stable form and their rotatory dispersion curves show negative Cotton effects. The 17α-H-20-keto compounds, the less stable form, show positive Cotton effects. The ratios of these two epimers were calculated from the optical rotatory dispersion curves and varied with the influence of neighboring groups.

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100. Seiji Miyano, Nobuhiro Abe, and Akiko Uno : Reductive Benzylation of Aromatic Nitro Compounds by Means of Benzyl Alcohol.

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It has been known for a long time that nitrobenzene was reduced to azoxybenzene with methanol or ethanol in the presence of caustic alkali.[*2,1,2] Although the same reduction was also effected[3,4] by benzyl alcohol and potassium hydroxide at an elevated temperature,[*3] no work to achieve further reduction leading to amines by means of benzyl alcoholic potassium hydroxide has appeared so far.

More recently Sprinzak[*4,5] reported that a number of aromatic primary amines can be benzylated readily with benzyl alcohol in the presence of potassium hydroxide to give N-benzylanilines at a temperature between 250~280°.[*5]

The Sprinzak's report prompted us to reinvestigate the reduction of aromatic nitro compounds by means of benzyl alcoholic potassium hydroxide with the expectation that successful reduction to amines might be followed by Sprinzak's benzylation to yield N-benzylamines (I) as final products. Thus an attempt to combine (1) reduction of nitrobenzene and (2) benzylation of the resulting aniline into a single operation was made. (Chart 1).

$$C_6H_5NO_2 \xrightarrow[(1)]{C_6H_5CH_2OH\text{-}KOH} [C_6H_5NH_2] \xrightarrow[(2)]{C_6H_5CH_2OH\text{-}KOH} \underset{\text{I}}{C_6H_5NHCH_2C_6H_5}$$

Chart 1.

In this investigation modified conditions, *e. g.* use of large excess of the reagent, removal of water as it was formed and higher reaction temperature[*6] (225~260°)

*1 Nanakuma, Fukuoka (宮野成二, 安倍宣博, 宇野昭子).

*2 Isopropyl alcohol is capable of reducing nitrobenzene to aniline in the presence of sodium hydroxide : R. Lyons, M. Pleasant : Ber., **62B**, 1723 (1929).

*3 The reduction was carried out in boiling xylene.

*4 An earlier paper also revealed that U. O. P. nickel catalyst was capable of N-benzylation : E. F. Pratt, E. J. Frazza : J. Am. Chem. Soc., **76**, 6174 (1954).

*5 At this temperature range it is to be considered that potassium hydroxide would be converted to potassium benzylate. See ref. 5.

*6 The previously reported reductions of nitrobenzene by the reagent were run at much lower temperatures. See ref. 1~4.

1) Houben-Weyl : "Die Methoden der Organische Chemie," 3 Aufl., Band 2, 342 (1922).
2) W. Schraube : Ber., **8**, 619 (1875).
3) H. Fry, J. Cameron : J. Am. Chem. Soc., **49**, 864 (1928).
4) K. Ino, R. Oda : J. Soc. Chem. Ind. Japan, **46**, 1182 (1943); C. A., **42**, 6334 (1948).
5) Y. Sprinzak : J. Am. Chem. Soc., **78**, 3207 (1956); Org. Syntheses, Coll. Vol., **IV**, 92 (1958).

were employed. The reductive benzylation occurred as expected and various nitro compounds were converted in one step to the corresponding N-benzylamines. (TABLE I).

TABLE I. Reductive Benzylation of Aromatic Nitro Compounds[a)]

Nitro Compounds	(g.)	Benzyl Alcohol (g.)	KOH (g.)	Final temp. (°C)[b)]	Product	Yield (g.)	Yield (%)
Nitrobenzene	12.3	75	28	240	N-benzylaniline	6.0	32.8
o-Nitrotoluene	13.7	90	28	250	N-benzyl-*o*-toluidine	10.2	51.3
m-Nitrotoluene	13.7	75	28	235	N-benzyl-*m*-toluidine	5.5	27.9
p-Nitrotoluene	13.7	75	28	260	N-benzyl-*p*-toluidine	6.4	32.5
p-Chloronitrobenzene	15.6	80	28	250	N-benzylaniline	6.8	31.3
2-Nitropyridine	12.4	75	28	230	2-benzylaminopyridine	6.5	35.3
4-Nitropyridine-1-oxide	14.0	80	28	225	4-benzylaminopyridine	2.0	10.9

a) In all instances reaction time was limited to 2 hr.
b) Bath temperatures at which the reaction was stopped.

