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Isophorone–Aniline Condensation Product

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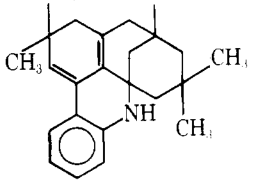
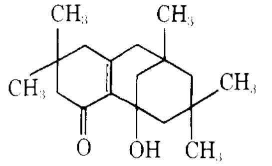
Received September 5, 1978

Isophorone, aniline, and hydrogen chloride, as catalyst, when heated together give a novel heterocyclic compound (I), mp 153–155 °C. Isophorone anil, when heated with HCl as catalyst, gives the same product. Cyclohexylamine, isophorone, and HCl as catalyst gives imine but no dimeric products. A reaction mechanism is proposed for the formation of I.

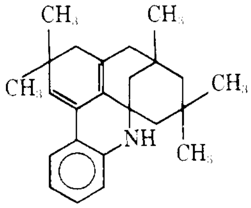


I

It is known that isophorone is dimerized by basic catalysts, such as alkali hydroxides[1-3] or sodium amide,[4,5] to give a dimer of structure[6] 1. Acidic catalysts have not been reported to give this product. Surprisingly, we find that isophorone and aniline, using acidic catalysts, such as hydrogen chloride or *p*-toluenesulfonic acid, give a novel heterocyclic compound 2, which has a structure similar to the above dimer 1. This product is also obtained when isophorone anil is heated with acids.



1



2

This structural assignment is based on the infrared spectrum (KBr), which possesses absorptions at 3330 (secondary amine),[7] 1630 (conjugated double bond), 1310 (secondary aromatic amine), and 755 (ortho-substituted aromatic ring) cm^{-1}. The chemical ionization mass spectrum of 2 shows a strong molecular ion at *m/e* 333. It also shows a strong M + 1, which indicates a stable molecule. The proton NMR spectrum in deuteriochloroform has absorptions at 0.6–1.4 (19 H, large singlets and small multiplets, CH_3 and CH_2), 1.7–2.4 (6 H, group of multiplets, C=CCH and CH), 3.47 (1 H, singlet, N–H), 5.26 (1 H, singlet, C=CH), and 6.3–7.2 (4 H, multiplet, Ar–H) ppm downfield from internal Me_4Si. Table I contains the ^{13}C NMR spectral data of 2. It shows that 2 has a total of five aromatic and olefinic carbons which are not attached to hydrogen atoms. Two of these are carbons which are in the aromatic nucleus, and the other three are in the conjugated diene. There are four aromatic carbons and one olefinic carbon which are substituted with a hydrogen atom. In the aliphatic region, there are four carbon atoms which do not contain hydrogens, five methylene carbons, and five methyl carbons.

Scheme I

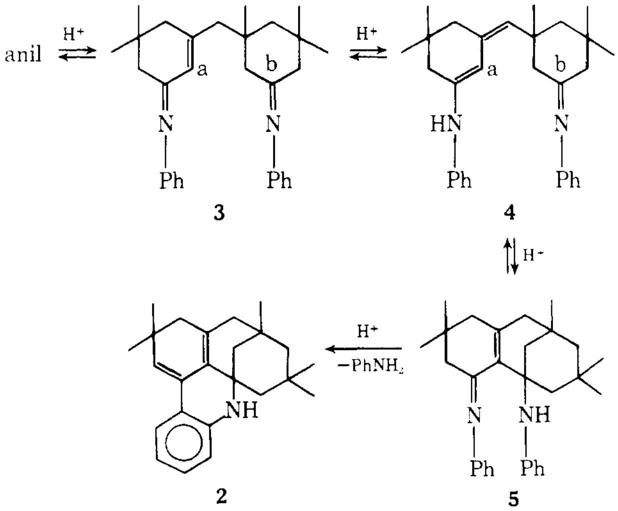


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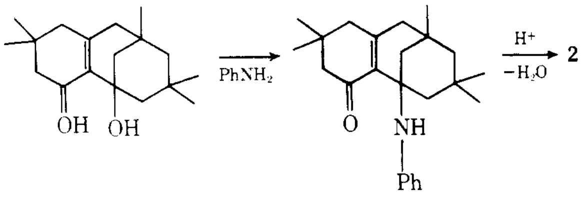
Table I. ^{13}C NMR Data of 2[a]

	OR decoupled	
chemical, ppm[b]	multiplet[c]	origin
aromatic and olefinic carbons		
143.72	s	C
133.65	d	CH
132.35	s	C
129.91	s	C
127.54	d	CH
124.71	s	C
124.06	s	C
123.15	d	CH
117.85	d	CH
113.34	d	CH
aliphatic carbons		
53.14	s	C
52.04	t	CH_2
50.77	t	CH_2
48.17	t	CH_2
43.75	t	CH_2
39.56	t	CH_2
37.22	q	CH_3
34.91	s	C
31.17	s	C
30.94	q	CH_3
30.29	q	CH_3
29.71	s	C
29.19	q	CH_3
26.36	q	CH_3

[a] 1 g of 2 in 2 mL of $CDCl_3$. [b] Relative to Me_4Si, $\delta = 0.00$. [c] s = singlet, d = doublet, t = triplet, and q = quartet.

