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116. Shigehiko Sugasawa and Tozo Fujii: Debenzylation of N-Benzyl-acylamides.

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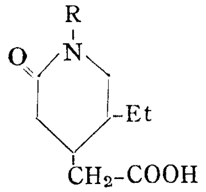
In connection with the synthesis of emetine, debenzylation of 1-benzyl-2-oxo-5-ethyl-4-piperidineacetic acid (I)[11] was attempted to prepare the corresponding debenzylated compound (II).



(I) $R=C_6H_5-CH_2-$

(II) $R=H$

Hydrogenolysis in the presence of a suitable catalyst such as palladium on carbon is a method of choice for debenzylation of various benzylamines, of which *tert*-benzylamines are most amenable to this reaction.

There is, however, no record in the literature that debenzylation of N-benzyl-acylamides was carried out successfully by hydrogenolysis. Thus, Birkofer[1] recovered N, N'-dibenzyloxamide and ethyl N,N-dibenzylcarbamate unchanged when he treated these compounds with hydrogen activated over palladium oxide in acetic acid solution. According to McMillan and Albertson[2] 2-benzylamino-N-benzylsuccinimide, when reduced catalytically in the presence of palladium on carbon at 50° in acetic acid, yielded 2-amino-N-benzylsuccinimide, showing that it was the benzyl group on the basic nitrogen which suffered cleavage, while the benzyl group on the imido-nitrogen remained intact.

The only known example of debenzylation experiment of N-benzyl-lactam, was provided by Adams and Miyano[3] in which debenzylation of N-benzyl-6-ethoxycarbonylmethyl-2-pyridone was not effected by catalytic hydrogenation in the presence of palladium catalyst.

Thus it appeared quite improbable that the debenzylation of (I) will be achieved by hydrogenolysis and, in order to explore other method of debenzylation, 1-benzyl-2-piperidone was chosen as a model compound for debenzylation experiment.

The cleavage of lactam ring through the agency of acid is well known. Thus, when 1-benzyl-2-piperidone was refluxed with conc. hydrochloric acid there was obtained 5-benzylaminovaleric acid hydrochloride in an excellent yield. As was expected the latter suffered debenzylation through catalytic hydrogenation over palladium catalyst and from the resultant 5-aminovaleric acid, 2-piperidone was recovered by the known method.

Consequently the ring cleavage of (I) was now attempted with boiling conc. hydrochloric acid but without effect. Neither conc. hydrobromic acid nor hydrogen bromide in acetic acid proved to be effective. Towards boiling sodium, potassium, or barium hydroxide solution the compound (I) was found quite resistant. Therefore, the attempt to cleave the lactam ring of (I) was abandoned in favor of a search for some other method.

Attention was next turned to the fact that S-benzyl group can usually be cleaved by treating with metallic sodium in liquid ammonia, e.g. S-benzylcysteine undergoes debenzylation by this means to give cystine and dibenzyl.[4]

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[1] L. Birkofer: Ber., **75**, 429(1942).

[2] F. H. McMillan, N. F. Albertson: J. Am. Chem. Soc., **70**, 3778(1948).

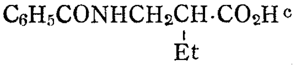
[3] R. Adams, S. Miyano: *Ibid.*, **76**, 3168(1954).

[4] R. H. Sifferd, V. du Vigneaud: J. Biol. Chem., **108**, 753(1935). Several other examples are found in the brilliant synthesis of Oxytocin by V. du Vigneaud, *et al.*: J. Am. Chem. Soc., **76**, 3115(1954).

When 1-benzyl-2-piperidone was treated with sodium in liquid ammonia there was obtained 2-piperidone in a good yield and in this case the benzyl moiety of the original compound was recovered as toluene. The presence of dibenzyl was not traced in the reaction product.

The scope of this debenzylation technique was then examined with several other N-benzyl-acylamides and N-benzyl-lactams and, so far as the present experiments are concerned, this method can be regarded as a general method for debenzylation of N-benzyl-acylamides and N-benzyl-lactams, including the compound (I). The results are given in Table I.

