248. N-*Oxides and Related Compounds.*[1] *Part X.** *The Hydrogenation of Some Pyridine* 1-*Oxides.*

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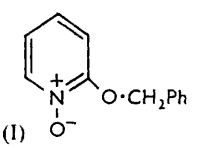
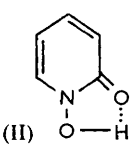
3- and 4-Substituted pyridine 1-oxides are smoothly hydrogenated to pyridines over palladium; 2-substituents somewhat hinder the reduction. Carbon–carbon double bonds and chlorine tend to be reduced before an *N*-oxide group. The rate of reduction of such substituents is not very different from the rate in the corresponding pyridine.

MANY individual observations, but no systematic investigation, of the catalytic hydrogenation of pyridine 1-oxides containing other reducible groups have been made. Ochiai [2] emphasised the comparative resistance to reduction of aromatic *N*-oxides. Indeed other groups have often been selectively reduced, but in other work 1-oxide functions were lost.

Shaw [3] debenzylated 2- and 4-benzyloxypyridine 1-oxide (cf. I) to 1-hydroxy-2- and -4-pyridone (cf. II) (see ref. 4 for further examples), and the isomeric compound (III) behaved similarly.[5] However, the 4-isomer of (I) has also given 4-pyridone; [6] 4-methoxy-, 4-ethoxy-, and 4-phenoxy-pyridine 1-oxides over palladium [7] or nickel [8] gave the alkoxy-pyridine (also true in quinoline series [9]), and 4-hydroxy-1-oxides gave 4-pyridone and 4-quinolone.[8,9]



(I)



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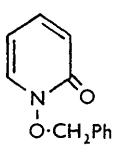

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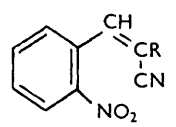

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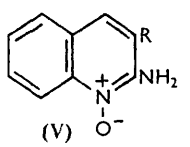

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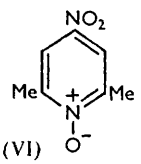
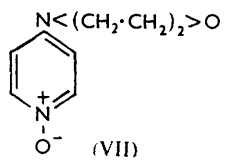


(VI)



(VII)

The nitro-cyanides (IV; R = Ph or CO_2Et) were hydrogenated [10] to aminoquinoline 1-oxides (V), implying resistance of the latter to reduction. 4-Nitro-pyridine and -quinoline

* Part IX, preceding paper.

[1] For general review see Katritzky, *Quart. Rev.*, 1956, **10**, 395.
[2] Ochiai, *J. Org. Chem.*, 1953, **18**, 534.
[3] Shaw, *J. Amer. Chem. Soc.*, 1949, **71**, 67.
[4] Lott and Shaw, *ibid.*, p. 70.
[5] Part V, Gardner and Katritzky, *J.*, 1957, 4375.
[6] Ochiai, Teshigawa, Oda, and Naito, *J. Pharm. Soc. Japan*, 1945, **65**, 5/6*A*, 1; *Chem. Abs.*, 1951, **45**, 8527.
[7] Ochiai and Katada, *J. Pharm. Soc. Japan*, 1943, **63**, 265; *Chem. Abs.*, 1951, **45**, 5152.
[8] Ishii, *J. Pharm. Soc. Japan*, 1951, **71**, 1092; *Chem. Abs.*, 1952, **46**, 5046.
[9] Ishii, *J. Pharm. Soc. Japan*, 1952, **72**, 1317; *Chem. Abs.*, 1953, **47**, **12**, 386.
[10] Bauer, *Ber.*, 1938, **71**, 2226.