We propose that the isophorone–aniline condensation product **2** forms from isophorone anil by the mechanism shown in Scheme I, which is analogous to the base-catalyzed Michaels condensation mechanism proposed[8] for the formation of isophorone dimer **1**. The first step is the aldol condensation of isophorone anil to give **3**. This enolizes to **4** and undergoes an internal aldol condensation between the negatively charged atom a and the positively charged atom b to give **5**. The last step in this sequence is a nonreversible cycloalkylation of the aromatic ring, with loss of aniline, to give **2**. Cycloalkylation reactions of this type are common and are used to explain the formation of 2,2,4-trimethyl-1,2-dihydroquinoline from aniline, acetone, and HCl.[9]

Another possible mechanism for the formation of **2** is the formation of isophorone dimer **1** by the base-catalyzed, that is aniline, reaction of isophorone followed by the solvolysis of the bridgehead hydroxyl group to give **6**, which cycloalkylates, with the loss of water, to give **2**. Although the hydroxyl group of isophorone dimer is on a bridgehead carbon, it is known to be very easily solvolyzed.[6,10–12]



6

This mechanism is possible since we find that dimer **1** gives **2** along with isophorone anil when heated with aniline and HCl. Nevertheless, the experimental data favor the anil mechanism. The dimer mechanism requires the formation of dimer **1** under the reaction conditions. But we never detected **1** under a wide variety of conditions. Thus, dimer **1** is not formed when isophorone is heated with amines (basic catalysts), such as aniline, *N*-methylaniline, and *N,N*-dimethylaniline. Dimer **1** is also not formed when isophorone is heated with acidic catalysts, such as *p*-toluenesulfonic acid. Neither is **1** formed when isophorone is heated with a mixture of both an acid and an amine base. For example, isophorone, cyclohexylamine, and HCl give the imine but no **1**. Isophorone, *N,N*-dimethylaniline, and HCl give no **1**; only a small amount of isophorone aldol condensation dimer is formed. The possibility that dimer **1** forms transiently and thus is not detected is ruled out since we find that **1** reacts very slowly with aniline and HCl to give **2**. Dimer **1**, *N*-methylaniline, and HCl give no reaction products. If the formation of **2** occurs through **1**, it is expected that this reaction would give the *N*-methyl derivative **2**.

In support of the anil mechanism, we find that isophorone anil, when heated with acids, gives **2**. In this reaction no dimer **1** can form, and the analogous intermediate **6** is not formed from anil during its synthesis (aniline catalyst). The formation of **2** from aniline, isophorone, and HCl was followed by GC and compared with the formation of **2** from isophorone anil and aniline hydrochloride. We found that the HCl-catalyzed reaction of aniline and isophorone rapidly gives anil. In the first 10 min of the reaction, the anil builds to a level of about 40% of the reaction mixture and remains there for an hour. During this time, all of the isophorone is consumed and product **2** forms at a more or less constant rate. Then, the anil concentration decreases and the formation of **2** slows. On the other hand, in the pure anil reaction the anil concentration decreases rapidly and product **2** forms rapidly in the first 30 min. Then as the anil concentration decreases, the product forms more slowly. These reactions both show a similar dependence on the anil concentration, and this supports the theory that the anil is the key intermediate in the formation of **2**.

The formation of **2** from **1** might be explained by the intermediate formation of anil from **1**. More work is necessary in this interesting area of acid-catalyzed reactions of isophorone dimer.

This condensation reaction appears to be general for 3-methyl substituted cyclohexanones. Thus, 3,5-dimethylcyclohexen-1-one, aniline, and aniline hydrochloride give the condensation product in 72% yield. Substituted anilines also can be used in this reaction. *m*-Toluidine gives an isophorone condensation product in 63% yield.

Experimental Section

Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. The IR spectra (KBr pellets) were recorded on a Perkin-Elmer 467. Elemental analyses were obtained on a Hewlett Packard CHN analyzer Model 185. ^1H NMR spectra were obtained on a Varian Model A-60 with Me_4Si as an internal standard using 10% solutions in deuteriochloroform. The ^{13}C NMR spectrum was obtained using 50% solutions in deuteriochloroform on a Bruker Model HX-90E. The EI mass spectrum was obtained on a DuPont 21-49 with a 21-094B data system. A Hewlett Packard Model 5710A gas chromatograph with 3 ft × 3/16 in., 10% UC98W columns was used for GC work.

