

Reaction of α -Chloro-N-arylisobutyrimidyl Chloride with Ethyl Malonate¹⁾

Akira TAKEDA, Satosi WADA, and Yutaka OHMURA*

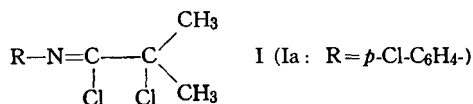
Department of Industrial Chemistry

(Received November 20, 1965)

α -Chloro-N-arylisobutyrimidyl chloride (I) reacted with ethyl sodiomalonate to afford N-aryl-2,2-dimethyl-3-carbathoxysuccinimide. This reaction seems to proceed in a different mechanism from that of the synthesis of tetronic acids²⁾ and is supposed to involve a primary attack of the carbanion at the α -carbon atom of the chloride followed by the cyclization.

It has been known that α -chloroacetyl chloride reacts with ethyl sodiomalonate to give α -carbathoxytetronic acid.²⁾ The reaction probably involves the nucleophilic attack of carbanion derived from malonate upon the carbonyl carbon of α -chloroacetyl chloride followed by the ring closure of the condensation product.

Based on the fact that the treatment of α -chloro-N-arylisobutyrimidyl chloride with water leads to the formation of α -chloro-N-arylisobutyrimide and hydrochloric acid,³⁾ it might be assumed that the carbonyl carbon of I should be enough reactive to undergo nucleophilic attack of malonic ester anion. The reaction of I (R = C₆H₅, *p*-Cl-C₆H₄, *p*-CH₃-C₆H₄) with ethyl sodiomalonate was attempted by the authors in order to prepare imino derivatives (VI) related to tetronic acid, however, the sole product isolated and identified in this reaction was a succinimide derivative, which was not expected from the above assumption. The present report describes and discusses the result of the reaction, exemplified by the reaction sequence of α -chloro-N-(*p*-chlorophenyl)isobutyrimidyl chloride (Ia) as shown in Scheme I.



The reaction of Ia with ethyl sodiomalonate in the excess of ethyl malonate at 120–130° afforded colorless crystals (II) of m. p. 80–81°, whose analytical values correspond to the molecular formula of C₁₅H₁₆O₄ClN. The infrared spectrum of II exhibits three carbonyl bands at 1785, 1740, and 1710 cm⁻¹. When treated with

concentrated hydrochloric acid at 100°, II was readily hydrolyzed to give the corresponding carboxylic acid (III). When heated above its melting point, III was easily decarboxylated to give colorless crystals (IV) of m. p. 69–71°.

The infrared spectrum of IV shows absorption bands at 1770 and 1705 cm⁻¹ for the cyclic imide carbonyl group.⁴⁾ Principal features of the n. m. r. spectrum of IV taken in chloroform were a C-methyl singlet (τ 8.85) and a carbonyl-methylene singlet (τ 7.40).

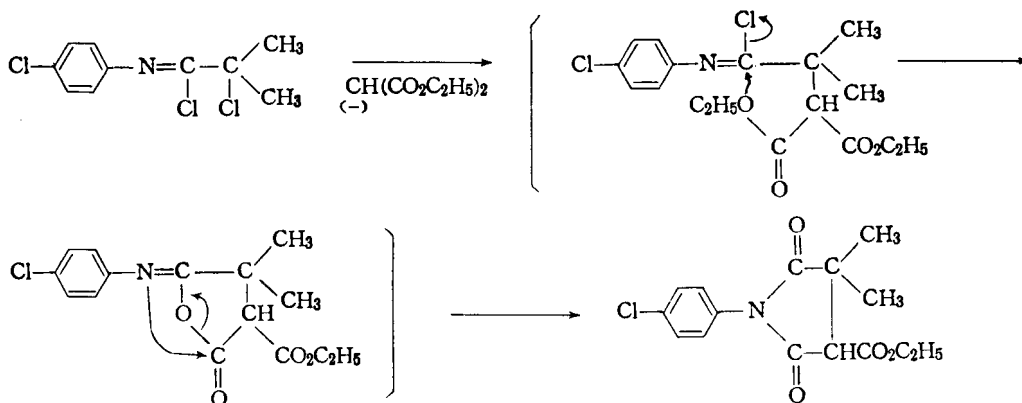
From these data together with the correct analysis the structure of N-arylsuccinimide derivatives rather than the lactones has now been assigned to IV. The identity of both infrared spectrum and melting point of IV with those of authentic sample prepared from α , α -dimethylsuccinic anhydride and *p*-chloroaniline substantiates the structure.

The reaction of Ia with methyl sodiomalonate, carried out in the same manner as with ethyl ester, gave colorless crystals (V), m. p. 101–103°, which was shown identical with methylation product of III, by means of infrared spectra (1735 cm⁻¹ for ester carbonyl group; 1780 and 1710 cm⁻¹ for cyclic imide carbonyl group). All these data and the reaction sequence support the structure of N-(*p*-chlorophenyl)-2,2-dimethyl-3-carbathoxysuccinimide for the product II. N-Aryl-2,2-dimethyl-3-carbathoxysuccinimides obtained similarly are listed in Table I.

The mechanism of the reaction is postulated in Scheme II to fit the formation of II which suggests the primary attack of ethyl malonate anion on α -carbon atom of I, followed by the cyclization to an intermediary lactone and the internal rearrangement to II.