No.	Pyridine reduced [a]	Condns.[b]	H_2 (mols.)	Time (hr.)	Pyridine obtained [a]	Yield (%)	How isolated [c] and m. p.	M. p. in lit.	Ref.	Analysis
1	1-O	S	1	1·5	—	84	P 162—163° M	165—166°	*d*	—
2	4-Me, 1-O	S	1	2	4-Me	82	P 165 M	166—167	*e*	—
3	2-Me, 1-O	S	1	6	2-Me	73	P 163—164 M	163	*f*	—
4	4-Ph, 1-O	S	1	40	4-Ph	89	P 194	195—196	*g*	*h*
5	2-Ph, 1-O	S	1	10	2-Ph	87	P 172—174 M	175—176	*g*	—
6	2-CH_2Ph, 1-O	S	1	22	2-CH_2Ph	84	P 139 M	139—140	*j*	—
7	4-NH_2, 1-O	S	1	4	4-NH_2	77	156—158 M	158	*k*	—
8	2-NH_2, 1-O	S	1	70	2-NH_2	85	L 269 [l] M	269—271	*m*	—
9	4-OMe, 1-O	S	1	0·8	4-OMe	92	P 171—172 M	171—172	*n*	—
10	4-CH_2·CH_2·CO·NH_2, 1-O	T	1	6	4-CH_2·CH_2·CO·NH_2	88	163—165 M	165—166	*o*	—
11	4-CO·NH·CH_2Ph, 1-O	T	1	*ca.* 6	4-CO·NH·CH_2Ph	86	89—91 M	90—92	*p*	—
12	4-CO_2Et, 1-O	S	1	2·2	4-CO_2Et	58	P 124—125 M [q]	147	*r*	*s*
13	4-CO_2Et, 1-O	S	4	60	[t]	70	P 172—174	172	*u*	*v*
14	3-CO_2Et, 1-O	S	1	1	3-CO_2Et	60	P 144 M	147·5—148	*w*	—
15	4-OH, 1-O	S	1	3	4-OH	85	P 236 M [x]	238—239	*y*	—
16	4-CH:CH·CO_2Et, 1-O	S	1	2	4-CH_2·CH_2·CO_2Et, 1-O	60 [z]	A 225—226 M	227·5	*p*	—
17	,, ,,	T	2	5·5	4-CH_2·CH_2·CO_2Et	75	A 162—165 M	165—166	*o*	—
18	4-CH:CH·CO_2Et	S	1	2	4-CH_2·CH_2·CO_2Et	88	B. p. 122°/1·4 mm.	133°/9 mm.	*o*	—
19	3-CH:CH·CO_2Et, 1-O	S	1	2	3-CH_2·CH_2·CO_2Et, 1-O	42 [aa]	A 224	—	—	*ab*
20	,, ,,	S	2	4·5	3-CH_2·CH_2·CO_2Et	58	P 78 [q]	103—104	*ac*	*ad*
21	3-CH:CH·CO_2Et	S	1	2	,,	84	{ B. p. 138—140°/5 mm. P 78 M	138—140°/3 mm. 78	*ac* *ae*	— —
22	4-CH:CH·CO·NH_2, 1-O	U	1	1·2	4-CH_2·CH_2·CO·NH_2, 1-O	77	225—227 M	227	*p*	—
23	,, ,,	U	2	6	4-CH_2·CH_2·CO·NH_2	83	162—164 M	166—167	*o*	—
24	3-CH:CH·CO·NH_2, 1-O	U	1	0·4	3-CH_2·CH_2·CO·NH_2, 1-O	77	220—222 M	224	*af*	—
25	,, ,,	U	2	1·3	3-CH_2·CH_2·CO·NH_2	80	116—117 [q] M	136	*ac*	*ah*
26	4-CH:CH·CO_2H, 1-O	V	2	5	4-CH_2·CH_2·CO_2H	15	224—227 M	228—230	*o*	—
27	3-CH:CH·CO_2H, 1-O	V	2	3·5	3-CH_2·CH_2·CO_2H	63	154	157—158	*ai*	*ai*
28	4-CH:CHPh, 1-O	S	1	2	4-CH_2·CH_2Ph, 1-O	90	117	—	—	*aj*
29	,, ,,	S	2	7·5	4-CH_2·CH_2Ph	89	70	70—71	*ag*	*ak*
30	4-CH:CHPh	S	1	3·5	,,	77	69 [a]	70—71	*ag*	—
31	2-CH:CHPh, 1-O	S	1	2	2-CH_2·CH_2Ph, 1-O	45	78—79	—	—	*am*
32	2-CH:CHPh	S	1	4	2-CH_2·CH_2Ph	84	P 125	125—127	*ag*	*an*
33	4-Cl, 1-O	S	1	0·25	1-O	85	L 179—182 M	182—184	*ao*	—
34	,,	S[ap]	2	2	—	16	P 161—163 M	165—166	*d*	—
35	4-Cl	S[ap]	1	0·35	—	76	P 162—164 M	165—166	*d*	—
36	4-O·CH_2Ph, 1-O	S	2	5·5	4-OH	80	P 236—237	238—239	*y*	*aq*
37	4-NO_2, 1-O	S[ar]	4	3	4-NH_2	90	156—158 M	158	*k*	—
38	4-COMe, 1-O	S	1	0·7	4-COMe	29	P 126—128 M	129—130	*as*	—
39	3-COMe, 1-O	S	1	1·1	3-COMe	70	P 130	130	*at*	*au*

