**63. Shigehiko Sugasawa, Norio Sugimoto, Jun-ichi Iwao and Yutaro Nakamura :
Syntheses of *p*-Nitrophenyl-ketones. I. Synthesis of *p*-Nitro-acetophenone.**

(Pharmaceutical Institute, Medical Faculty, University of Tokyo,* and Osaka Resarch Laboratory,
Gohei Tanabe & Co., Ltd.**)

p-Nitro-acetophenone is now an important material for the synthesis of chloramphenicol, and so its preparation was investigated.

Bertingozzi¹⁾ obtained this ketone by oxidizing *p*-nitrophenyl methyl carbinol, which he claimed to have prepared from *p*-nitrobenzaldehyde and methylmagnesium iodide, but we were unable to reproduce his result.

Moore and Ryden²⁾ nitrated phenyl methyl carbinol acetate and fractionated the *o*- and *p*-isomers by distillation; the latter compound was then hydrolyzed and oxidized to give *p*-nitro-acetophenone. This method yielded the nitroketone in 10-20% over-all yield in our hands.

In their paper upon the synthesis of chloramphenicol, Long and Troutman³⁾ made known that *p*-nitro-acetophenone is best obtained from *p*-nitrobenzoyl chloride and diethylethoxy-Mg-malonate via *p*-nitrobenzoylmaleic ester, followed by hydrolysis and decarboxylation of the latter. Though their method gives a good result, there is something left to be desired from the economical point of view.

Although the introduction of the aromatic nitro-group by Sandmeyer's reaction has long been known, no example of its application upon *p*-aminophenylketones has been found in the literature. We, therefore, attempted to prepare *p*-nitro-acetophenone from *p*-amino-acetophenone via this route and succeeded in obtaining the nitroketone in 60-65% yield. Since *p*-amino-acetophenone is a readily accessible substance from acetanilide and acetyl chloride by the usual Friedel-Crafts reaction, we believe our method of preparation of *p*-nitro-acetophenone is the excellent one for being simple in manipulation and also from the economical view-point.

Various other nitroketones are now being prepared in the similar manner.

Experimental

***p*-Amino-acetophenone**—From acetoanilide (100 g.), acetyl chloride (76 g.) and AlCl₃ (250 g.) by the usual method. *p*-Acetoamino-acetophenone obtained was hydrolyzed by boiling with dil. sulfuric acid and basified. Yield of *p*-amino-acetophenone, 63 g; yellow crystals of m.p. 104-106° (b.p.₁₅ 145-147°).

***p*-Nitro-acetophenone**—The foregoing ketone (10 g.) was dissolved in dil. nitric acid (prepared from 15.9 g. of sp. gr. 1.43 and 100 cc. water), and diazotized by adding the solution of sodium nitrite (14.2 g. of 90%) in water (28 cc.) at 0° to 5°; then an excess of sodium nitrite was added to form diazonium-nitrite salt. On the other hand, copper sulfate (18.5 g. of crystals) was dissolved in water (60 cc.) and to this solution was added sodium sulfite (18.5 g.) with stirring. Sodium nitrite (22.8 g. of 90%) was now introduced, forming cupronitrite solution. The diazotized solution obtained above was then poured into the latter solution with vigorous stirring without cooling. The brisk evolution of N₂ was soon observed, followed by the separation of *p*-nitro-acetophenone. After an hour's stirring the crystalline precipitate was collected, dissolved in ether, dried and evaporated. The residue came over at 165-167°/5 mm. and soon solidified. Yield, 8 g. or 65%, m.p. 78-80°. The recrystallized product melted at 80-81° alone or admixed with the authentic specimen prepared by the alternate method.

The decomposition of the diazotized solution was also undertaken in the presence of other metal catalysts,⁴⁾ none of which, however, was proved to be superior to copper as is shown in the following table:—

* Motofuji-cho, Bunkyo-ku, Tokyo.

** Honjo-Kawasaki, Ohyodo-ku, Osaka.

1) C. A., 1934, 5053. 2) J. Chem. Soc., 1946, 679. 3) J. Am. Chem. Soc., 71, 2473 (1949).

4) cf. Hodgson and Marsden: J. Chem. Soc., 1944, 22.

Catalyst	Yield	
	in g.	%
1. Cu-catalyst from 18.5 g. of $\text{CuSO}_4 + \text{NaNO}_2$ 37 g. + H_2O 60 cc.	6.0	49
2. CuO-catalyst „ „ „	7.3	60
3. Ni-hydroxide from NiSO_4 21 g. „ „ 80 cc.	3.5	29
4. CuSO_4 18.5 g. „ „ 90 cc.	5.7	47
5. Fe_2SO_4 21 g. „ „ 60 cc.	3.0	25
6. NiSO_4 21 g. „ „ 80 cc.	2.0	16.5
7. No catalyst „ „ 60 cc.	0	

The following table shows the influences of the amounts of the reagents used upon the yields of the product:—

	$p\text{-NH}_2\text{-C}_6\text{H}_4\text{-COCH}_3$	HNO_3	H_2O	NaNO_2	H_2O	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$	Na_2SO_3	NaNO_2	H_2O	Yield	
										g.	%
1	10.0	15.9	100	14.2	28	18.5	18.5	22.8	60	8.0	65
2	10.0	20.6	140	19.0	38	18.5	18.5	37.0	60	7.4	61
3	10.0	20.6	140	17.0	40	18.5	18.5	37.0	60	6.7	55
4	10.0	12.1	82	11.4	30	18.5	18.5	37.0	60	5.5	45
5	10.0	17.0	120	17.0	40	8.5	8.5	17.0	30	5.4	44
6	10.0	17.8	126	17.0	40	12.0	12.0	25.0	40	6.5	53
7	10.0	17.8	126	17.0	40	18.5	18.5	19.0	60	6.7	55
8	10.0	6.2	360	6.1	15.0	21.1	21.1	47.0	77	6.7	55

- 1) The standard method as described above.
- 2) Increase in the amount of NaNO_2 has no effect.
- 3) After the diazotization the solution was neutralized with CaCO_3 .
- 4) HNO_3 and NaNO_2 were used in the calculated amounts.
- 5, 6, 7) The ratio in the amounts of HNO_3 and NaNO_2 was changed.
- 8) H_2SO_4 in lieu of HNO_3 shows no marked effect on the yield.

Summary

p-Nitro-acetophenone, an important starting material for the synthesis of chloramphenicol, was prepared from *p*-amino-acetophenone by the Sandmeyer's reaction in a 65% yield. This method will be recommended for its simplicity in manipulation and also from the economical view-point.

(Received September 29, 1950)

64. Masao Tomita, Eiichi Fujita and Fujio Murai: Studies on the Alkaloids of Menispermaceae Plants. LXXX. On the Structure of Biscoclaurine Alkaloids. (1).

Cleavage of Isotetrandrine with Metallic Sodium in Liquid Ammonia and the Structure of Alkaloids in the Oxyacanthine-Berberamine Series.

(Pharmaceutical Institute, Medical Faculty, University of Kyoto*)

Biscoclaurine or bisbenzylisoquinoline alkaloid¹⁾ is a generic term for alkaloids of a group having a structure in which two benzylisoquinoline molecules are combined with

* Yoshidakonoe-cho, Sakyo-ku, Kyoto.

1) T. A. Henry: The Plant Alkaloids, 4th Ed., 346 (1949).