* Kurasiki Rayon Co., Ltd., Kurasiki, Japan

SCHEME II

**Experimental****

The following experiments illustrate the manner in which the reaction was carried out.

Starting Materials. — *N*-(*p*-Chlorophenyl)-isobutyramide*** was prepared by the reaction of isobutyryl chloride and *p*-chloroaniline in benzene (Yield 88.8%, m. p. 150–151°. *Anal.* Calcd. for $C_{10}H_{12}ClNO$: C, 60.76; H, 6.12; N, 7.09. Found: C, 61.01; H, 6.22; N, 7.14.) α -Chloro-*N*-(*p*-chlorophenyl)isobutyrimidyl chloride*** (B. p. 158°/18 mm. *Anal.* Calcd. for $C_{10}H_{10}Cl_2N$: C, 47.93; H, 4.02; N, 5.60. Found: C, 48.52; H, 4.20; N, 5.71.) and α -chloro-*N*-(*p*-tolyl)isobutyrimidyl chloride*** (B. p. 147°/17 mm. *Anal.* Calcd. for $C_{11}H_{13}Cl_2N$: C, 57.41; H, 5.69; N, 6.09. Found: C, 57.25; H, 5.77; N, 6.39.) were obtained by the procedure described for the preparation of the phenyl derivative,³⁾ in good yields (80–90%).

Reaction of α -Chloro-*N*-(*p*-chlorophenyl)isobutyrimidyl Chloride (Ia) with Ethyl Malonate — To a stirred solution of 3.4 g. (0.148 mole) of sodium dissolved in 71 g. (0.444 mole) of ethyl malonate was added 18.8 g. (0.074 mole) of α -chloro-*N*-(*p*-chlorophenyl)isobutyrimidyl chloride at 120–130°. The mixture was stirred at room temperature for 5 hr. and was allowed to stand for overnight. The reaction mixture, after the addition of water, was extracted with ether. The ether extract was washed with water and dried over anhydrous sodium sulfate. After the removal of solvent under reduced pressure, a thick oil remained. This was fractionally distilled, collecting 8.9 g. (38.8%) of heavy oil boiling at 188–190° (1.5 mm.). After a while this oil (II)

solidified and was recrystallized from *n*-hexane, m. p. 80–81°.

Anal. Calcd. for $C_{15}H_{16}ClNO_4$: C, 58.11; H, 5.28; N, 4.52. Found: C, 58.30; H, 5.27; N, 4.56.

Hydrolysis and Decarboxylation of II. — A mixture of 1.2 g. (0.004 mole) of II and 10 ml. of concentrated hydrochloric acid was vigorously stirred under reflux for 5 hr. Upon cooling to room temperature, the mixture solidified to give 1.0 g. (88.5%) of III. III dissolved in aqueous sodium hydrogen carbonate.

A mixture of 0.5 g. (0.0018 mole) of III and 0.05 g. of potassium hydrogen sulfate was heated for 10 min. at above its melting point and there was obtained as neutral substance, 0.2 g. of α , α -dimethyl-*N*-(*p*-chlorophenyl)succinimide (IV), m. p. 69–71°.

Anal. Calcd. for $C_{12}H_{12}ClNO_2$: C, 60.63; H, 5.09; N, 5.89. Found: C, 60.69; H, 5.05; N, 6.05.

Esterification of *N*-(*p*-chlorophenyl)-2,2-dimethyl-3-carboxysuccinimide (III) with Diazomethane. — A solution of 0.5 g. (0.0018 mole) of III in 10 ml. of ether was treated with an excess of diazomethane in 30 ml. of ether and allowed to stand at room temperature for overnight. The ether solution was extracted with saturated sodium hydrogen carbonate, washed with water and dried over anhydrous sodium sulfate. After the removal of solvent, an oil remained, which, on standing, solidified and was recrystallized from *n*-hexane to give methyl ester of III (V), m. p. 99–101°.

Anal. Calcd. for $C_{14}H_{14}ClNO_4$: C, 56.86; H, 4.77; N, 4.74. Found: C, 57.09; H, 4.84; N, 4.47.

** All melting points are uncorrected.

*** New compound.

Reaction of α -Chloro-N-(*p*-chlorophenyl)-isobutyrimidyl Chloride (Ia) with Methyl Malonate. — This reaction was carried out in the same manner as with ethyl malonate, using 1.4 g. (0.06 mole) of sodium, 23.8 g. (0.18 mole) of methyl malonate and 7.5 g. (0.03 mole) of I, yield 2.2 g. (24.8%), b. p. 195–203° (2.5 mm.). On standing it solidified and was recrystallized from *n*-hexane, m. p. 101–103°.

Anal. Calcd. for $C_{14}H_{14}ClNO_4$: C, 56.86; H,

4.77; N, 4.74. Found: C, 56.96; H, 4.76; N, 4.58.

References

- 1) Presented at the 18th Annual Meeting of the Chemical Society of Japan, Osaka, April 3, 1965.
- 2) E. Benary: Ber. 40, (1907) 1079.
- 3) J. v. Braun, F. Jostes and W. Munch: Ann. 453, (1927) 127.
- 4) K. Nakanishi: "IR Absorption Spectroscopy-Practical", Nankodo, Tokyo, 1960, pp. 52.