TABLE II. N-Benzylanilines

Compounds	m.p. (°C)	b.p. (°C)	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
N-Benzylaniline	37 ~ 38.5	175~177/15	85.20	7.15	7.64	85.25	6.97	7.69
N-Benzyl-*o*-toluidine	59.5~ 61	155~162/7	85.23	7.66	7.10	85.21	7.59	7.28
N-Benzyl-*m*-toluidine·HCl	193 ~195	150~157/6[a)]	71.93	6.90	5.99	72.06	6.84	6.18
N-Benzyl-*p*-toluidine·HCl	173 ~174	154~157/5[a)]	71.93	6.90	5.99	71.85	6.83	6.14
2-Benzylaminopyridine	95 ~ 96	155~163/7	78.23	6.57	15.21	78.67	6.50	15.29
4-Benzylaminopyridine	109.5~110	188~190/5	78.23	6.57	15.21	78.51	6.62	15.17

a) Boiling points of free bases.

When the reaction was carried out at 200~210° an intermediary aniline was isolated in 21.5% yield and this observation indicates that under these conditions nitrobenzene was reduced to aniline which was then benzylated in a manner described by Sprinzak[5)] to yield N-benzylaniline. (Chart 1).

Although as high as 51% yield was observed in N-benzyl-*o*-toluidine, yields are generally lower (I) and this might be due to the side reactions (Chart 2 and 3) leading to the formation of benzylaminodiphenylamines or pyridones as by-products. Actually

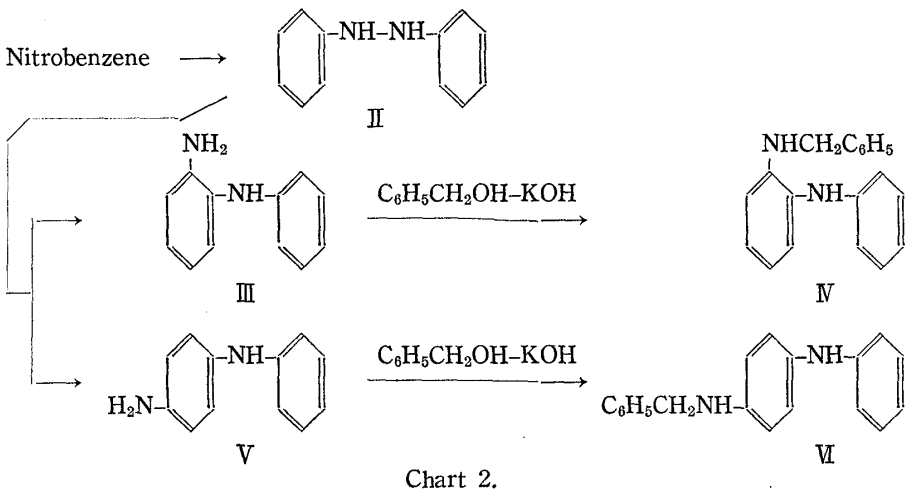

Chart 2.

reductive benzylation of nitrobenzene gave *o*- and *p*-benzylaminodiphenylamines, (Ⅳ) and (Ⅵ), in 10.3 and 6.2% yield, respectively, together with the main product (Ⅰ). The formation of Ⅳ and Ⅵ is considered to be the result of the following sequence of transformations (Chart 2).

Thermal rearrangement of hydrazobenzene (Ⅱ), a possible intermediate in reduction of nitrobenzene, to *o*- and *p*-semidines, (Ⅲ) and (Ⅴ), was reported recently by Večeřa, *et al*[6], Krolik and Lukashevich[7], and Hashimoto, *et al*[8]. The subsequent steps, N-benzylations of Ⅲ and Ⅴ, were supported by our experiments in which Ⅳ and Ⅵ were readily obtained from Ⅲ and Ⅴ under the procedure conditions.

In reductive benzylation of *p*-chloronitrobenzene N-benzylaniline was yielded instead of expected *p*-chloro-N-benzylaniline, the chlorine atom attached to benzene nucleus being reduced.

When 4-nitropyridine 1-oxide (Ⅶ) was subjected to reductive benzylation 4-benzylaminopyridine (Ⅸ) and 4-pyridone (Ⅹ) were obtained in 10.9 and 26.5% yield, respectively.

