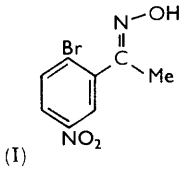
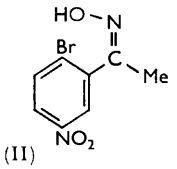
820. *The Effect of Polyphosphoric Acid on the α- and the β-Form of 2-Bromo-5-nitroacetophenone Oxime.*

By N. H. P. Smith.

The two stereoisomeric forms of 2-bromo-5-nitroacetophenone oxime have been isolated; in polyphosphoric acid, each gives the normal product of Beckmann rearrangement. Under the conditions of the rearrangement, no stereochemical interconversion was detected.

The two stereoisomers of 2-bromo-5-nitroacetophenone oxime were isolated by Meisenheimer and his co-workers,[1] who designated them α- (I) and β- (II). On Beckmann rearrangement the α-form gave 2-bromo-5-nitroacetanilide (III), whereas the β-form resisted rearrangement. The effect of polyphosphoric acid, a vigorous reagent for the Beckmann rearrangement,[2] has been investigated, particularly on the β-oxime.


(I)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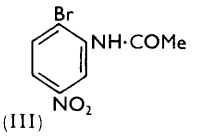
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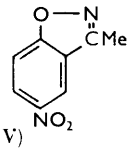
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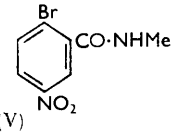
(V)

In view of the wastefulness of the initial stage of the published synthesis [1] of 2-bromo-5-nitroacetophenone, this ketone was prepared by the reactions:

$$o\text{-}C_6H_4(NH_2)\cdot CO_2H \longrightarrow o\text{-}C_6H_4Br\cdot CO_2H \longrightarrow o\text{-}C_6H_4Br\cdot COCl \longrightarrow o\text{-}C_6H_4Br\cdot COMe \longrightarrow 5,2\text{-}NO_2\cdot C_6H_3Br\cdot COMe$$

the third step involving reaction with ethoxymagnesiomalonic ester, followed by hydrolysis and decarboxylation. Each of the pure stereoisomers (I) and (II) was isolated by fractional crystallization. The acetate obtained from the α-form was stereochemically homogeneous; however, repeated recrystallization of the acetylation product of the β-oxime caused a steady rise in its melting point, but a widening melting range. It appears

[1] Meisenheimer, Zimmermann, and von Kummer, *Annalen*, 1926, **446**, 205.
[2] Horning and Stromberg, *J. Amer. Chem. Soc.*, 1952, **74**, 2680.

that transformation of the β- into the α-form occurs during crystallization, for whereas alkaline hydrolysis at room temperature of the α-acetate regenerated the stereochemically pure α-oxime, similar treatment of the β-acetylation product gave the benzisoxazole (IV) together with α-oxime; the nearer the melting point of the recrystallized acetylation product approached that of the α-acetate the greater was the amount of α-oxime obtained on hydrolysis.

Beckmann rearrangement of the α-oxime proceeded smoothly in polyphosphoric acid and gave the anilide (III) in high yield. The β-oxime was recovered unchanged after being heated at 100° for 30 minutes in concentrated sulphuric acid (cf. Meisenheimer [1]); in polyphosphoric acid it reacted smoothly, though apparently not as readily as did the α-oxime, and gave exclusively the hitherto unknown 2-bromo-*N*-methyl-5-nitrobenzamide (V). This was extremely resistant to hydrolysis, boiling concentrated hydrochloric acid, and 60% v/v sulphuric acid being without effect on it; its structure was therefore proved by synthesis as follows:

$$o\text{-}C_6H_4Br\cdot CO_2H \longrightarrow 5,2\text{-}NO_2\cdot C_6H_3Br\cdot CO_2H \longrightarrow 5,2\text{-}NO_2\cdot C_6H_3Br\cdot CO\cdot NHMe \quad (V)$$

Experimental

Oximes of 2-Bromo-5-nitroacetophenone.—A solution of diethyl ethoxymagnesiomalonate in ether (sodium-dried; 70 ml.) was prepared (cf. ref. 3) from diethyl malonate (14·3 g.), magnesium 2·2 g.) and ethanol (magnesium ethoxide-dry; 11 ml.). To this was added during 15 min. a olution in dry ether (25 ml.) of *o*-bromobenzoyl chloride (17·8 g.), b. p. 123—125°/18 mm. (Found: Cl, 16·0. Calc. for C_7H_4BrClO: Cl, 16·2%), prepared from *o*-bromobenzoic acid [4] and thionyl chloride. The mixture was heated under reflux for 4 hr. during which a grey-white solid separated. Hydrolysis with sulphuric acid gave *o*-bromoacetophenone (14 g., 87%), b. p. 111—113°/8 mm., n_D^{21} 1·5669 [semicarbazone [5] (from aqueous pyridine), plates, m. p. 176·5—177°]. 2-Bromo-5-nitroacetophenone, obtained from *o*-bromoacetophenone by the published procedure,[1] was converted in the usual manner [1] into the oxime, the two stereoisomeric forms of which were readily separated by fractional crystallization, the α-oxime as needles, m. p. 171—172°,[1] from aqueous ethanol, the β-oxime as prisms, m. p. 132·5—134°, from ethanol.

