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THE N-ACYLATION OF N-(4-METHOXYPHENYL)-4-CHLOROANTHRANILIC ACID

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In connection with certain studies in the acridine series, the problem arose of N-acetylating N-(4-methoxyphenyl)-4-chloroanthranilic acid (I) without, simultaneously, cyclizing the acid to the corresponding acridone (II). It it generally known that acids of this type show a strong tendency to cyclize under a variety of conditions (1): especially those that would operate in the acetylation of diphenylamine derivatives which, owing to their low order of basicity, require such strongly acidic catalysts as zinc chloride (2), *p*-toluenesulfonic acid (3), sulfuric acid (4), aluminum chloride (4), and perchloric acid (5). Any one of these, in the presence of hot acetic anhydride, would undoubtedly bring about partial, if not complete, cyclization of the above-mentioned acid; an obesrvation which was confirmed experimentally.

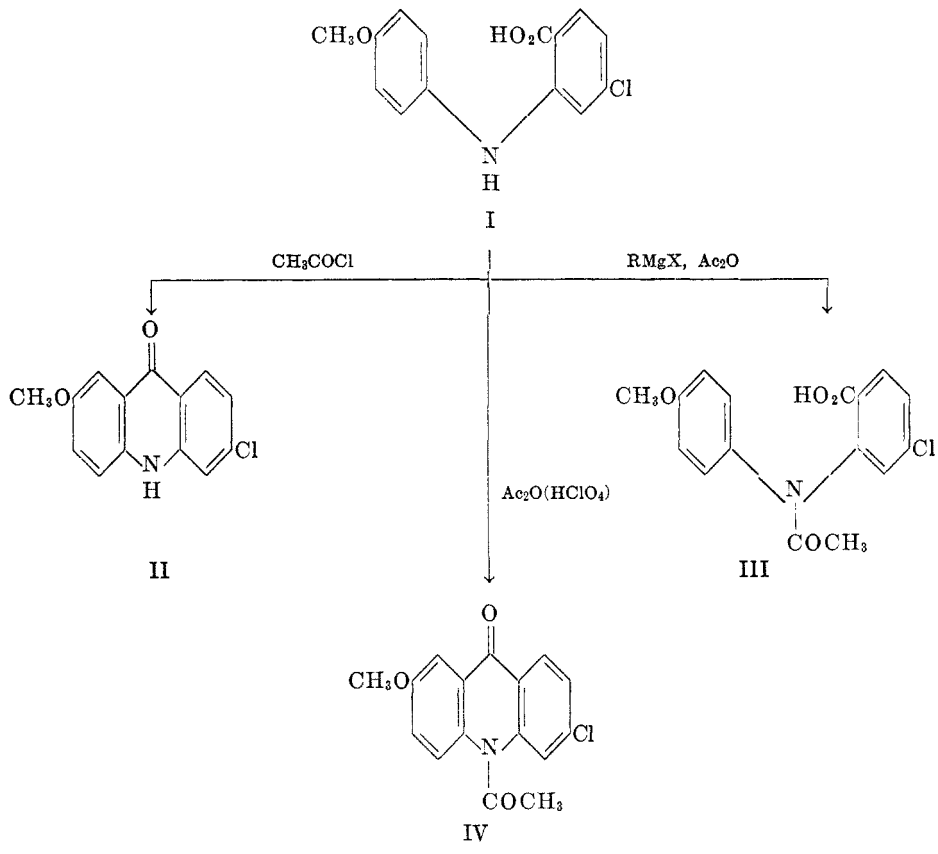
In view of the foregoing, attention was directed to the comparatively mild acetylation technique introduced by Houben (6) for the esterification of certain hydroxyl groups. The method consists of treating the carbinol with a Grignard reagent followed by reaction of the ROMgX compound with acetic anhydride at room temperature. Decomposition of the complex with ice and mineral acid affords the O-acetyl derivative in good yield. A variation of this technique was employed recently by Small and Rapoport (7) in acetylating the tertiary hydroxyl group in 6-methyldihydrocodeine. These investigators substituted methyllithium for Grignard reagent; treatment of the lithium salt with acetic anhydride led to the desired ester. Thus, while this method has proved successful in the acylation of certain, comparatively unreactive, hydroxyl functions it appears, to date, not to have been applied to the imino group.