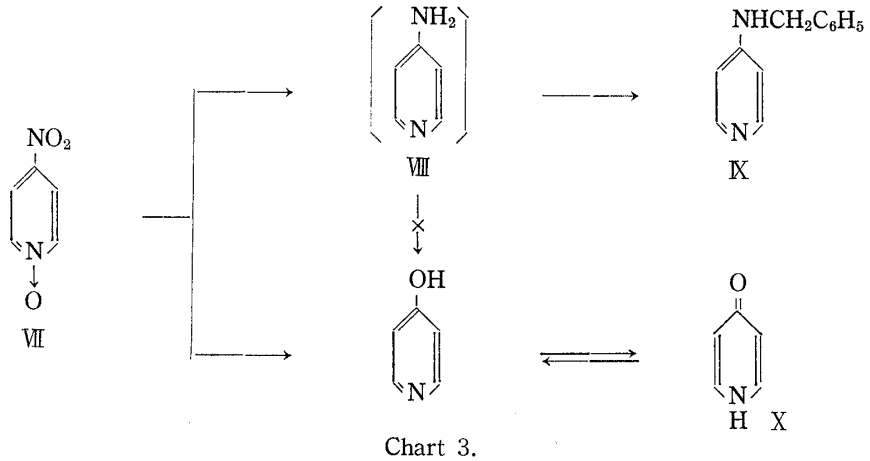

Chart 3.

The formation of these products (Ⅸ and Ⅹ) can be explained by considering two reaction paths (Chart 3), one involving reduction and deoxygenation of Ⅶ to 4-aminopyridine (Ⅷ) and subsequent N-benzylation of Ⅷ to Ⅸ and the other involving deoxygenation and hydrolysis of Ⅶ leading to Ⅹ. The ease with which deoxygenation of N-oxides occurred under the procedure condition is apparent from the report by one of the authors,*7 whereas hydrolysis of 4-nitro group in pyridine to hydroxyl group was previously reported by Katada.[9] Hydrolysis of Ⅷ to Ⅹ is not likely because the reaction between Ⅷ and benzyl alcohol in the presence of potassium hydroxide gave Ⅸ as a sole product.

Reductive benzylation of 2-nitropyridine also afforded a mixture of 2-benzylaminopyridine and 2-pyridone.

Experimental*8

General Procedure of Reductive Benzylation——Preparation of N-benzyl-*o*-toluidine is illustrated as follows :

*7 Pyridine and quinoline 1-oxides can be deoxygenated by means of benzyl alcoholic potassium hydroxide at 160~170°(bath temperature) : S. Miyano : This Bulletin, **14**, 663 (1966).

*8 Melting point, boiling point, and analyses of the products are shown in Table Ⅱ.

6) M. Večeřa, J. Gasparič, J. Petránek : Chem. & Ind. (London), **1961**, 299.
7) L. G. Krolik, V. O. Lukashevich : Doklady Akad. Nauk. S. S. S. R., **139**, 110 (1961); C. A., **56**, 1371 (1961).
8) S. Hashimoto, I. Shinkai, J. Sunamoto : Abstract of papers presented at the Kyushu District Joint Meeting of Chemical Society of Japan and allied societies, July 17, 1965, Fukuoka.
9) M. Katada : Yakugaku Zasshi, **67**, 59 (1947); C. A., **45**, 9537 (1951). Also see E. Klinsberg : "Heterocyclic Compounds, Pyridine and Its Derivatives" Part 3,583, Interscience Publishers (1962).

N-Benzyl-*o*-toluidine——A solution of *o*-nitrotoluene (13.7 g., 0.1 mole) in benzyl alcohol (15 g., 0.14 mole) was added dropwise under stirring into a solution*9 of KOH (28 g., 0.5 mole) in benzyl alcohol (75 g., 0.55 mole) at 170°. Vigorous reaction ensued with separation of H_2O which was removed by distillation as it formed. After the reaction subsided the mixture was stirred and refluxed at 250° for 1.5 hr. H_2O was added to dissolve precipitated potassium benzoate,*10 the resulting solution extracted with ether, and the ether layer dried over anhydrous K_2CO_3. Removal of ether and vacuum distillation of the residue gave 10.2 g., (51.3%) of N-benzyl-*o*-toluidine which boiled at 155~162°/7 mm., reported[10] 176°/10 mm., m.p. 59.5~61° (from EtOH), reported[10] 56°(from EtOH), 60°(from ether).

Reductive Benzylation of Nitrobenzene——Nitrobenzene (12.3 g., 0.1 mole) was heated with a mixture of KOH (28 g., 0.5 mole) and benzyl alcohol (60 g., 0.55 mole) at 250° for 1.5 hr. according to the general procedure. The reaction mixture was worked up as in N-benzyl-*o*-toluidine to give N-benzylaniline (I) (6.0 g., 32.8%), b.p. 175~177°/15 mm. It solidified to colorless needles, m.p. 37.5~38°(from EtOH-H_2O), reported[11] 36°.

