Preparation of Benzimidazole *N*-Oxides by Catalytic Hydrogenation

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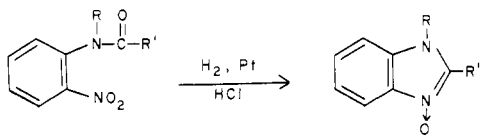
Several 1-substituted-benzimidazole-3-oxides have been prepared by acid-catalyzed hydrogenation of o-nitroanilides.

THE PREPARATION of 2-methyl-1-phenylbenzimidazole-3-oxide (II*a*) by the catalytic hydrogenation of either 2′-nitro-*N*-phenylacetanilide (I*a*) or 2-chloro-2′-nitro-*N*-phenylacetanilide (I*f*) has been reported recently (*7*). The reaction has been extended to several related amides and acid-catalyzed reduction has been found to provide a general method for the synthesis of 1-substituted benzimidazole-3-oxides (Table I).



I II

a. R=C_6H_5, R′=CH_3
b. R=R′=CH_3
c. R=CH_3, R′=C_6H_5
d. R=R′=C_6H_5
e. R=CH_3, R′=H
f. R=C_6H_5, R′=CH_2Cl
g. R=C_6H_5, R′=$CHCl_2$
h. R=CH_3, R′=CH_2Cl

Although hydrogenation in neutral medium generally furnished the *o*-aminoanilide, *N*-methyl-*o*-nitroformanilide (I*e*) was an exception, the *N*-oxide being the major product. This was converted by ethanolic HCl into the hydrochloride, identical with the product from the acid-catalyzed reduction of I*e*. Refluxing the base in acetone effected rearrangement of II*e* to 1-methylbenzimidazol-2-one (*12*). The ultraviolet spectrum of II*e* corresponded closely to the published spectrum of the dihydrate (*10*).

Attempts to extend the acid-catalyzed reaction to synthesis of *N*-oxides unsubstituted at the 1-position failed, neither I, R=H, R′=CH_3, nor I, R=R′=H, giving the desired product. Hydrogenation of I, R=R′=H, under neutral conditions in ethanol did give a small amount of benzimidazole-3-oxide (II, R=R′=H), but the major product was 2′-aminoformanilide. When the reduction was carried out in the less polar solvent ethyl acetate, cyclization was suppressed and 2′-aminoformanilide resulted in high yield, its structure being confirmed by thermal conversion to benzimidazole.

EXPERIMENTAL

Nitroanilides I. *N*-Methyl-2′-nitroacetanilide I*b* (*6*) was prepared in 92% yield from *N*-methyl-*o*-nitroaniline and excess acetyl chloride in refluxing benzene. I*c* (*4, 9*), I*e* (*10*), and I*h* (*2*) were prepared according to the literature. 2′-Nitro-*N*-phenylbenzanilide I*d* was prepared by a modification of the literature method (*1*). The Chapman rearrangement (*8*) of 13 grams of *o*-nitrophenyl-*N*-phenylbenzimidate (*13*) (prepared in 73% yield from *N*-phenylbenzimidoyl chloride, *o*-nitrophenol, and sodium methoxide) was carried out in 13 ml. of refluxing *o*-dichlorobenzene for one hour. Dilution with ethanol and recrystallization of the resulting solid from ethanol (charcoal) gave 11.2 grams (86%) of yellow I*d*.

2,2-Dichloro-2′-nitro-*N*-phenylacetanilide Ig. A solution of 21.4 grams (0.1 mole) of *o*-nitrodiphenylamine and 29.5 grams (0.2 mole) of dichloroacetyl chloride in 30 ml. of toluene was refluxed for 24 hours. Addition of ethanol and cooling gave 22.8 grams of very dark solid, m.p. 143–145° C. Three recrystallizations from absolute ethanol, one with charcoal, afforded 10.5 grams (32%) of tan solid, m.p. 151.5–153° C.

Anal. Calcd. for $C_{14}H_{10}Cl_2N_2O_3$: C, 51.71; H, 3.10; N, 8.61. Found: C, 51.80; H, 3.25; N, 8.79.

Benzimidazole-3-oxides II. To 0.02 mole of anilide I in absolute ethanol was added 100 mg. of platinum oxide and 0.022 mole of ethanolic HCl. The mixture, total volume 100 ml., was shaken under hydrogen on a Parr hydrogenator at up to 50 p.s.i. for about 30 minutes, approximately 0.05 mole of hydrogen being absorbed. Removal of catalyst

Table I.

Compound Reduced	Product	Recrystallization Solvent	Recrystallization Yield, %	Corrected M.P., °C.	Analytical Data, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
I*b*	II*b*·HCl	2-propanol–ether	62	196–202	54.40	5.58	14.10	54.05	5.91	13.93
	II*b*, base[a]	ethyl acetate		162–174 dec.	66.64	6.21		66.52	6.57	
I*h*	II*b*·HCl		43	190–197						
I*c*	II*c*·HCl[b]	ethanol	77	235–240 dec.	64.49	5.03	10.74	64.17	5.15	10.48
I*d*	II*d*·HCl	2-propanol	76	233–238 dec.	70.69	4.68	8.68	70.76	4.76	8.72
	II*d*, base	ethyl acetate		192–195 dec.	79.71	4.93	9.79	79.98	5.38	9.79
I*e*	II*e*·HCl	2-propanol	58	209–214	52.05	4.91	15.18	52.19	4.60	15.05
I*e*[c]	II*e*·H_2O[d,e]	ethyl acetate	59	85.5–88	57.81	6.06	16.86	56.80	6.72	16.33
I*g*	II*a*·HCl[f]	acetone-ether	57	201–205						

