Attempt of synthesis of 6-azauridine (VI) by way of 6-azacytidine (V) by employing mercury salt of 4-N-acetyl-6-azacytosine was abandoned.

Summary

Our previous method of prepraring azapyrimidine nucleosides is suitable for the preparation of 2-*β*-D-ribofuranosyl-5-amino-*as*-triazine-3(2*H*)-one (6-azacytidine) (V). For the preparation of 2-*β*-D-ribofuranosyl-*as*-triazine-3,5(2*H*,4*H*)-dione (6-azauridine) (VI), however, an alternative route by way of 2-(2′,3′,5′-tri-O-benzoyl-*β*-D-ribofuranosyl)-5-methylmercapto-*as*-triazine-3(2*H*)-one (III) was found to be more convenient than the previous one. The procedure was also improved.

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49. Kunio Nakagawa and Teruji Tsuji : Oxidation with Nickel Peroxide. II.*1 Oxidation of Amines.

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In the preceding paper, it was proved that a variety of alcohols could be converted to the corresponding carbonyl compounds by treatment with nickel peroxide in organic solvents.

Further studies were now undertaken on the oxidation of aromatic and aliphatic amines. Some monosubstituted anilines were readily oxidized to give the corresponding symmetrical azo-compounds with nickel peroxide in benzene solution. On the other hand, benzylamine and its derivatives bearing a substituent in the benzene ring could be easily oxidized by the same oxidant to give the corresponding nitriles in good yields regardless of position and kind of a substituent. Alkylamines also underwent the same oxidation and gave the corresponding nitriles.

Oxidation of Anilines

Oxidation of anilines has already been reported by other investigators using chlorcalk, manganese dioxide, phenyl iodosoacetate and lead tetraacetate.[1-4]

However, the only solid oxidant so far employed and reported with a detailed procedure was manganese dioxide, and so it seemed interesting to compare the oxidizing power of nickel peroxide with that of manganese dioxide.

In the present series of experiments, nickel peroxide was added to the benzene solution of anilines and the heterogeneous mixture was allowed to react under efficient stirring at room temperature or under refluxing. These reactions were conducted by employing nickel peroxide 1.2 times as much as the theoretical amount based on the available oxygen-contents which were determined by means of iodometry, and there

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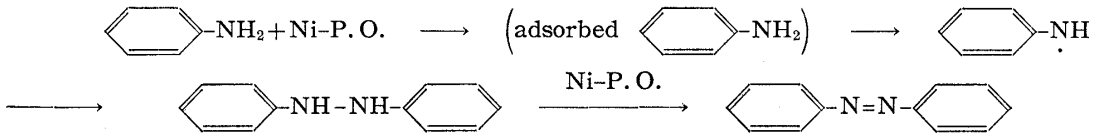
*1 Part I : J. Org. Chem. **27**, 1597 (1962).
*2 Fukushima-ku, Osaka (中川国夫, 辻 照二).
1) W. Meigen, W. Normann : Ber., **33**, 2711 (1900).
2) M. Z. Barakat, *et al.* : J. Chem. Soc., **1956**, 4685.
3) K. H. Pausacker : *Ibid.*, **1953**, 1989.
4) K. H. Pausacker, J. G. Scroggie : *Ibid.*, **1954**, 4003.

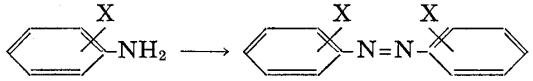
were obtained the corresponding azo-compounds along with some amount of resinous substances.

In the initial stage of this oxidation, a specific coloration for each amine was produced immediately as shown in Table I. This observation leads us to believe that the phenylimino-radical may be produced at the first step of oxidation. Subsequent coupling of two imino-radicals gives a hydrazobenzene, which is eventually converted into azobenzene by dehydrogenation. Thus the mechanism may be expressed as follows :



Ni-P.O. = nickel peroxide

This scheme seems reasonable since hydrazobenzene is quantitatively oxidized to azobenzene by nickel peroxide in benzene. Moreover, the fact that diphenylamine was converted into tetraphenylhydrazine apparently through the formation and association of diphenyl imino-radical supports this radical mechanism. The results of the oxidation of anilines are shown in Table I.