Acetyl Derivatives.—A solution of α-oxime (0·26 g.) and redistilled acetic anhydride (0·5 ml.) in anhydrous pyridine (0·8 ml.) at room temperature deposited needles overnight. Decomposition of the mixture with ice-water and hydrochloric acid gave the *α-acetate* (0·28 g.). This separated from light petroleum (b. p. 80—100°)–benzene as needles, m. p. 156—156·5° (Found: C, 40·2; H, 3·1; N, 9·4; Br, 26·2. $C_{10}H_9BrN_2O_4$ requires C, 39·9; H, 3·01; N, 9·3; Br, 26·5%). In daylight these crystals became pink, a phenomenon noted [6] also for acyl derivatives of other oximes.

A yellow colour developed immediately when a warm (40°) solution of the α-acetate derivative (0·23 g.) in dioxan (2 ml.) was treated with N-sodium hydroxide (3·1 ml.). After 2 hr. at room temperature, acidification of the mixture gave the α-oxime (0·19 g.), m. p. and mixed m. p. 171—172°.

A product prepared as above from the β-oxime had m. p. 87—98°. When this was hydrolysed as in the former case, needles of the isoxazole [1] (IV), m. p. 130—130·5°, began to separate almost at once from the deep yellow solution. These were filtered off; acidification of the filtrate gave the α-oxime, m. p. and mixed m. p. 171·5—172°.

Beckmann Rearrangements.—The following general procedure was used: The oxime was added portionwise to hot polyphosphoric acid [from syrupy phosphoric acid (150 ml.) and phosphorus pentoxide (320 g.) (cf. ref. 7)]. Between additions, the mixture was stirred and any lumps of solid were crushed; portions of oxime were added only when the material of the previous addition had almost completely dissolved. After further heating, the mixture period was decomposed by ice-water, and the solid was collected.

The α-oxime (1·0 g.), when kept in polyphosphoric acid (30 g.) at 100° for 30 min.,

[3] Reynolds and Hauser, *Org. Synth.*, 1950, **30**, 70.
[4] Graebe, *Annalen*, 1893, **276**, 56.
[5] Elson, Gibson, and Johnson, *J.*, 1930, 1131.
[6] Shine, *J. Org. Chem.*, 1958, **23**, 318.
[7] Uhlig, *Angew. Chem.*, 1954, **66**, 435; Badger and Sasse, *J.*, 1957, 4.

gave 2-bromo-5-nitroacetanilide (0·76 g.), which separated from aqueous ethanol as needles, m. p. 180—180·5° (Meisenheimer [1] gives m. p. 180°) (Found: C, 37·3; H, 2·6; N, 10·9. Calc. for $C_8H_7BrN_2O_3$: C, 37·1; H, 2·6; N, 10·8%). The β-oxime (0·5 g.), when kept in polyphosphoric acid (15 g.) at 100° for 1 hr., gave *2-bromo-N-methyl-5-nitrobenzamide*, needles (from benzene), m. p. 185·5—186°, undepressed by admixture with a specimen synthesized as below (Found: C, 37·3; H, 2·8; N, 11·0. $C_8H_7BrN_2O_3$ requires C, 37·1; H, 2·7; N, 10·8%).

2-Bromo-N-methyl-5-nitrobenzamide.—2-Bromo-5-nitrobenzoic acid [8] (prepared by the nitration of *o*-bromobenzoic acid) was converted by thionyl chloride into the *acid chloride*, b. p. 111°/1·66 × 10^{-2} mm., pale yellow rhombs [from light petroleum (b. p. 40—60°)], m. p. 62—64° (Found: Cl, 13·2. $C_7H_3O_3BrClN$ requires Cl, 13·4%). A solution of this compound (2·0 g.) in dry dioxan (10 ml.), was treated with 25% w/v aqueous methylamine (4·0 ml.). The exothermic reaction gave the amide (1·6 g.), which separated from aqueous ethanol as needles, m. p. 185·5—186° (Found: C, 37·2; H, 2·9; N, 10·8; Br, 30·7. Calc. for $C_8H_7BrN_2O_3$: C, 37·1; H, 2·7; N, 10·8; Br, 30·8%).

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MANCHESTER, 1. [*Received, April 18th,* 1961.]

[8] Holleman and de Bruyn, *Rec. Trav. chim.*, 1901, **20**, 206; cf. Rhalis, *Annalen*, 1879, **198**, 110.