In the initial application of Houben's technique, the finely powdered diphenylamine carboxylic acid was added to the Grignard reagent. After treating with acetic anhydride, the complex was decomposed with ice and mineral acid and the desired N-acetyl acid (III) obtained in 26% yield. The oily by-products were not investigated. Of the reactive centers present in the original acid, the imino and carboxyl groups would be expected to react first with Grignard's reagent, while the chlorine atom might be regarded as a third (possible) reactive center. It was, therefore, necessary to consider how best to minimize the irreversible coupling reaction which could conceivably occur between the halogen atom and the reagent. When the powdered acid is added *to* the reagent, the latter, present in excess, is potentially capable of reacting with all three reactive centers, either stepwise or concurrently. On the other hand, by reversing the order of addition of reagents, *i.e.*, adding the Grignard reagent to a suspension of the acid in ether, the imino and carboxyl groups, by virtue of their active hydrogens, should instantaneously react with the reagent to the practi-

cally complete exclusion of the chlorine atom. Thus, by-product formation should be diminished and superior yields of the desired product obtained; this has been verified.

The use of methyllithium in this investigation was contraindicated when it was observed that, in addition to reacting with the carboxyl and imino groups, the halogen atom was attacked, *i.e.*, one mole of the acid consumed more than 2 moles of methyllithium (Michler's ketone test).

CHART I



The N-acetyl group is readily hydrolyzed by alkali, under mild conditions, and the original acid results——proof that no structural alterations occurred during acetylation.

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EXPERIMENTAL

Melting points are uncorrected.

N-Acetyl-N-(4-methoxyphenyl)-4-chloroanthranilic acid. A. Addition of RMgX to the acid. To a stirred and cooled (3°) suspension of 4 g. (0.014 mole) of finely powdered N-(4-

methoxyphenyl)-4-chloroanthranilic acid (8) in 40 ml. of dry ether, 36 ml. (0.035 mole) of approximately 1.0 *M* ethylmagnesium bromide was added during 22 mins. After warming (45°) and stirring for an additional 40 mins. the system was cooled in ice (color change from yellow-orange to light green) and treated with a solution of 3.5 ml. (0.034 mole) of acetic anhydride in 20 ml. of dry ether. The reaction mixture was refluxed for 30 mins. and then mechanically shaken for 12 hrs. Decomposition of the complex was effected with ice and 2 *N* H_2SO_4. The product was taken up in ether, the latter washed with water, dried and concentrated (*vacuo*) to give 2.8 g. (60%) of a yellow, tacky solid. Trituration with cold 3:1 ether-petroleum ether (30–60°) mixture removed most of the oil. Another trituration with a few ml. of cold methanol afforded 2.4 g. (53%) of a virtually colorless, crystalline powder, m.p. 192–194° dec. The N-acetyl derivative crystallizes in small, colorless, truncated prisms from methanol-water; after four crystallizations, m.p. 196–198° dec.

Anal. Calc'd for $C_{16}H_{14}ClNO_4$: C, 60.1; H, 4.41.
Found: C, 60.0; H, 4.43.

The N-acetyl acid is readily soluble either in warm sodium bicarbonate solution or in warm 2 *N* NaOH. On cooling, the sodium salt separates as colorless, hexagonal plates in both cases. Treatment of this salt with cold 2 *N* H_2SO_4 regenerates the N-acetyl acid (m.p. and mixture m.p.).

Deacetylation. A suspension of 0.4 g. of N-acetyl acid in 4 ml. of ethanol was treated with 2 ml. of 40% aq. KOH and warmed on the steam-bath for 2 hrs. Acidification of the cooled solution (2 *N* H_2SO_4) gave 0.3 g. (86%) of a pale yellow solid, m.p. 213–215°; not depressed when mixed with the original N-(4-methoxyphenyl)-4-chloroanthranilic acid.

