Acyl Migration in 2-Hydroxylalkyl Aminimides

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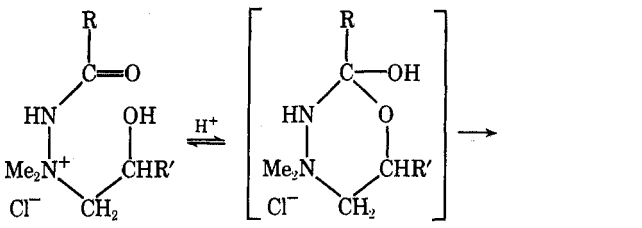
Since the discovery of a convenient and general one-step synthesis of 2-hydroxyalkyl dimethylaminimides $RCON^-N^+Me_2CH_2CH(R')OH$ from carboxylic esters, epoxides, and 1,1-dimethylhydrazine,[1] these compounds have been extensively evaluated.[2] The protonated aminimide of methacrylic acid (1c) was shown[3] to be a much more reactive monomer in radical polymerizations than the unprotonated derivative. Certain anomalies which were noted in the acid properties of this compound and its polymer and copolymers now appear to be the result of a facile, acid-catalyzed acyl migration.



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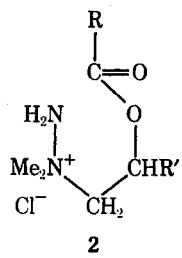

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1a, R = *p*-tolyl; R′ = H

b, R = *trans*-CH=CH-(fumaroyl bis amide); R′ = CH_3

c, R = $-C(CH_3)CH{=}CH_2$; R′ = CH_3

The rearrangement products from the hydrochlorides of bis[1,1-dimethyl-1-(2-hydroxypropyl)amine]fumaroylbisimide and of 1,1-dimethyl-1-(2-hydroxyethyl)amine-*p*-toluylimide have been isolated and characterized. The assignment of structure **2** to these products was based on the following observations.

(a) The protonated aminimides **1** are acids which can be titrated with aqueous alkali (phenolphthalein) to a sharp end point. In contrast, the rearranged compounds are neutral. Argentometry indicates an unchanged equivalent weight.

(b) The rearranged compounds show a NH_2 band at 1615–1625 cm^{-1}, which is also displayed by trimethylhydrazinium chloride ($Me_3N^+NH_2Cl^-$), but which is absent in the protonated aminimides. The carbonyl band, which for aminimide salts approaches, but does not exceed, 1700 cm^{-1}, is shifted to around 1720 cm^{-1} after rearrangement, which is the range of ester carbonyl absorption.

(c) The relevant NMR signals before and after rearrangement were compared, and the recorded changes were consistent with structure **2**.

The acyl migration is clearly acid catalyzed: protonated 1,1-dimethyl-1-(2-hydroxyethyl)amine-*p*-toluimide (**1a**) was rearranged more than 60% in a methanolic HCl solution at 60° in 3 hr, with negligible reaction in methanol alone after 28 hr. Acyl migration competes successfully with hydrolysis even in strong aqueous acids: the aminimide mentioned above rearranged completely in the course of 3 hr when dissolved in concentrated aqueous HCl; some hydrolysis to toluic acid became evident only after 12 hr. (See Experimental Section.)

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Experimental Section

Dimethylhydrazine was from F. M. C. Corp., propylene oxide from Jefferson, methyl *p*-toluylate from Hercules Inc., and dimethyl maleate from Eastman (Yellow Label). NMR spectra were recorded on a Varian A-60A 60-MHz instrument.