1-oxides have given the 4-amino-analogues with [1,11–13] and without [9,13–15] retention of the 1-oxide function. 4-Nitro-2 : 6-lutidine 1-oxide (VI) gave [12] the azo-1 : 1′-dioxide in hydrochloric acid, the amino-1-oxide in water, and the aminolutidine in acetic acid. 4-Morpholinopyridine 1-oxide (VII) was hydrogenated [16] to the corresponding pyridine.

The conditions varied largely in the above work. We reduced some pyridines and 1-oxides under uniform conditions (palladium, room temperature and pressure) to investigate: (i) the reduction of the 1-oxide group in compounds without another easily reducible group; (ii) the order and selectivity of reduction in 1-oxides with such another group; and (iii) the effect of the 1-oxide function on the ease of reduction of other groups. The results are recorded in the Table.

(i) Pyridine 1-oxide is readily hydrogenated to pyridine (No. 1). A variety of 4-substituted pyridine 1-oxides (nos. 2, 4, 7, 9—12, 15) with no reduction-sensitive groups gave the analogous pyridines at rates which bore no obvious relation to the character of the substituent, and, except for phenyl, differed by a factor of less than 10. The results for 3-ethoxycarbonyl- and 3-acetyl-pyridine 1-oxide (nos. 14 and 39) and the differences in the times of uptake of one and two mols. of hydrogen by β-3-pyridylacrylic ester (nos. 19 and 20) and the amide 1-oxide (nos. 24 and 25) indicate similar behaviour in the 3-series. 2-Substituted pyridine 1-oxides (nos. 3, 5, 6, 8), except the phenyl compound, are

[11] Berson and Cohen, *J. Org. Chem.*, 1955, **20**, 1461; Kato, Hamaguchi, and Oiwa, *Pharm. Bull. Japan*), 1956, **4**, 178.
[12] Kato and Hamaguchi, *Pharm. Bull.* (*Japan*), 1956, **4**, 174.
[13] Naito, *J. Pharm. Soc. Japan*, 1945, **65**, 3; *Chem. Abs.*, 1951, **45**, 8528.
[14] Ishii, *J. Pharm. Soc. Japan*, 1952, **72**, 1315; *Chem. Abs.*, 1953, **47**, 12, 386.
[15] Ishii, *J. Pharm. Soc. Japan*, 1952, **72**, 665.
[16] Ochiai, Itai, and Yoshino, *Proc. Imp. Acad.* (*Tokyo*), 1944, **20**, 141; *Chem. Abs.*, 1954, **48**, 12,100.