TABLE I. 

Amine	Intermediate color	Reaction		Azo compd.		Analysis (%) Calcd.			Found		
		Time (hr.)	Temp.	Yield (%)	m.p. (°C)	C	H	N	C	H	N
Aniline	violet	6	80	44.1	65	79.09	5.53	15.38	79.34	5.63	15.30
o-NO_2	blue	6	80	20.4	209~210	52.94	2.97	20.58	53.01	3.17	20.80
m-NO_2	red	6	80	40.6	148~150	52.94	2.97	20.58	52.75	3.03	20.85
p-NO_2	〃	6	80	63.8	220~222	52.94	2.97	20.58	53.02	2.97	20.70
〃	〃	8.5	22	50.8	220~222						
o-Cl	blue	6	80	19.5	127~130	57.39	3.21	11.16	58.18	3.06	11.01
m-Cl	yellowish green	6	80	16.3	100~101	57.39	3.21	11.16	57.32	3.21	10.85
〃	〃	7	21	21.4	100~101						
p-Cl	orange	6	80	27.5	177~178	57.39	3.21	11.16	57.53	3.21	10.85
o-CH_3O	〃	6	80	12.5	154~155	69.40	5.83	11.57	69.16	5.90	11.81
m-CH_3O	green	6	80	13.7	75~76	69.40	5.83	11.57	69.72	6.03	11.67
p-CH_3O	〃	6	80	25.0	158~160	69.40	5.83	11.57	69.12	5.86	11.84
o-CH_3	dark orange	6	80	trace	54~55						
m-CH_3	green	6	80	〃	50~52	79.96	6.71	13.33	79.68	6.83	13.58
〃	〃	7	22	17.8	50~52						
p-CH_3	yellow	6	80	2.6	140~141	79.96	6.71	13.33	79.95	6.85	13.58
〃	〃	7	22	25.0	140~141						
m-$COCH_3$	red	6	80	5.7	120~128	72.15	5.30	10.52	71.61	5.44	10.37
〃	〃	7	22	33.1	120~128						

Barakat, *et al.*[2] studied the oxidation of anilines with manganese dioxide, and found that nitroanilines were not oxidized to the azo-compounds. Whereas, in our study, the oxidation with nickel peroxide afforded azo-compounds without the formation of resineous substances. In the cases of other anilines such as chloroanilines, anisidines or toluidines, the corresponding azo-compounds were obtained in poor yields together with resinous products. In these reactions, since the imino-radical once formed gives a series of resonance hybrids, it is very likely that the complicated reactions of their radicals take place spontaneously to give the byproducts.

Thus, although both nickel peroxide and manganese dioxide are considered to be oxidants of the same type, the oxidizing power of the former is stronger than that of the latter in the oxidation of anilines.

Oxidation of Benzylamines

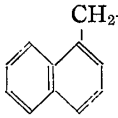
Although there are several references on the oxidation of benzylamine with various oxidants, attempts to prepare benzonitrile from benzylamine by oxidation with potassium permanganate[5] or manganese dioxide[6] were found unsuccessful, and with Caro's acid[7] or N-bromosuccinimide[8], benzonitrile was obtained only in low yield along with other byproducts.

In our experiments, benzylamine was treated with nickel peroxide 1.5 times as much as the theoretical amount for 1.5 hours at 60° in aqueous or benzene solution, whereby benzonitrile was obtained in a good yield.

The use of nickel peroxide was similarly proved effective in the oxidations of other benzylamine derivatives bearing a substituent in its nucleus, such as methyl-, chloro-, methoxy-, and nitrobenzylamines, and also of 1-aminomethyl naphthalene. Since benzylamine derivatives are generally difficult to purify in the form of free amines, they were purified by conversion into their hydrochloride salts, prior to the oxidation procedure, and treated with nickel peroxide in the presence of sodium hydroxide in aqueous solution.

