_{12}H_{12}N_2O_4,\frac{1}{4}H_2O$ requires C, 57·5; H, 4·2; N, 11·2%). Carbonyl absorption occurred near 5·5, 5·7, and 5·8 μ, and N–H stretching absorption near 3·1 μ.

1,3′,5,6-*Tetramethyloxindole-3-spiro-5′-oxazolidine-2′,4′-dione*.—A mixture of 5,6-dimethyl-3-spiro-5′-oxazolidine-2′,4′-dione (1 g.) anhydrous potassium carbonate (5 g.), methyl iodide (5 g.), and acetone (100 ml.) was stirred and boiled under reflux for 15 hr. 1,3′,5,6-*Tetramethyloxindole-3-spiro-5′-oxazolidine-2′,4′-dione* crystallised from ethanol as prisms (0·95 g., 94%), m. p. 219° (Found: C, 61·4; H, 5·2; N, 10·3. $C_{14}H_{14}N_2O_4$ requires C, 61·3; H, 5·2; N, 10·2%). Carbonyl absorption occurred near 5·55, 5·70, and 5·85 μ, but there was no absorption in the range 2·5—3·1 μ. The methylated spiran (0·36 g., 65%) was also obtained by similar methylation of the ureide (0·53 g.).

5,6-*Dimethoxyoxindole-3-spiro-5′-oxazolidine-2′,4′-dione* (IX; R = R′ = OMe) *and its Potassium Salt*.—Ammonia was liberated immediately and the ureide (1·5 g.) dissolved when stirred with 50% aqueous potassium hydroxide (10 ml.). The *dipotassium salt* (1·8 g., 92%) of the oxazolidinedione separated from the solution, and crystallised from aqueous ethanol as needles, m. p. *ca.* 330—335° (decomp.) (Found: C, 33·9; H, 3·1; N, 7·4. $C_{12}H_8K_2N_2O_6,2H_2O$ requires C, 33·8; H, 3·1; N, 7·2%). The nuclear magnetic resonance spectrum of the potassium salt in D_2O showed two aromatic protons as singlets (3·03, 3·21) and methoxyl absorptions at 6·07 and 6·17.

Acidification of an aqueous solution of the potassium salt (1·0 g.) with dilute sulphuric acid gave 5,6-*dimethoxyoxindole-3-spiro-5′-oxazolidine-2′,4′-dione* (0·7 g., 92%) which crystallised from water as prisms, m. p. 195—196° (Found: C, 48·1; H, 4·5; N, 9·4. $C_{12}H_{10}N_2O_6,H_2O$ requires C, 48·6; H, 4·1; N, 9·5%). Carbonyl absorption occurred near 5·5, 5·7, and 5·8 μ and N–H stretching absorptions at 2·75 and 3·1 μ.

5,6-*Dimethoxy-1,3′-dimethyl-3-spiro-5′-oxazolidine-2′,4′-dione*.—(*a*) A mixture of 5,6-dimethoxydioxindole-3-carboxyureide (1 g.), anhydrous potassium carbonate (5 g.), methyl iodide (5 g.), and acetone (100 ml.) was stirred and boiled under reflux for 18 hr. 5,6-*Dimethoxy-1,3′-dimethyloxindole-3-spiro-5′-oxazolidine-2′,4′-dione* (0·85 g., 82%) crystallised from ethanol as colourless prisms, m. p. 250° (Found: C, 55·4; H, 4·8; N, 9·3. $C_{14}H_{14}N_2O_6$ requires C, 54·9; H, 4·6; N, 9·2%). Carbonyl absorption occurred at 5·5, 5·7, and 5·8 μ.

(*b*) Methylation of 5,6-dimethoxyoxindole-3-spiro-5′-oxazolidine-2′,4′-dione under similar conditions to those described above gave the dimethyl derivative as prisms (86%), m. p. 250° alone and when mixed with that described under (*a*).

Hydrolysis of Dioxindole-3-carboxyureides to Isatins (VIII).—(*a*) 5,6-Dimethoxydioxindole-3-carboxyureide (2·95 g.) was boiled under reflux with 5% aqueous hydrochloric acid (20 ml.) for 1 hr. and then evaporated to dryness under reduced pressure. The residue was dissolved in 10% aqueous potassium hydroxide (10 ml.), and the filtered yellow solution was aerated for 1 hr. The solution was acidified with concentrated hydrochloric acid (10 ml.) and kept at 2—3°

for 10 hr. before collection of the dark red isatin (1·1 g., 53%). Recrystallisation from aqueous ethanol gave 5,6-dimethoxyisatin as dark red needles, m. p. 254° (lit.,[14] 250—252°) (Found: C, 57·4; H, 4·3; N, 6·9. Calc. for $C_{10}H_9NO_4$: C, 58·0; H, 4·4; N, 6·8%); $\lambda_{max.}$ 269 (ε 22,000), 320 (ε 7500), and 470 mμ (ε 1400); $\lambda_{min.}$ 290 (ε 2000) and 372 mμ (ε 400). Its infrared spectrum ($CHCl_3$) showed absorption at 5·7 and 5·8 μ.

(*b*) Hydrolysis of 5,6-dimethyldioxindole-3-carboxyureide with 5% hydrochloric acid for 2 hr. and then basification and aeration followed by reacidification, as described above for the dimethoxy-analogue, gave 5,6-dimethylisatin (37%) as orange-red needes, m. p. 214° (lit.,[15] 214—215°). Its infrared spectrum ($CHCl_3$) showed carbonyl absorptions at 5·7 and 5·8 μ.

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[14] G. Hahn and M. R. Tulus, *Ber.*, 1941, **74**, 518.
[15] E. Giovannini, P. Portmann, A. Jöhl, K. Schnyder, B. Knecht, and H. P. Zen-Ruffinen, *Helv. Chim. Acta*, 1957, **40**, 249; P. Kränzlein, *Ber.*, 1937, **70**, 1776.