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a, Substituents are given. *b*, " S " indicates the standard conditions (cf. text). " T " indicates that 0·25 g. of the oxide in 15 c.c. of ethanol with 0·08 g. of Pd–C (5%) was used, but with conditions otherwise as above. " U " indicates that 0·41 g. of the oxide, 10 c.c. of ethanol, 4 c.c. of water, and 0·1 g. of catalyst were used. " V " indicates that the acid (0·5 g.) in 0·14N-aqueous sodium hydroxide (20 c.c.) was shaken over the catalyst (0·1 g.); after filtration and concentration addition of acetic acid gave the product. *c*, " P ", " L ", and " A " indicate that the reduction product was isolated respectively as picrate, picrolonate, or amide. " M " indicates that a mixed m. p. with an authentic specimen was not depressed. *d*, Brandes and Stoehr, *J. prakt. Chem.*, 1896, **54**, 488. *e*, Clemo and Gourlay, *J.*, 1938, 478. *f*, Hess and Grau, *Annalen*, 1925, **441**, 101. *g*, Haworth, Heilbron, and Hey, *J.*, 1940, 349. *h*, Found: C, 53·0; H, 3·1. Calc. for $C_{17}H_{12}O_7N_4$: C, 53·1; H, 3·1%. *j*, La Forge, *J. Amer. Chem. Soc.*, 1928, **50**, 2484. *k*, den Hertog and Overhoff, *Rec. Trav. chim.*, 1950, **69**, 468. *l*, With decomp. *m*, Wagstaff, *J.*, 1934, 276. *n*, Chiang and Hartnung, *J. Org. Chem.*, 1945, **10**, 21. *o*, Katritzky, *J.*, 1955, 2581. *p*, Katritzky and Monro, *J.*, in the press. *q*, Apparently a new polymorph. *r*, Clemo and Hogarth, *J.*, 1941, 41. *s*, Authentic ethyl *iso*nicotinate picrate separated from ethanol as a new *polymorph*, needles, m. p. 124—125° (Found: C, 44·2; H, 3·3; N, 15·0. $C_{14}H_{12}O_9N_4$ requires C, 44·2; H, 3·2; N, 14·7%). *t*, 4-Ethoxycarbonylpiperidine. *u*, Clemo and Metcalfe, *J.*, 1937, 1523. *v*, Found: C, 44·0; H, 4·8. Calc. for $C_{14}H_{18}O_9N_4$: C, 43·5; H, 4·7%. *w*, Badgett, Provost, Ogg, and Woodward, *J. Amer. Chem. Soc.*, 1945, **67**, 1135. *x*, Mixed m. p. with end-product of no. 36. *y*, den Hertog, Broekmann, and Combé, *Rec. Trav. chim.*, 1951, **70**, 105. *z*, 10% of starting material also recovered. *aa*, 3% of starting material also recovered. *ab*, *β-3-Pyridylpropionamide 1-oxide* formed rods from ethanol (Found: C, 57·9; H, 6·1. $C_8H_{10}O_2N_2$ requires C, 57·8; H, 6·1%). *ac*, Graef, Fredericksen, and Burger, *J. Org. Chem.*, 1946, **11**, 257. *ad*, Authentic ethyl β-3-pyridylpropionate picrate separated from ethanol as a new *polymorph*, prisms (Found: C, 47·6; H, 3·8. $C_{16}H_{16}O_9N_4$ requires C, 47·1; H, 3·9%). *ae*, No. 20. *af*, No. 19. *ag*, Bergstrom, Norton, and Siebert, *J. Org. Chem.*, 1945, **10**, 452. *ah*, Authentic specimen prepared by treating ethyl β-3-pyridylpropionate with aqueous-methanolic ammonia, to give β-3-pyridylpropionamide as a new *polymorph*, plates (from ethanol), m. p. 117° (Found: C, 64·2; H, 6·7. $C_8H_{10}ON_2$ requires C, 64·0; H, 6·7%). *ai*, Livshits *et al.*, *J. Gen. Chem.* (*U.S.S.R.*), 1951, **21**, 1360; *Chem. Abs.*, 1952, **46**, 5051 (Found: C, 63·6; H, 6·2; N, 9·2. Calc. for $C_8H_9O_2N$: C, 63·6; H, 6·0; N, 9·3%). *aj*, *4-Phenethylpyridine 1-oxide*, prisms from ethyl acetate (Found: C, 78·7; H, 7·1. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·6%). *ak*, Found: C, 85·1; H, 7·1. Calc. for $C_{13}H_{13}N$: C, 85·2; H, 7·1%. *al*, Mixed m. p. with end-product of no. 29 not depressed. *am*, *2-Phenethylpyridine 1-oxide*, prisms from light petroleum (b. p. 40—60°) (Found: C, 78·7; H, 6·8. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·6%). *an*, Found: C, 55·5; H, 3·7. Calc. for $C_{19}H_{16}O_7N_4$: C, 55·3; H, 3·9%. *ao*, Katritzky, *J.*, 1956, 2404. *ap*, Treated with potassium carbonate in chloroform to remove hydrogen chloride. *aq*, Found: C, 41·3; H, 2·6; N, 16·9. Calc. for $C_{11}H_8O_8N_4$: C, 40·8; H, 2·5; N, 17·3%. *ar*, Fine suspension of substrate used. *as*, Pinner, *Ber.*, 1901, **34**, 4250. *at*, Frankenburg, Gottscho, Mayaud, and Tso, *J. Amer. Chem. Soc.*, 1952, **74**, 4309. *au*, Found: C, 44·6; H, 3·1. Calc. for $C_{13}H_{10}O_8N_4$: C, 44·6; H, 2·9%.