TABLE I. Debenzylation of N-Benzyl-acylamides

Expt. No.	A Starting material	Mol. ratio Na/A	B Debenzylated product	B b.p. or m.p. (°C)	B Yield (%)	Derivatives of B
1	1-Benzyl-2-pyrrolidone (III)	2	2-pyrrolidone	b.p_{18} 134~135	93.9	$C_6H_5CONH(CH_2)_3CO_2H$ (VII) m.p. 79~80° p-$CH_3C_6H_4SO_2NH(CH_2)_3CO_2H$ (VIII) m.p. 137~139°
2	1-Benzyl-2-piperidone (IV)	2	2-piperidone	b.p_{11} 128~131 (Solidified)	72.7	$C_6H_5CONH(CH_2)_4CO_2H$ m.p. 106~107° p-$CH_3C_6H_4SO_2NH(CH_2)_4CO_2H$ m.p. 95~97°[f]
3	1-Benzyl-2-oxohexamethylenimine (V)	2	ε-caprolactam	b.p_{19} 149~151 (m.p. 65~68)	96.8	$C_6H_5CONH(CH_2)_5CO_2H$ m.p. 80~81° p-$CH_3C_6H_4SO_2NH(CH_2)_5CO_2H$ m.p. 106~108°
4	1-Benzyl-2-oxo-5-ethyl-4-piperidine-acetic acid (I)	3	2-oxo-5-ethyl-4-piperidineacetic acid[c] (II)	m.p. 147~149 m.p. 205~207	65.8	ethyl ester[c] m.p. 93~94° b.$p_{0.02}$ 165~166°
5	2-[(N-Benzylacetamido)methyl]-butyric acid[a]	3	2-(acetamidomethyl)butyric acid	ethyl ester[d] b.p_3 125~128	78.7	$C_6H_5CONHCH_2\underset{Et}{CH}\cdot CO_2H$[c] m.p.140~141°
6	N-Benzyl-N-methylbutyramide[b]	2	N-methylbutyramide	b.p_{17} 116~117	91.9	Identified by I. R. absorption spectrum[e]
7	N-Benzylbutyramide (VI)	1.44	butyramide	m.p. 115~116 (b.p. 223~225)	33.3	

All melting and boiling points are uncorrected.

a) This acid was obtained from ethyl 2-[(N-benzylacetamido)methyl]butyrate[11] in a yield of 98.6% by the action of equivalent amount of KOH in ethanolic solution at room temperature as a colorless viscous syrup, and subjected to debenzylation reaction without purification.

b) This amide was obtained as a colorless oil of b.$p_{2.5}$ 115~116° in a yield of 97% from N-methylbenzylamine, 10% Na_2CO_3, and butyryl chloride in benzene solution under Schotten-Baumaun condition. *Anal.* Calcd. for $C_{12}H_{17}ON$: N, 7.3. Found: N, 7.1. I.R. $\nu_{\max}^{\text{Capil.}}$ 1637 cm^{-1} (CON<).

c) The detailed data will appear in the forthcoming number of this Bulletin.

d) *Anal.* Calcd. for $C_9H_{17}O_3N$: N, 7.5. Found: N, 7.1. I.R. $\nu_{\max}^{\text{Capil.}}$ cm^{-1}: 3276, 3064 (NH), 1726 ($COOC_2H_5$), 1655 (CONH), 1552 (NH).

e) The I.R. absorption spectrum in capillary phase was well superimposable with that of an authentic sample[12] (b.p_{13} 118~119°) prepared from methylamine and butyryl chloride under Schotten-Baumann condition.

f) *Anal.* Calcd. for $C_{12}H_{17}O_4NS$: C, 53.1; H, 6.3; N, 5.2. Found: C, 53.5; H, 6.4; N, 4.8. I.R. $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3322 (NH), 1700 (COOH), 1332, 1165 (-SO_2-N-).

When debenzylation products are solid they were identified with authentic specimens, and in case they are liquid they were converted into solid derivatives for characterization. The structure of some of the liquid products were also proved through their infrared spectra.

Toluene was recovered as a fraction boiling at 108~110° and was proved by converting it into benzoic acid and also by its ultraviolet spectrum. Its low yield in contrast to the nitrogenous cleavage product is ascribable to its volatility.

From the present experiments it was revealed that one mole of *sec*-N-benzyl-acylamides and -lactams consume two atoms of sodium to yield the debenzylation products in a smooth reaction and usually in good yields, while in case of *prim*-N-benzylacylamides, having only one hydrogen atom on nitrogen, the consumption of sodium was rather sluggish and the yield of the product was poor.

The result of debenzylation of aromatic N-benzyl-acylamides, such as N-benzylbenzamide, was not clear-cut. This is probably due to possibility that the benzoyl moiety of the original amide undergoes Birch-type reduction to a certain extent.