B. Addition of the acid to the RMgX. In an apparatus similar to that employed above, 5 g. (0.018 mole) of finely powdered N-(4-methoxyphenyl)-4-chloroanthranilic acid was added during 20 mins. to 60 ml. (0.06 mole) of approximately 1.0 *M* ethylmagnesium bromide at 3°. The system was gently warmed (reflux) for 45 mins. then cooled in ice and treated (during 25 mins.) with a solution of 6 ml. (0.06 mole) of acetic anhydride in 40 ml. of dry ether. After refluxing for 30 mins., some lumpy material was broken up and the mixture mechanically shaken for 3 hrs., then kept overnight. The product was worked up as before and gave 1.4 g. (26%) of a nearly colorless solid, m.p. 192–194° dec., identical with the N-acetyl derivative described above.

Direct acetylation attempts. Method I. To a solution of 1.2 g. of N-(4-methoxyphenyl)-4-chloroanthranilic acid in 20 ml. of dry benzene, 3 ml. of acetyl chloride was added and the system refluxed for 2 hrs. Concentration (*vacuo*) and trituration of the residue with 50 ml. of cold, dry ether afforded 1 g. of a yellow solid. A clarified (Norit) solution of this in 8 ml. of methanol was diluted with water (light turbidity) and seeded with the above-described N-acetyl acid. After 15 hrs., 0.5 g. of tan crystals was collected, m.p. 180–190°. A solution of the latter in 4 ml. of methanol was diluted slightly with water; in 3 hrs. 0.2 g. (crop I) of light pink needles separated, m.p. 260–262° dec. The mother liquor, on further dilution with water, deposited yellow needles (crop II). Recrystallized from methanol-water, m.p. 215–216°, alone or in mixture with N-(4-methoxyphenyl)-4-chloroanthranilic acid (starting material).

Recrystallization of crop I from methanol, afforded light-pink needles, m.p. 274–276° dec., insoluble in hot (100°) 2 *N* NaOH. The rather high melting point as well as alkali-insolubility suggest an acridone structure and this appears to be supported by the analytical data required by 2-methoxy-6-chloro-9-acridone.

Anal. Calc'd for $C_{14}H_{10}ClNO_2$: C, 64.8; H, 3.88.
Found: C, 64.9; H, 4.01.

The recorded m.p. for 2-methoxy-6-chloro-9-acridone is given as > 270° (8).

Method II. A suspension of 0.8 g. of the acid in 3.2 ml. of acetic anhydride was treated with one drop of aqueous perchloric acid (60%) and heated on the steam-bath for 8 mins. Addition of ice precipitated an orange oil which solidified to a tacky solid after 24 hrs. Trituration with cold 3:1 ether-petroleum ether (30–60°) mixture removed the oil and left a nearly colorless solid, 0.44 g., m. p. 185–190° dec. A solution of this is 20 ml. of methanol

(Norit) was diluted slightly with water. Overnight, 0.1 g. of small, nacreous plates separated, m.p. 293–295° dec. After two crystallizations, m.p. 301–303° dec. The substance was insoluble in hot 2 *N* NaOH and the analytical data agree with the values required by N-acetyl-2-methoxy-6-chloro-9-acridone (IV) indicating that, to a certain extent, concurrent cyclization and N-acetylation had taken place.

Anal. Calc'd for $C_{16}H_{12}ClNO_3$: C, 63.7; H, 4.01.
Found: C, 63.7; H, 4.21.

The aqueous-methanolic mother liquor was strongly diluted with water; overnight, 0.2 g. of a practically colorless solid separated, m.p. 190–193° dec. The substance was freely soluble in 2 *N* ammonium hydroxide as well as in 2 *N* sodium hydroxide; from the latter the characteristic sodium salt separated in colorless, hexagonal plates. Recrystallization of the acid from methanol-water afforded clusters of colorless prisms, m.p. 192–194° dec. alone or in mixture with the N-acetyl acid obtained by Houben's method.

In repeating the above experiment at 85°, using one drop of 30% perchloric acid as catalyst, the desired N-acetyl acid (m.p. 192–194° dec.) was obtained in ca. 30% yield; the remainder of the product consisted of starting material. Numerous, standard acetylation procedures afforded only unchanged starting material.

SUMMARY

The N-acetylation of N-(4-methoxyphenyl)-4-chloroanthranilic acid by two procedures is described.

The formation of N-acetyl-2-methoxy-6-chloro-9-acridone in one of the acetylation attempts has been observed.

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