Bis[1,1-dimethyl-1-(2-hydroxypropyl)amine]fumaroylbisimide. Dimethyl maleate (144 g, 1 mol), 135 g (2.25 mol) of 1,1-dimethylhydrazine, 131 g (2.25 mol) of propylene oxide, and 250 ml of 2-propanol were stirred slowly under nitrogen in a 1-l. flask fitted with a thermometer, a dry ice–acetone cooler with a NaOH drying tube, and a nitrogen inlet. The temperature rose spontaneously to 65° in the course of 20 min (vigorous reflux) and was kept between 60 and 65° by intermittent cooling in ice–water. After about 1 hr, the reaction product began to precipitate. The temperature was held at 70° by gentle heating during the following 4 hr. The resulting thin slurry was then cooled to 15° and stirred for 1 hr. The precipitate was collected, washed with 2-propanol and then with acetone, and air dried. Bisaminimide was obtained as a white powder: mp 205–220° dec (239 g, 75% yield); equiv wt 161 (by titration with 0.1 *N* $HClO_4$ in acetic acid, crystal violet as the indicator) (calcd, 158); ir (KBr) 1580 (aminimide carbonyl)[2] and 970 cm^{-1} (trans CH=CH); NMR (D_2O) δ 3.43 [d, 6, $-N(CH_3)_2$], 3.5–4.65 [m, 3, $-N^+(Me)_2CH_2CH(Me)O-$], 6.62 (s, 2, vinylic H). After recrystallization from methanol–2-propanol the product was pure. Anal. Calcd for $C_{14}H_{28}O_4N_4$: C, 53.14; H, 8.92; N, 17.71. Found: C, 53.07; H, 9.09; N, 17.48.

From dimethyl fumarate, the same product is obtained, indicating cis–trans isomerization during the reaction of dimethyl maleate.

Bis[1,1-dimethyl-1-(2-hydroxylpropyl)amine]fumaroylbisimide Hydrochloride (1b). Bis[1,1-dimethyl-1-(2-hydroxypropylamine]fumaroylbisimide (22.1 g, 0.07 mol) was added to 40 ml of methanol containing 5.1 g (0.14 mol) of HCl. The resulting solution was filtered, cooled, and diluted with 400 ml of 2-propanol. After standing for 1 hr, the precipitate was collected, washed with 2-propanol and then with acetone, and air dried. Bishydrochloride was obtained as a white powder (23.1 g): mp 164–166° dec (85% yield); NMR (D_2O) δ 3.79 [d, 6, $-N(CH_3)_2$], 4.0–4.5 [m, 3, $-N^+(Me)_2CH_2CH(Me)O-$], 6.00 (s, 2, vinylic H); equiv wt (0.1 *N* aqueous NaOH, phenolphthalein) 197 (calcd, 194.5). Anal. Calcd: Cl^-, 18.25. Found: Cl^- (Volhard), 18.38. ir (KBr) 1695 cm^{-1} (aminimide salt carbonyl).[2]

Rearrangement. 1b, bis[1,1-dimethyl-1-(2-hydroxypropyl)-amine]fumaroylbisimide (31.6 g, 0.1 mol), was dissolved in 50 ml of methanol containing 11 g (0.3 mol) of HCl, and kept at 65° during 8 hr, with exclusion of moisture. Solvent was then removed by evaporation at 60° (20 mm). The residue, consisting of **2b,** crystallized on addition of 50 ml of 2-propanol. It was recrystallized from methanol–2-propanol, mp 235–245° dec. Anal. Calcd: Cl^-, 18.25. Found: Cl^-, 18.15. Ir (KBr) 1730 (ester carbonyl) and 1625 cm^{-1} ($-NH_2$) ($H_2N-N^+Me_3Cl^-$ has a band at 1630 cm^{-1}); NMR (D_2O) δ 3.48 [d, 6, $-N(CH_3)_2$], 5.4–5.9 [m, 1, $-CH(Me)O-$], 6.99 (s, 2, vinylic H).

1,1-Dimethyl-1(2-hydroxyethyl)amine-*p*-toluimide. A solution of 60 g (1.36 mol) of ethylene oxide in 150 ml of 2-propanol was added to 75 g (1.25 mol) of 1,1-dimethylhydrazine and 150 g (1 mol) of methyl *p*-toluate in 100 ml of 2-propanol, in a reaction vessel as for the preparation of the fumaroyl bisaminimide. The temperature rose slowly to 55° and was kept between 55 and 60° by cooling in ice–water. After 0.5 hr, cooling was interrupted, and the mixture kept at 70° during 4 hr under gentle heating.

Volatiles were removed at 50° (25 mm) and then at 1 mm in a rotatory evaporator. The very viscous, nearly colorless residue was diluted with 700 ml of ethyl acetate, and the mixture kept in ice–water during 2 hr. The precipitate was collected, washed with ice-cold ethyl acetate, and air dried. 1,1-Dimethyl-1-(2-hydroxyethyl)-amine-*p*-toluimide was obtained as a white powder (201 g): mp 123–125° (yield 90%); equiv wt (0.1 *N* $HClO_4$, see above) 224 (calcd, 222); NMR (D_2O) δ 3.46 [s, 6, $-N(CH_3)_2$], 3.6–4.3 [m, 4, $-N(Me)_2CH_2CH_2O-$].