Benzylamine derivatives used in this work were prepared by Sommelet reaction from chloromethyl compounds. The results of oxidation of some benzylamines with nickel peroxide are shown in Table II.

Table II. Oxidation of Some Benzylamines

Amine	Reaction Temp. (°C)	Conditions (hr.)	Nitrile m.p. (°C)	Yield (%)	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Benzylamine	60	1.5	185~191[a]	78.5	81.34	5.19	13.47	81.31	5.14	12.98
p-Methoxy	60	1.5	58~59	87.5	72.20	5.28	10.47	71.93	5.36	10.15
p-Methyl	60	1.5	88.9/11mm[a]	75.2	82.02	6.02	11.95	82.35	6.21	12.37
m-Methyl	60	1.5	213[a]	78.7	82.02	6.02	11.95	82.04	6.07	11.96
o-Methyl	60	1.5	75/10mm[a]	76.8	82.02	6.02	11.95	82.17	6.20	12.06
p-Nitro	60	1.5	149~150	55.5	56.76	2.72	18.92	56.27	3.06	18.97
o-Nitro	60	1.5	109~110	87.0	56.76	2.72	18.92	56.88	2.85	18.54
p-Chloro	60	1.5	89~91	73.0	61.11	2.93	10.18	61.31	3.01	9.83
m-Chloro	60	1.5	35	69.5	61.11	2.93	10.18	57.80	2.93	9.90
o-Chloro	60	1.5	44~45	86.7	61.11	2.93	10.18	61.80	3.22	8.85
	60	1.5	37	90.5	86.24	4.61	9.14	87.18	4.73	9.13
Furfurylamine	5	0.5	142~145	62.5	64.54	3.24	15.01	64.29	3.48	14.84

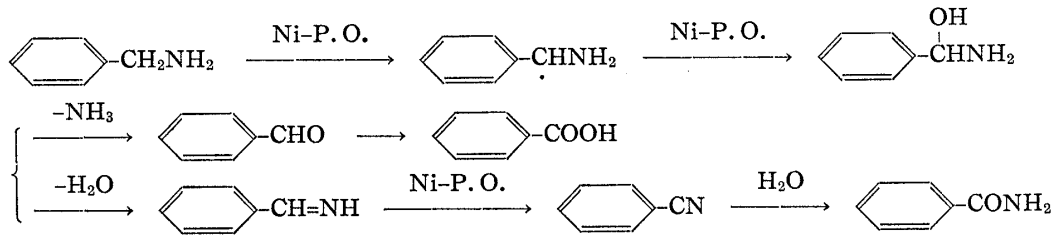
a) boiling point.

As shown in Table II, although benzylamine derivatives bearing electronically and sterically different substituents were used, the corresponding nitriles were obtained in good yields in spite of the effects of substituents. Accordingly, it appears that these reactions may furnish a very convenient means for the preparation of benzonitrile derivatives.