Ether was added to the syrupy residue, the separated *o*-benzylaminodiphenylamine (Ⅳ) filtered, and the filtrate was submitted to chromatography over Al_2O_3. The eluate gave Ⅳ (yield combined with the first crop, 2.8 g., 10.3%) and *p*-benzylaminodiphenylamine (Ⅵ) (1.8 g., 6.2%). Ⅳ was recrystallized from EtOH, m.p. 109.5~110°, reported[12] 108~109.5°. IR ν_{max}^{KBr} cm^{-1} 3401, 3367 (secondary amino group). *Anal.* Calcd. for $C_{19}H_{18}N_2$: C, 83.17; H, 6.61; N, 10.21. Found: C, 83.52; H, 6.20; N, 10.05.

The compound (Ⅵ) was recrystallized from EtOH, m.p. 73~74.5°, reported[13] 74~75° (from EtOH). Ⅵ was also identified as its hydrochloride, m.p. 178~179° (decomp.) (from EtOH-ether). *Anal.* Calcd. for $C_{19}H_{19}N_2Cl$: C, 73.42; H, 6.16; N, 9.01. Found: C, 73.31; H, 6.19; N, 9.38.

The reaction was conducted in the same scale at lower temperature (200~210°) for 1.5 hr. and worked up as before. The fore-run boiling under 113°/33 mm. was shaken with 10% HCl, the aqueous layer neutralized with K_2CO_3, extracted with ether. Removal of ether and distillation of the residue gave 2.0 g. of aniline (21.5%), b.p. 113~117°/60 mm. Hydrochloride showed no depression of melting point with authentic sample. Distillation of the higher boiling fraction gave 1.6 g. (8.7%) of N-benzylaniline (I), m.p. 37~38°(from EtOH-H_2O).

Reductive Benzylation of *o*-Aminodiphenylamine——*o*-Aminodiphenylamine (Ⅲ) (2.1 g., 0.0114 mole) was treated with a mixture of KOH (0.2 g., 0.0036 mole) and benzyl alcohol (1.4 g., 0.013 mole) in a similar manner as described above. After heating for 40 minutes at 220~245° the resulting mixture was triturated with H_2O, extracted with $CHCl_3$, the $CHCl_3$ layer dried over anhydrous K_2CO_3, and the solvent removed. The residue was recrystallized from EtOH to give 2.1 g. (67.3%) of Ⅳ, m.p. 108~110°. This was shown to be identical with the Ⅳ formed in reductive benzylation of nitrobenzene by melting point of a mixture, comparison of their infrared spectra.

Reductive Benzylation of *p*-Aminodiphenylamine——A mixture of *p*-aminodiphenylamine (Ⅴ) (4.6 g., 0.025 mole), KOH (0.45 g., 0.008 mole), and benzyl alcohol (3.0 g., 0.028 mole) was heated at 220~240° for 2 hr. The reaction mixture was extracted with ether, the ether layer dried over anhydrous K_2CO_3 and the solvent removed. The residual crystals were recrystallized from EtOH to give 5.0 g. (72.5%) of *p*-benzylaminodiphenylamine (Ⅵ), m.p. 73~74°. No depression of melting point was observed on admixture with authentic sample which was obtained in reductive benzylation of nitrobenzene.

Reductive Benzylation of 4-Nitropyridine 1-Oxide——To a solution of KOH (28 g., 0.5 mole) in benzyl alcohol (60 g., 0.55 mole) was added dropwise a solution of 4-nitropyridine 1-oxide (14 g., 0.1 mole) in benzyl alcohol (25 g., 0.23 mole) at 170°. After the addition was complete the mixture was stirred for 1.5 hr. at 200~225°. H_2O was added to dissolve potassium benzoate, the aqueous solution extracted with ether, the ether layer dried over anhydrous K_2CO_3, and the ether removed. Distillation of the residue gave 4-benzylaminopyridine (Ⅷ) (2.0 g., 10.9%), b.p. 188~190°/5 mm., m.p. 109.5~110°, reported[14] 108~109.5°. 4-Pyridone (Ⅹ) was obtained from the aqueous layer in the following way:

The aqueous phase was acidified with HCl, extracted with ether to remove benzoic acid, and the aqueous layer neutralized. The neutral solution was concentrated *in vacuo*. The residue was triturated with EtOH to separate NaCl and KCl and the filtrate again evaporated *in vacuo* to leave a residual crystalline, which

*9 When a mixture of potassium hydroxide and benzyl alcohol was heated at 160~170° potassium hydroxide pellets gradually came into solution.