Isophorone–Aniline Condensation Product (2). Isophorone (276 g, 2.0 mol), 186 g (2.0 mol) of aniline, 26 g (0.2 mol) of aniline hydrochloride, and 75 mL of toluene were refluxed (145–150 °C), and the water was collected as it formed in a Dean-Stark trap. In 4 h, the theoretical amount of water had formed. The mixture was neutralized with 12 g (0.3 mol) of NaOH in 100 mL of water, washed with water, and rotovaped. Distillation gave 35 g of isophorone anil, bp 108–110 °C (0.1 mm), 191 g (66%) of product **2**, bp 204–208 °C (0.5 mm), and 90 g of pot residues. The product was 98% pure by GC. It was recrystallized from hexane to give 110 g (38%) of a yellow solid: mp 153–155 °C; UVλ_{max} (MeOH) 250 nm (ϵ 29 000), 292 (10 660), 355 (7300).

Anal. Calcd for $C_{24}H_{31}N$: C, 86.43; H, 9.37; N, 4.19. Found: C, 86.27; H, 9.42; N, 4.16.

Isophorone (276 g, 2 mol), 93 g (1 mol) of aniline, 5 g of *p*-toluenesulfonic acid, and 75 mL of toluene were refluxed at 140–150 °C, and

Table II

time, min	wt % anil	wt % product **2**
5	36.4	6.0
10	41.0	7.2
15	42.8	10.4
30	43.5	14.0
60	36.1	39.9
75	29.9	47.9
120	10.2	68.2

Table III

time, min	wt % anil	wt % product **2**
5	65.6	20.0
10	57.0	22.9
15	47.8	28.1
30	31.4	34.1
45	15.2	41.0
60	11.6	44.6
75	7.6	48.6
120	5.5	54.7

the water was collected as it formed. In 12 h, 94% of the theoretical amount of water had formed and GC showed that about 20% of the anil was not converted to product. The mixture was heated for 10 h more, neutralized with 10 g (0.25 mol) of NaOH in 200 mL of water, rotovaped, and distilled to give 119 g (41%) of **2**, bp 203–209 °C (0.5 mm). The pot residue weighed 153 g, which shows that **2** undergoes acid-catalyzed side reactions.

p-Toluenesulfonic acid (1.5 g) and 50 mL of toluene were refluxed, and the water was removed in a Dean-Stark trap. Isophorone anil (43 g, 0.20 mol) was added and the mixture refluxed at 155 °C. GC showed that in 2 h most of the anil was converted to product. After 5 h, the reaction mixture was made basic with 5 g of Na_2CO_3 in 100 mL of water, separated, rotovaped, and distilled to give 15 g (52%) of **2**, bp 198–206 °C (0.4 mm). It was recrystallized from ethanol to give a solid, mp 153–155 °C, which was proven to be **2** by mixture melting point and IR spectrum.

Isophorone anil (335 g, 1.57 mol) and 21 g (0.158 mol) of aniline hydrochloride were heated together at 148 °C. The reaction was followed by GC. In 2 h, about 80% of the anil had reacted. After 10 h, the mixture was dissolved in toluene and neutralized with 20 g (0.5 mol) of NaOH in 250 mL of water, and the organics were separated, rotovaped, and distilled to give 142 g (63%) of **2**, bp 196–206 °C (0.4 mm), and 101 g of undistillable materials.

A mixture of 138 g (1.0 mol) of isophorone, 93 g (1.0 mol) of aniline, and 50 mL of toluene was heated to 120 °C, and 13 g (0.1 mol) of aniline hydrochloride was added. The mixture was heated to 150 °C, and the water was collected as it formed. Samples were removed periodically and analyzed by GC, temperature programmed from 82–300 °C at 16 °C/min. The weight percents of anil and **2** in the measurable part of the reaction mixture are recorded in Table II. Since a wide variety of reactions give high boiling nondetectable products, this is not a true kinetic study.

In the same way, 189 g (1.37 mol) of isophorone anil and 50 mL of dried toluene were heated to 150 °C, 13 g (0.1 mol) of aniline hydrochloride was added, and samples were periodically taken and analyzed by GC (Table III).

Isophorone (141 g, 1.02 mol), 152 g (1.42 mol) of *N*-methylaniline, and 50 mL of toluene were refluxed at 153 °C for 6 h. GC showed that no reaction had occurred.

Isophorone (152 g, 1.1 mol), 157 g (1.3 mol) of *N*,*N*-dimethylaniline, and 50 mL of toluene were refluxed at 150–156 °C for 8 h. GC showed that no reaction had occurred.