To make certain the merit of the present method of debenzylation, all compounds tabulated above were subjected to catalytic hydrogenation over palladium catalyst under a variety of working conditions, but they were recovered quantitatively.

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Experimental

1-Benzyl-2-pyrrolidone (III)—A xylene suspension of K-salt of 2-pyrrolidone was prepared from K-dust (11.3 g.) and 2-pyrrolidone (24.5 g.) in pure xylene. This was mixed with $PhCH_2Cl$ (36.4 g.) in xylene with cooling and the whole was then refluxed in an oil bath kept at 160~170° for ca. 40 hrs. in the presence of Cu powder (2 g.). The dark-colored reaction product was filtered from the precipitate, which was washed with xylene. The combined xylene solution was washed with H_2O, dried, and the solvent was removed *in vacuo* to give an orange brown residue, which was distilled, yielding a fraction of b.p_4 144~146°5) as a colorless oil in a yield of 39.1 g. or 77.6% based on 2-pyrrolidone. The redistilled product, b.$p_{3.5}$ 144~145°, was analyzed and submitted to the debenzylation study. *Anal.* Calcd. for $C_{11}H_{13}ON$: N, 8.0. Found: N, 7.7. IR $\nu_{max}^{Capil.}$ 1677 cm^{-1} (-CON<).

For structural proof of this product the ring was cleaved by boiling with conc. HCl as usual to yield 4-benzylaminobutyric acid, which was benzoylated. The benzoyl derivative thus obtained formed silky needles of m.p. 120~121° from dil. EtOH. *Anal.* Calcd. for $C_{18}H_{19}O_3N$: N, 4.7. Found: N, 4.75.

1-Benzyl-2-piperidone (IV)—1-Benzyl-2-pyridone in EtOH was reduced catalytically over Raney Ni catalyst. The product distilled at 164~165°/4.5 mm. as a colorless oil.6) The yield was nearly quantitative. *Anal.* Calcd. for $C_{12}H_{15}ON$: N, 7.4. Found: N, 7.9.

By ring fission with conc. HCl this was converted to 5-benzylaminovaleric acid hydrochloride* which formed colorless prisms of m.p. 155~157°7) from EtOH. *Anal.* Calcd. for $C_{12}H_{18}O_2NCl$: C, 59.1; H, 7.4; N, 5.75. Found: C, 59.0, H, 7.5; N, 5.4.

The benzoyl derivative formed colorless needles of m.p. 124~125° from dil. EtOH. *Anal.* Calcd. for $C_{19}H_{21}O_3N$: C, 73.3; H, 6.8; N, 4.5. Found: C, 73.3; H, 6.6; N, 4.35

1-Benzyl-2-oxohexamethylenimine (V)—Prepared in a yield of 81.4% by benzylating ε-caprolactam as above. This formed colorless oil of b.p_4 157~159°, which solidified on standing and then melted at 56~57°. *Anal.* Calcd. for $C_{13}H_{17}ON$: N, 6.9. Found: N, 6.8.

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* Though 5-benzylaminovaleric acid hydrochloride was indifferent toward H_2 activated over Pd-C under atmospheric pressure and at room temp., a smooth hydrogenolysis took place at higher temp. Thus the substrate (15.1 g.) in 50% EtOH absorbed 1410 cc. of H_2 (theoretically 1380 cc.) in 3 hrs. in the presence of 2 g. of 20% Pd-C at ca. 60°. The yield of pure 5-aminovaleric acid (colorless featherly crystals of m.p. 157~158°, effervesced at 159°) was 6.02 g. or 84.8%, from 3 g. of which 2.17 g. or 85.4% of 2-piperidone (b.p_4 108~110° and solidified) was obtained by the known method (O. Wallach: Ann., **312**, 179 (1900)).

5) b.p_2 122.5~123° according to W. E. Hanford and R. Adams (J. Am. Chem. Soc., **57**, 924(1935)).

6) b.p_8 193° according to A. Binz and C. Räth (Ann., **489**, 107(1931)).

7) m.p. 120° according to A. Binz and C. Räth (*loc. cit.*).

For the purpose of structural proof of this product, it was ring-cleaved as usual and the resultant 6-benzylaminocaproic acid was converted to *p*-toluenesulfonyl derivative, which separated as white silky needles of m.p. 79∼80° from dil. EtOH. *Anal.* Calcd. for $C_{20}H_{25}O_4NS$: N, 3.7. Found: N, 4.0.