1,1-Dimethyl-1-(2-hydroxyethyl)amine-*p*-toluimide Hydrochloride (1a). Treatment of 44.4 g (0.2 mol) **1a,** suspended in 50

ml of methanol, with a solution of 7.6 g (0.21 mol) of HCl in 25 ml of methanol gave a solution which was concentrated at 30° (20 mm) to a viscous syrup and then treated with 400 ml of ethyl acetate. The precipitate was collected after 2 hr, washed with ethyl acetate, and air dried, giving 50.0 g of the hydrochloride as a white powder (97% yield): mp 154–155° dec; equiv wt (0.1 *N* aqueous NaO, phenolphthalein) 262 (calcd, 258.5); ir (KBr) 1680 cm^{-1} (aminimide salt carbonyl);[2] NMR (D_2O) δ 4.00 [s, 6, $-N(CH_3)_2$], 4.1–4.6 [m, 4, $-N^+(Me)_2CH_2CH_2O-$].

Rearrangement. A solution of 4.44 g (20 mmol) of 1,1-dimethyl-1-(2-hydroxyethyl)amine-*p*-toluimide in 25 ml of ice-cooled 10 *N* aqueous HCl was kept at room temperature during 6 hr. The $-N^+(CH_3)_2$ singlet had by now completely shifted from δ 4.0 to 3.66 (see below). After evaporation in vacuo to dryness at room temperature (0.2 mm), the residue was dissolved in 15 ml of methanol, and the solvent evaporated again. The crystalline residue was recrystallized from 2-propanol–ethyl acetate and dried in vacuo over solid NaOH, giving 3.2 g **2a**, mp 154–156°. Anal. Calcd: Cl^-; 13.71. Found: Cl^-, 13.55. Ir (KBr) 1710 (ester carbonyl) and 1615 cm^{-1} ($-NH_2$); NMR (D_2O) δ 3.73 [s, 6, $-N(CH_3)_2$], 4.1–5.1 [d of m, 4, $-N^+(Me)_2CH_2CH_2O-$].

Kinetics by NMR. 1,1-Dimethyl-1-(2-hydroxyethyl)amine-*p*-toluimide (860 mg, 3.88 mmol) was dissolved under cooling in 5 ml of 10 *N* aqueous HCl, giving a 0.75 *M* solution. The solution was quickly brought to room temperature and was monitored by NMR, using the $-N^+(CH_3)_2$ singlet at δ 4.0 for unrearranged aminimide hydrochloride and at δ 3.66 for the rearranged product. The *p*-$CH_3C_6H_4$ singlet at δ 2.42 is a useful internal standard. Water of the aqueous acid does not interfere, since its signal is offset, and a spectrum can be recorded from 6 ppm upfield.

Acknowledgment. The author is indebted to Dr. P. J. Menardi of the Analytical Department (Ashland) for numerous NMR spectra and their interpretation.

Registry No.—**1a**, 57428-01-0; **1b**, 57428-02-1; **2a**, 57428-03-2; **2b**, 57428-04-3; bis[1,1-dimethyl-1-(2-hydroxypropyl)amine]fumaroylbisimide, 57428-05-4; dimethyl maleate, 624-48-6; 1,1-dimethylhydrazine, 57-14-7; propylene oxide, 75-56-9; dimethyl fumarate, 624-49-7; 1,1-dimethyl-1-(2-hydroxyethyl)amine-*p*-toluylimide, 57428-06-5; ethylene oxide, 75-21-8; methyl *p*-toluate, 99-75-2.

References and Notes

(1) R. C. Slagel, *J. Org. Chem.*, **33**, 1374 (1968).
(2) W. J. McKillip, E. A. Sedor, B. M. Culbertson, and S. Wawzonek, *Chem. Rev.*, **73**, 255 (1973).
(3) B. M. Culbertson and N. A. Randen, *J. Appl. Polym. Sci.*, **15**, 2609 (1971); H. J. Langer, unpublished work.