reduced more slowly than the corresponding 4-substituted compound, presumably because of steric hindrance. The ring was hydrogenated much more slowly (cf. no. 13).

(ii) The hydrogenation of compounds with a conjugated carbon–carbon double bond was next investigated. The 1-oxides of β-3- and -4-pyridylacrylic esters, amides, and acids and 4-styrylpyridine 1-oxide each absorbed two mols. of hydrogen at comparable rates, giving the corresponding saturated pyridine (nos. 17, 20, 23, 25—27, 29). Interruption after absorption of one mol. gave good yields of 4-phenethylpyridine 1-oxide (no. 28) and the pyridylpropionic amide 1-oxides (nos. 22, 24), and fair yields of the ester 1-oxides (nos. 16, 19); only mixtures were obtained from the acids. In 2-styrylpyridine 1-oxide (no. 31) the second molecule was absorbed only very slowly (incomplete after 3 days).

4-Chloropyridine 1-oxide absorbed 1 mol. of hydrogen, to give pyridine 1-oxide (nos. 33, 34), but both 3- and 4-acetylpyridine 1-oxide lost the oxide function before attack on the ketone group occurred (nos. 38, 39). It is of interest that 4-chloropyridine 1-oxide with iron–acetic acid gives 4-chloropyridine.[17] Previous work in this laboratory [5] has supported statements in the literature (above) that 4-nitro- and 4-benzyloxy-pyridine 1-oxide can be hydrogenated to 4-amino- and 4-hydroxypyridine 1-oxide. We now show that further reduction to the corresponding pyridines occurs readily (nos. 36 and 37).

(iii) 2- and 4-Styrylpyridine, β-3- and β-4-pyridylacrylic ester, and 4-chloropyridine were hydrogenated under the same conditions as their 1-oxides (nos. 18, 21, 30, 32, 35). The functional group was reduced at the same rate as, or a little slower than, in the 1-oxides.

The structures assigned to the reduction products are supported by infrared and ultraviolet spectra.

Experimental.—Hydrogenations under standard conditions. The substrate (0·01 mole) in ethanol (20 c.c.) over 5% palladium–charcoal (0·3 g.) was shaken under hydrogen at room temperature and pressure. After absorption of the required amount of hydrogen, or after absorption had ceased, catalyst was filtered off and washed with ethanol, and the filtrate and washings were evaporated, or the product, if volatile, was converted directly into a derivative.

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[17] den Hertog and Combé, *Rec. Trav. Chim.*, 1951, **70**, 581.