*10 In all instances of this investigation potassium benzoate was separated as in Sprinzak's N-benzylation. See ref. 5.

10) I. Heilbron: "Dictionary of Organic Compounds," Vol. I, 284 (1953), Oxford University Press, New York.
11) H. Rupe, E. Hodel: Helv. Chim. Acta, **6**, 874 (1923).
12) J. A. Chenicek, W. Gleim, R. Rosenwald, H. A. Cyba: Belg. Pat., 631,334; C. A., **60**, 14430 (1964).
13) Y. Sprinzak: J. Am. Chem. Soc., **78**, 3208 (1956).
14) T. Kato, M. Ohta: J. Pharm. Soc. Japan, **71**, 217 (1951); C. A., **46**, 4541 (1952).

was identified as 4-pyridone H_2O (3.0 g., 26.5%), m.p. 64.5~65° (from $CHCl_3$), reported[15] 66~67°. No depression of melting point was observed on admixture with authentic sample.

Reductive Benzylation of 2-Nitropyridine——The reaction was conducted according to the *General Procedure*. 2-Benzylaminopyridine was obtained in 35.3% yield (Table I), m.p. 95~96° (from isopropyl alcohol), reported[5] m.p. 96~96.5° (corr.). On working up the aqueous layer in a similar manner as in preceding example, 0.8 g. (8.4%) of 2-pyridone was obtained, m.p. 107~107.5° (from benzene), reported[16] 104~106°. No depression of melting point was observed on admixture with authentic sample.

The authors wish to thank Miss H. Ohta of the Faculty of Pharmaceutical Sciences, Nagasaki University for microanalyses.

Summary

Aromatic nitro compounds, when heated with benzyl alcohol and potassium hydroxide over 200°, underwent reductive benzylation to give aromatic benzylamines. Some side reactions were described.

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16) J. H. Bayer, D. I. McCane, W. J. McCarville, A. T. Tweedie: J. Am. Chem. Soc., **75**, 5298 (1953).

[Chem. Pharm. Bull. 14(7) 735~741 (1966)] *UDC 547.597.02 : 541.63 : 582.975 : 581.19*

101. Hiroshi Hikino, Yasuyoshi Takeshita, Yasuko Hikino, and Tsunematsu Takemoto: Structure and Absolute Configuration of Fauronyl Acetate and Cryptofauronol.*1

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As part of investigations directed towards a study of the constituents of plants belonging to the valerianaceous family, we first carried out analysis of the essential oils of several cultivated Japanese valerians and found that these can be classified into two different series from the viewpoint of their chemical components.[1,2] Besides the cultivated valerians, there grows a wild valerian named "Kanoko-so" in the upper grasslands in the central and southern part of Japan. The taxonomical relationships of the original plants of those valerians have, however, not been clarified. Although no wild Japanese valerians seem to have been used medicinally, we examined the composition of the oil from a valerian indiginous to Mt. Ibuki with a view to investigating its relationship to the cultivated valerians from the standpoint of their chemical constituents and found that the composition was considerably different from those of the cultivated ones.[3] In this examination, we isolated two hitherto unknown sesquiterpenoids, fauronyl acetate and cryptofauronol, and, in a preliminary communication,[4] established their structure and absolute configuration as shown in formulae I

*1 This paper constitutes Part III in the series on Sesquiterpenoids. Preceding paper, Part II, H. Hikino, Y. Hikino, T. Takemoto: This Bulletin, **13**, 1417 (1965).
*2 Kita-4-bancho, Sendai (ヒキノヒロシ, 竹下保義, 曳野靖子, 竹本常松).
1) H. Hikino, Y. Hikino, H. Kato, Y. Takeshita, T. Takemoto: Yakugaku Zasshi, **83**, 219 (1963).
2) H. Hikino, Y. Hikino, Y. Takeshita, Y. Isurugi, T. Takemoto: *Ibid.*, **83**, 555 (1963).
3) H. Hikino, Y. Hikino, Y. Takeshita, H. Kato, T. Takemoto: *Ibid.*, **85**, 179 (1965).
4) H. Hikino, Y. Takeshita, Y. Hikino, T. Takemoto: This Bulletin, **13**, 631 (1965).