Reduction of 4-Benzoyl-2-piperazinone with Sodium Borohydride in Triethylamine

Kuniyoshi MASUZAWA, Morimichi KITAGAWA and Hiroaki UCHIDA

Kyorin Chemical Laboratory, Ukima, Kita-ku, Tokyo

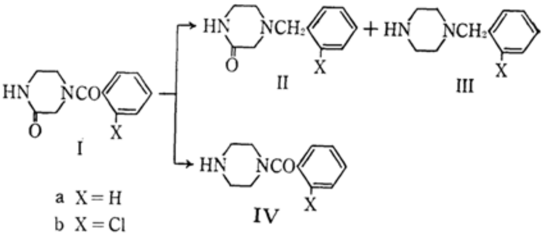
(Received November 15, 1966)

It has been shown that tertiary amides can be reduced to the corresponding tertiary amines with sodium borohydride in refluxing pyridine,[1] while the treatment of secondary amides with sodium borohydride affords only a complex containing boron, the expected reduction doesn't occur.[2]

Contrary to these reports, however, we have now succeeded in the reduction of cyclic secondary amides. We wish to report about the reduction of 4-benzoyl-2-piperazinone (Ia) with sodium borohydride.

When Ia was reduced with sodium borohydride in pyridine using the technique of Yamada[1] for tertiary amides, 1-benzylpiperazine (IIIa) was obtained, together with the expected 4-benzyl-2-piperazinone (IIa). The formation of the former product (IIIa) was based on an unexpected reaction in which the reduction of the secondary amide was included.

Since it is known that the reduction ability of sodium borohydride has a better potential in pyridine than in methanol, this reduction was then carried out in triethylamine (pK_b 3.25) in place of pyridine (pK_b 8.85); this yielded 1-benzoylpiperazine (IVa) in a 54.1% yield, and 32.2% of the starting material was recovered.



The reduction of 4-(2-chlorobenzoyl)-2-piperazinone (Ib) by a similar technique was then carried out in pyridine and in triethylamine. The experimental results, as well as characteristic infrared spectral data, are summarized in Table 1.

It is of deep interest that only the secondary amide group in Ia or Ib was selectively reduced in refluxing triethylamine, while in refluxing pyridine the reduction occurred mainly on the tertiary amide group.

TABLE 1.

Starting material	Solvent, reaction time, hr	Product	Yield %	Constants °C	IR[a] cm⁻¹	Derivative
Ia	Pyridine, 20	IIa	43.3	155—156[4]	1665	—
		IIIa	27.9	120/2 mmHg	—	Picrate mp 271—273
Ia	Triethylamine, 20	IVa	54.1	64—65	1620	Dibenzoylpiperazine mp 190—192[3]
Ib	Pyridine, 20	IIb	22.5	95—97[b]	1665	—
		IIIb	16.0	—	—	Picrate[c] mp 250—251
Ib	Triethylamine, 20	IVb	36.8	—	1620	Dichlorobenzoyl[d] piperazine mp 214—216

a) Found: C, 58.59; H, 6.10; N, 12.39%. Calcd: C, 58.80; H, 5.83; N, 12.47%.
b) Found: C, 41.46; H, 3.33; N, 16.24%. Calcd: C, 41.29; H, 3.16; N, 16.75%.
c) Found: C, 59.35; H, 4.51; N, 7.27%. Calcd: C, 59.51; H, 4.44; N, 7.71%.

---

1) S. Yamada, Y. Kikugawa and S. Ikegami, *Chem. Pharm. Bull.*, **13**, 394 (1965).
In this paper, it is reported that primary amide can be converted to the corresponding nitrile with sodium borohydride in refluxing pyridine.

2) Y. Ogata, "The Oxidation and Reduction in Organic Compounds," Nankodo, Tokyo, (1963), p. 862.

3) A. W. Hofmann, *Ber.*, **23**, 3301 (1890).

4) H. S. Mosher, J. Cornell, Jr., O. L. Stafford and T. Roe, Jr., *J. Am. Chem. Soc.*, **75**, 4949 (1953).