[a] References (*10, 11*); the initially obtained base, m.p. 116–120° C., apparently a monohydrate, was dried at 75° C. in vacuo. [b] Reference (*9*). [c] HCl was not used in this run. [d] Satisfactory analyses were not obtained, but the data, including an analysis of water content, corresponded best to the monohydrate. [e] References (*10, 12*). [f] Reference (*7*).

and solvent followed by recrystallization gave the hydrochloride (Table I). Treatment of the hydrochloride with aqueous sodium hydroxide followed by extraction with chloroform (salted out with aqueous potassium carbonate) gave the free base which was dried either by heating in vacuo or azeotroping with chloroform. The amides I which contained chlorine were hydrogenated without added HCl since this was formed by hydrogenolysis. Hydrogenation of I*e* without added HCl gave material which furnished the hydrochloride of II*e* upon addition of ethanolic HCl or the hydrated base of II*e* upon recrystallization. The other amides I*a*-I*d*, when hydrogenated under neutral conditions, gave the *o*-aminoanilides which, when treated with ethanolic HCl in acetone, gave high yields of substituted benzimidazole hydrochlorides.

2′-Aminoformanilide. A mixture of 5.0 grams (0.03 mole) of 2′-nitroformanilide (*3*, *5*), 100 mg. of platinum oxide, and 150 ml. of ethyl acetate was shaken under hydrogen until about 0.095 mole had been absorbed. Removal of catalyst and solvent left a yellow solid which was recrystallized from ethyl acetate to yield 3.5 grams (85%) of white solid, m.p. 105–109° C. Recrystallization from benzene with minimal heating raised the m.p. to 107–110° C. When the product was refluxed in xylene for 6 hours, crude benzimidazole, m.p. and mixture m.p. 151–160° C., was obtained in 93% yield.

Anal. Calcd. for $C_7H_8N_2O$: C, 61.77; H, 5.92; N, 20.58. Found: C, 61.96; H, 5.88; N, 20.70.

Benzimidazole-3-oxide (1-Hydroxybenzimidazole). When the above hydrogenation was carried out in absolute ethanol, crystallization of the crude product from ethyl acetate gave 0.61 gram (15%) of *N*-oxide, m.p. 199–205° C., literature m.p. 210° C. (*5*); hydrochloride m.p. 199.5–207° C., literature m.p. 200–214° C. dec. (*5*). Ultraviolet spectra of both the base and the hydrochloride were compatible with the published curves (*10*). Impure 2′-aminoformanilide (2.64 grams), contaminated with considerable benzimidazole, was obtained from the mother liquors.

ACKNOWLEDGMENT

Analytical results were determined by K. D. Fleischer and staff. Spectral comparisons were made under the direction of R. K. Kullnig.

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RECEIVED for review February 1, 1968. Accepted April 23, 1968.

Characterization of the Diastereomers of 2,4-Dimethyl-3-oxapentane-1,5-diol

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The diastereomeric forms of the 2,4-dimethyl-3-oxapentane-1,5-diol diprimary dipropylene glycol have been synthesized by two routes: reduction of the diethyl dilactate ester with lithium aluminum hydride; and replacement of chlorine by an acetoxy group on 1,5-dichloro-2,4-dimethyl-3-oxapentane. The diprimary glycol is then obtained by an ester interchange with methanol and diacetate ester. The glycol diastereomeric forms are readily purified by distillation and/or preparative gas chromatography.

PREPARATION of the three isomers of dipropylene glycol was reported by Sexton and Britton, but their consideration did not extend to the diastereomeric forms of the glycols (*5*).

Later Summerbell, Jerina, and Grula reported the diastereomers of 4-oxaheptane-2,6-diol (I) (di-*sec*- dipropylene glycol) in connection with their studies of the conversion of glycols to dioxenes (*6*).

At this time, the authors report the preparation and characterization of the 2,4-dimethyl-3-oxapentane-1,5-diol (IV) (diprimary dipropylene glycol) diastereomeric forms.

In connection with the study of lactic acid metabolism, Vieles and coworkers (*7*) prepared a large number of derivatives of dilactic acid and determined their configurations relative to lactic acid. The authors also found in the case of diethyl dilactate (II), prepared from the sodium salt of ethyl lactate and ethyl α-bromopropionate, that the ratio of *dl* pairs to the meso form was 5 to 1 (*7*). The dilactate esters were separated by careful fractional distillation to obtain the lower boiling *dl* isomers. The meso ester remained in the residue and was further purified by preparative gas chromatography. To distinguish between the esters of the meso and *dl* forms, the diamides (III) were prepared by heating the appropriate diastereomeric ester with ammonia in a sealed tube and the melting points compared with those given by Vieles (*7*).

On reduction of both the *dl* and meso diethyl lactates (II) to the glycols (IV) with lithium aluminum hydride and dry diethyl ether, no apparent epimerization occurs. The course of this reduction was verified by gas chromatography using a Carbowax 20M column, which can be used to separate the esters or glycols easily. The bis-*p*-nitrobenzoate derivatives (Va) of the glycols were prepared by heating *p*-nitrobenzoyl chloride with either the meso or *dl* forms of IV (*2*).

Apparently, the melting points of the bis-*p*-nitrobenzoates