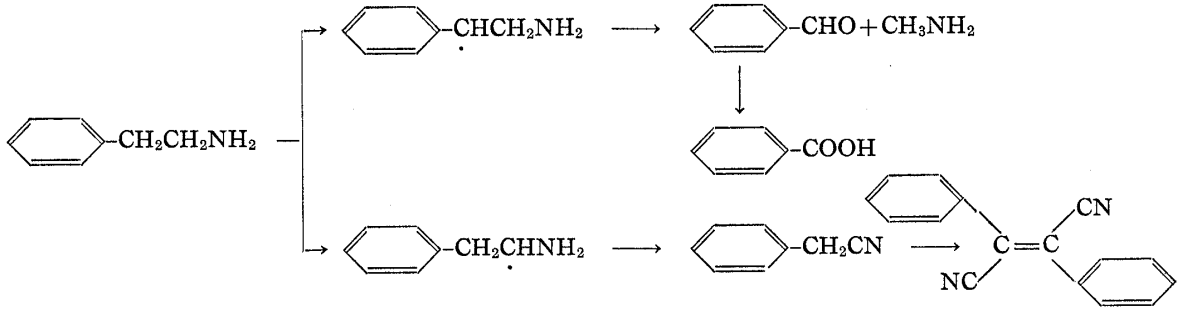
5) St. Goldschmitt : Ann., **435**, 271 (1923).
6) R. J. Highet, W.C. Wildman : J. Am. Chem. Soc., **77**, 4399 (1955).
7) E. Bamberger, T. Schentz : Ber., **34**, 2262 (1901).
8) L. Horner, E.H. Winkelmann : Ang. Chem., **71**, 349 (1959).

Furfurylamine which has a heterocyclic ring was too labile to react with nickel peroxide at room temperature and the cleavage reaction of the ring occurred. However, by oxidation under ice-cooling, furoic nitrile was obtained in 62.5% yield.

In these reactions, small quantities of corresponding amides and aldehydes or carboxylic acid were obtained as byproducts. Therefore, it appears that these reactions proceed as follows :



The course of this reaction may be initiated by the hydrogen radical abstraction from the methylene group by nickel peroxide. Of interest was the fact that benzoic acid and *trans*-α, α'-stilben dicarbonitrile were isolated in the oxidation of β-phenylethylamine. The mechanism for this transformation may be suggested as follows :



Formation of *trans*-α,α'-stilbene dicarbonitrile was verified by the reaction of phenylacetonitrile, prepared by another route, with nickel peroxide in benzene.

We have also found that by the same procedure the oxidation of alkylamines gave the corresponding nitriles in good yields. Table III shows the yields of various alkyl nitriles obtained by nickel peroxide at 1.5 times as much as the theoretical amount based on the available oxygen-content.

Table III. Oxidation of Some Alkylamines

Amine	Reaction Conditions		Nitrile	Yield	Analysis (%) Calcd.			Found		
	Temp.	(hr.)	b.p.	(%)	C	H	N	C	H	N
n-Hexylamine	reflux	1.5	90~92/90mm	73.0	74.19	11.41	14.42	73.76	11.42	14.59
Hexamethylenediamine	〃	1.0	126~127/3mm	23.0	66.64	7.46	25.91	66.57	7.64	25.45
n-Laurylamine	〃	1.5	122~124/5mm	80.6	79.49	12.79	7.73	78.77	12.60	8.24
n-Octylamine	〃	1.5	99~100/28mm	95.8	76.74	12.08	11.19	77.51	11.96	12.49

All oxidations were done with about 100 g. of a 5% benzene solution.

Considering these experiments, the behaviors of nickel peroxide as an oxidant are in keeping with the assumption that its surface can act as a source of hydroxyl radicals. These radicals do not become free, but when react with adsorbed amines they become detached from the oxidant and abstract hydrogen at the favorable position. Therefore, nickel peroxide may be considered to be an oxidant similar to active man-

ganese dioxide, but the oxidizing activity of the former is stronger than that of the latter.

Experimental

Oxidation of *p*-Nitroaniline——To a solution of 1.0 g. of *p*-nitroaniline in 100 cc. of benzene, 2.75 g. of nickel peroxide (1.2 times as much as the theoretical amount[9]) was added under stirring and the heterogeneous mixture was allowed to react for 6 hr. under reflux. The reaction mixture was filtered through a glass filter, washed repeatedly with hot benzene, and the combined filtrate were chromatographed on alumina. 4,4'-Dinitroazobenzene obtained from the first elute fraction was crystallized from Me_2CO, to show m.p. 220~222°.