Preparation and Condensations of 3-Lithiomethylquinoline

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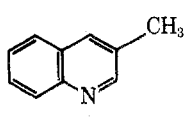
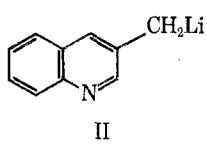
Though the chemical literature abounds with examples of metalation of 2- and 4-methylquinoline,[1] there appear to be no reports of similar reactions on 3-methylquinoline (I). This is perhaps not surprising when it is considered that, although the α carbanions from the 2- and 4-methyl isomers are stabilized by resonance directly involving the ring nitrogen atom, II from the 3-methyl isomer is incapable of such stabilization. Also, the known propensity of quinoline rings unsubstituted at the 2 and/or 4 positions to undergo addition at these positions by bases strong enough to effect metalation[1a] has probably discouraged further investigation.

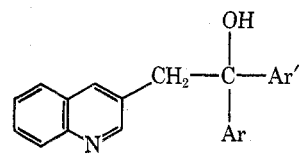


I

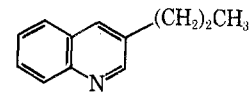


II

This note indicates that lateral metalation of 3-methylquinoline (I) to afford II can indeed be effected provided the proper choice of metalating agent is made. Thus, interaction of I with the strongly basic but weakly nucleophilic lithium diisopropylamide (LDIPA) in THF–HMPA at −78° gives a deep red solution which is apparently due to anion II since subsequent treatment with various electrophiles affords 3-substituted quinolines. For example, II and benzophenone afford III (61%). Similarly, the use of 4,4′-dimethylaminobenzophenone, *p*-chlorobenzophenone, and *p*-chlorobenzaldehyde yields IV (57%), V (36%), and VI (32%), respectively. Likewise, treatment of II with chalcone gives the 1,2-addition product VII (12%). Finally, II and ethyl bromide afford the alkylated product VIII (42%).



III, Ar = Ar′ = C_6H_5
IV, Ar = Ar′ = *p*-$(CH_3)_2NC_6H_4$
V, Ar = C_6H_5; Ar′ = *p*-ClC_6H_4
VI, Ar = *p*-ClC_6H_4; Ar′ = H
VII, Ar = C_6H_5; Ar′ = $CH{=}CHC_6H_5$



VIII

No attempt was made to maximize the conversion of I to II. However, a blank run using the mild conditions described (see Experimental Section) followed by the addition of deuterium oxide resulted in a 75% recovery of deuterated I; the remaining 25% of the material consisted of a tar. Likewise no attempt was made to maximize the yields of III–VIII. All the compounds except VIII are new; VIII was previously prepared (15%) by a Skraup synthesis.[2] Clearly, the preparation of this new organometallic derivative will allow facile synthesis of a variety of additional 3-substituted quinolines.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. All boiling points are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were recorded on a Perkin-Elmer 237B spectrophotometer and nuclear magnetic resonance spectra were obtained at 60 MHz on a Varian A-60 spectrophotometer using tetramethylsilane as an internal standard. 3-Methylquinoline was prepared by the method of Utermohlen.[3] *n*-Butyllithium was purchased from Apache Chemicals, Rockford, Ill. Commercial anhydrous tetrahydrofuran was distilled from solutions containing calcium hydride after preliminary drying over calcium oxide. Commercial anhydrous HMPA was distilled from solutions containing calcium hydride and stored in septum fitted dark bottles under a positive pressure of purified argon.

General Procedure for the Preparation of 3-Substituted Quinolines. To 0.71 g (0.007 mol) of diisopropylamine in 10 ml of THF at 0° under an argon atmosphere was added 4.4 ml (0.007 mol) of 1.6 *M* *n*-butyllithium in hexane followed, after 30 min, by 1.26 g (0.007 mol) of HMPA. Upon cooling to −78° with a dry ice–acetone bath, the solution was treated during 10 min with 1.0 g (0.007 mol) of 3-methylquinoline to afford a red solution which was stirred for 30 min. This solution was then treated during 5 min with 0.007 mol of an electrophile in 10 ml of THF at −78°. After 1 hr at −78°, the reaction mixture was poured into 100 ml of 10% hydrochloric acid, treated with 30 ml of ether, and made basic with potassium hydroxide pellets, and the product was extracted with three 20-ml portions of ethyl ether. The combined extracts were washed with water, dried (calcium chloride), and concentrated. Specific details follow.