Debenzylation Experiment—Debenzylation of 1-benzyl-2-pyrrolidone (III) and N-benzylbutyramide (VI) will be described as typical examples.

Debenzylation of 1-benzyl-2-pyrrolidone (III)—The N-benzyl-lactam (8.8 g., 0.05 mole) was dissolved in liquid ammonia (200∼300 cc.) in a three-necked flask with stirring to give a clear colorless solution, to which Na (2.3 g., 0.1 atom) was added in small pieces (ca. 1 hr.). Toward the end of the addition of Na, a permanent blue color was recognized. NH_3 was allowed to evaporate, leaving white powdery residue, which smelled of toluene. Na-salt of pyrrolidone thus obtained was now dissolved by adding ice-cold water in small portions, when toluene separated out and was collected in ether. From the ethereal solution, after being washed with H_2O and dried, toluene was obtained as a fraction of b.p. 108∼110° (1.3 g. or 28.3%). The aq. layer was acidified faintly with HCl, salted out by adding K_2CO_3, and 2-pyrrolidone separated was extracted with $CHCl_3$, dried, and evaporated. The residue was distilled *in vacuo*, when the product came over as a colorless transparent oil of b.p$_{18}$ 134∼135° in a yield of 93.9%. When ring cleaved with conc. HCl this yielded 4-aminobutyric acid, of which the benzoyl and *p*-toluenesulfonyl derivatives were prepared for identification. These were respectively identical with authentic samples by admixture.

Benzoyl derivative (VII): Colorless needles of m.p. 79∼80°.[8] *Anal.* Calcd. for $C_{11}H_{13}O_3N$: N, 6.8. Found: N, 7.1.

p-Toluenesulfonyl derivative (VIII): Colorless needles of m.p. 137-139°.[9] *Anal.* Calcd. for $C_{11}H_{15}O_4NS$: N, 5.4. Found: N, 5.3.

Debenzylation of N-Benzylbutyramide (VI)—The starting amide (7.1 g., 0.04 mole) in liquid NH_3 was treated with Na as above. After ca. 1 g. of Na had entered into reaction the consumption of the metal became sluggish, giving a lasting blue coloration. After 1.3 g. of Na (0.0565 atom) was added, NH_3 was allowed to evaporate and left white powdery residue, containing some unreacted Na. This was washed three times with pure ether, which removed toluene and the unreacted starting material. The ethereal solution was washed with H_2O, dried, and fractionated to give toluene as a fraction of b.p. 108∼110° (0.6 g. or 16.3%). The residue boiled out at 305° as a colorless syrup, which solidified on standing and melted at 41∼44° and amounted to 1.8 g.[10]

The powdery residue was dissolved in H_2O, which had been used to wash the ethereal solution mentioned above. Some undissolved matter was removed by shaking with ether, from which further 2.1 g. of the starting material was recovered. From the aq. layer there separated butyramide as a solid on being salted out with K_2CO_3. This was repeatedly extracted with ether, dried, and the solvent was evaporated. The residue distilled at 223∼225°, which solidified on cooling and then melted at 114∼115°. The yield was 1.16 g. or 33.3%. When purified from benzene this formed colorless scales of m.p. 115∼116°, which remained undepressed on admixture with an authentic specimen of the same melting point.

Summary

The inability of activated hydrogen to cleave the benzyl group from N-benzyl-acylamides, as is reported in literature, was confirmed. Metallic sodium in liquid ammonia was now found to be an excellent combination to debenzylate the above-mentioned type of compounds. Several N-benzyl-acylamides and N-benzyl-lactams were thus cleaved to yield the debenzylated products in a good yield. The benzyl moiety was recovered as toluene and the presence of dibenzyl in the reaction product was not traced.

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8) m.p. 79∼80° according to G. Zemplén and Z. Csürös (Ber., **62**, 2120(1929)).

9) m.p. 135°. cf. K. Thomas, M. G. H. Goerne: Z. physiol. Chem. (Hoppe-Seyler's), **104**, 82(1919).

10) The recovered material decolorized $KMnO_4$ in acetone quicker than the pure starting material. This is probably due to the presence of material produced by a partial hydrogenation of the aromatic ring.

11) S. Sugasawa, T. Fujii: This Bulletin, **3**, 47(1955).

12) b.p$_{60}$156° according to G. F. D'Alelio and E. E. Reid (J. Am. Chem. Soc., **59**, 109(1937)).