Oxidation of Hydrazobenzene——A mixture of 1.0 g. of hydrazobenzene and 1.83 g. of nickel peroxide in 100 cc. of benzene was stirred for 3.5 hr. at 20°. The color of the solution changed from green to red. The reaction mixture was filtered, the filtrate was concentrated to give 1.14 g. of azobenzene m.p. 62~63°, which after recrystallization from alcohol showed m.p. 65°(reported m.p. 68°).

Oxidation of Diphenylamine——To a solution of 5.0 g. of diphenylamine in 100 cc. of benzene was added 10 g. of nickel peroxide at 5° and the mixture stirred for 8 hr. The reaction mixture was filtered, washed with benzene and the combined filtrates were concentrated to give 8.1 g. of a red oil. A mixture of Et_2O and EtOH was added to the oil, allowed to stand overnight and the resulted crystals were recrystallized from EtOH to give 2.0 g. of tetraphenylhydrazine, m.p. 143~144°. *Anal.* Calcd. for $C_{24}H_{20}N_2$: C, 85.67; H, 5.99; N, 8.32. Found: C, 84.98; H, 6.09; N, 8.25.

Oxidation of Benzylamine——A) To a stirred solution of 6.42 g. of benzylamine in 150 cc. of H_2O was added in small portions 52.5 g. of nickel peroxide, while the reaction temperature gradually increased. After an additional stirring for 1.5 hr. at 60°, the reaction mixture was filtered to remove the nickel peroxide and washed with hot H_2O. The combined filtrates were acidified with dil. HCl, and extracted repeatedly with Et_2O. After evaporation of the Et_2O, 4.8 g. of benzonitrile was distillated at b.p. 186~188° and 0.72 g. of benzoic amide, m.p. 127.5° was obtained by recrystallization of the residue from benzene.

B) A solution of 4.28 g. of benzylamine in 100 cc. of benzene was stirred with 34.6 g. of nickel peroxide for 1.5 hr. under reflux. The reaction mixture was filtered and the nickel peroxide was washed with benzene. The combined filtrates were washed with dil. HCl to remove the unreacted amine, and then concentrated. Distillation of the residue gave 3.08 g. of benzonitrile, b.p. 185~191°. The peroxide washed with aqueous alkaline solution and 0.71 g. of benzoic acid was obtained.

Oxidation of β-Phenethylamine——To a solution of 3.0 g. β-phenethylamine in 100 cc. of benzene was added 17.0 g. of nickel peroxide and stirred for 6 hr. at room temperature. The nickel peroxide was filtered off and treated with dil. NaOH solution to give 30 mg. of benzoic acid. The filtrate was extracted with 10% HCl and 0.81 g. of the unreacted amine was recovered, which was characterized as the picrate, m.p. 160~163°. Removal of the solvent from the benzene solution afforded 1.09 g. of oil, which was chromatographed on alumina to give 70 mg. of crude crystals, m.p. 143°. Recrystallization from ligroin gave pure *trans*-α,α'-stilbene dicarbonitrile, m.p. 160~162°. *Anal.* calcd. for $C_{16}H_{10}N_2$: C, 83.45; H, 4.38; N, 12.16. Found: C, 83.45; H, 4.38; N, 12.16.

Oxidation of Phenylacetonitrile——In a similar way, a mixture of 2.5 g. of phenylacetonitrile and 7.0 g. of nickel peroxide in 50 cc. of benzene was stirred for 4 hr. under reflux. The reaction mixture was filtered, evaporated to remove benzene and the residue was chromatographed on alumina to give 0.41 g. of crude crystals, m.p. 158~160°. Recrystallization from EtOH gave pure *trans*-α,α'-stilbenedicarbonitrile, m.p. 160~161°. *Anal.* Calcd. for $C_{16}H_{10}N_2$: C, 83.45; H, 4.38; N, 12.16. Found: C, 83.45; H, 4.54; N, 12.15.

Oxidation of Hexylamine——A) To a solution of 5.0 g. of hexylamine hydrochloride and 17.4 g. of NaOH in 100 cc. of H_2O was added 30.6 g. of nickel peroxide and the mixture stirred for 1.5 hr. at 60°. After cooling, the reaction mtxture was filtered, extracted with Et_2O, and evaporated. Distillation of the residue yielded 2.33 g. of caproic nitrile.

B) A solution of hexylamine obtained from 10 g. of its hydrochloride and 200 cc. of benzene was subjected to oxidation with 62.6 g. of nickel peroxide for 1.5 hr. at 60°. By the usual procedure, 5.16 g. of caproic nitrile was obtained as a distillate.

Oxidation of Hexamethylenediamine——To a stirred solution of 5.0 g, of hexamethylenediamine in 100 cc. of benzene was added 59.5 g. of nickel peroxide and the mixture refluxed for 1.5 hr. Treatment by the usual method gave 1.07 g. of adiponitrile, $b.p_3$ 126~127°.

The authors express their thanks to Professors. E. Ochiai, S. Ueo, and Dr. K. Takeda for encouragement and helpful discussion.

9) Available oxygen-content in nickel peroxide was determined by iodometry as shown in Part I.

Summary

Solid nickel peroxide has been shown to be capable of oxidizing aromatic primary amines to the corresponding azo-compounds in benzene solution. Benzylamine and its derivatives bearing a substituent in the benzene ring could be easily oxidized by the same oxidant to give the corresponding nitriles in good yields regardless of the position and the variety of a substituent. Alkyl amines also underwent similar oxidation. In addition, the mechanisms of these oxidations were discussed.

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UDC 543.8〔547'211〕: 547.544.9

50. Tsutomu Momose, Yosuke Ohkura, and Kazuya Kohashi: Organic Analysis. XXXIX.*1 Improved Method of Detecting Active Methylene Compounds with Trinitrobenzene or Picric Acid.

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Trinitrobenzene or picric acid gave a red or orange coloration with active methylene compounds in alkaline medium, and was used for their detection[1] and estimation of both cardiac glycosides[2] and creatinine.[3] According to the original method of detection, however, a blank test showed a fairly colored solution, and was sometimes undistinguishable from the developed coloration with naked eye, especially in the case of trinitrobenzene.

In the previous paper[4] of this series, it was shown that the addition of sodium dihydrogen phosphate in the reaction mixture intensified the developed coloration by picric acid with creatinine, which was made possible to determine the latter compound in blood in a micro scale. The new method may be generally applicable to the detection of active methylene compounds, when the blank color of picric acid or trinitrobenzene diminishes or fades away, and then the developed coloration will be evidently increased even when observed with naked eye. Thus, a new sensitive spot test for the compounds has been established by selecting suitable reaction conditions.

Experimental

Reagents

0.1% 1,3,5-Trinitrobenzene solution: 100 mg. of trinitrobenzene, recrystallized from EtOH, m.p. 121°, is dissolved in 30 ml. of dimethylformamide, mentioned below, and diluted with H_2O to measure 100 ml., and stored in a light resistant container.

0.3% picric acid solution: 300 mg. of picric acid, JIS 1st grade, is dissolved in 100 ml. of H_2O.

2% and 10% NaOH solution: are prepared by the usual method, respectively.

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*1 Part XXXVIII. T. Momose, Y. Mukai: Rinshokensa, **5**, 529 (1961).

*2 Katakasu, Fukuoka (百瀬 勉, 大倉洋甫, 小橋一彌).

1) J. V. Janovsky: Ber., **24**, 971 (1891); M. Ishidate, T. Sakaguchi: Yakugaku Zasshi, **70**, 444 (1950).
2) M. Kimura: Yakugaku Zasshi, **71**, 991 (1951); F. K. Bell, J. C. Krantz Jr.: J. Pharmacol., **83**, 213 (1945).
3) O. Folin, H. Wu: J. Biol. Chem., **38**, 81 (1919).
4) T. Momose, Y. Mukai: Rinshokensa, **5**, 451 (1961).