Isophorone (185 g, 1.34 mol), 3 g of *p*-toluenesulfonic acid, and 45 mL of toluene were refluxed at 155–157 °C for 4 h. GC showed that no reaction had occurred.

Reduction of 2. To a refluxing solution of 55 g (0.165 mol) of **2** in 500 mL of isoamyl alcohol was added 23 g (1 mol) of sodium portionwise. After the sodium had dissolved, water was added and the solid was filtered and dried. It weighed 45 g (94%) and was recrystallized from hexane to give 38 g (79%) of a white solid, mp 177–179 °C. The IR spectrum showed a secondary amine band at 3330 cm^{-1} and an orthosubstituted aromatic ring at 755 cm^{-1}. The conjugated double-bond band of **2** at 1630 cm^{-1} was no longer present. The UV spectrum showed λ_{max} (MeOH) 232 nm (ϵ 27 300), 271 (3470), and 325 (3030).

Anal. Calcd for $C_{24}H_{35}N$: C, 85.40; H, 10.45; N, 4.15. Found: C, 85.61; H, 10.37; N, 4.11.

Isophorone–*m*-Toluidine Condensation Product. Isophorone (276 g, 2 mol), 53.6 g (0.5 mol) of *m*-toluidine, 20 mL (0.24 mol) of concentrated HCl, and 75 mL toluene were refluxed, and the water was collected in a Dean-Stark trap. After 9 h, the mixture was neutralized with 20 g (0.4 mol) of NaOH in 150 mL water and washed with water, and the organics were separated, rotovaped, and distilled to give 110 g (63%) of an oil, bp 210–220 °C (0.5 mm), which is 98% pure by GC and which crystallized on standing. An analytical sample was recrystallized from hexane to give yellow crystals: mp 190–192 °C; IR (KBr) 3350 cm^{-1} (NH); NMR ($CDCl_3$) δ 0.70–2.35 (m, 28 H, CH_2CH_3), 3.45 (s, 1 H, NH), 5.22 (s, 1 H, C=CH), 6.23–7.20 (m, 3 H, Ar–H).

Anal. Calcd for $C_{25}H_{33}N$: C, 86.40; H, 9.57; N, 4.03. Found: C, 86.28; H, 9.51; N, 3.99.

3,5-Dimethylcyclohexen-1-one–Aniline Condensation Product. 3,5-Dimethylcyclohexen-1-one (50 g, 0.4 mol), 37.5 g (0.4 mol) of aniline, 2.6 g (0.02 mol) of aniline hydrochloride, and 25 mL of toluene were refluxed (125–148 °C), and the water was collected as it formed in a Dean-Stark trap. In 4 h the theoretical amount of water had formed, the mixture was neutralized with 2 g (0.05 mol) of NaOH in 100 mL water and washed with water, and the organic layer was separated and rotovaped to give a solid which was recrystallized from EtOH–hexane to give 39 g (72%) of product, mp 154–160 °C. An analytical sample was recrystallized from ethanol to give yellow-green crystals: mp 163–166 °C; IR (KBr) 3340 (NH), 750 (ortho-substituted aromatic) cm^{-1}; NMR ($CDCl_3$) δ 0.62–2.50 (m, 21 H, CH_2, CH_3), 3.59 (s, 1 H, NH), 5.72 (s, 1 H, C=CH), 6.36–7.25 (m, 4 H, Ar–H).

Anal. Calcd for $C_{22}H_{27}N$: C, 86.50; H, 8.91; N, 4.59. Found: C, 86.42; H, 8.93; N, 4.54.

***N*-(3,5,5-Trimethyl-2-cyclohexenylidene)aniline (Isophorone Anil).** Aniline (93 g, 1 mol), 207 g (1.5 mol) of isophorone, 1 g of sodium acetate, 5 mL of hexanoic acid, and 150 mL of toluene were refluxed, and the water was separated as it formed. In 13 h, 90% of the theoretical amount of water was collected. Distillation gave 177 g (83%) of isophorone anil: bp 108–110 °C (0.4 mm); IR 1630 and 1610 cm^{-1} (C=N); NMR ($CDCl_3$) δ 0.89, 1.03 (two s, 6 H, CCH_3), 1.70 and 1.87 (two s, 3 H, $C{=}CCH_3$), 2.03 and 2.35 (two s, 4 H, $C{=}CH_2$), 5.83 and 6.13 (two s, 1 H, C=CH), 6.58–7.42 (m, 5 H, Ar–H). The NMR spectrum is consistent with an equal mixture of the syn and anti isomers of the anil.

Anal. Calcd for $C_{15}H_{19}N$: C, 84.45; H, 8.98; N, 6.57. Found: C, 84.39; H, 9.07; N, 6.51.

Isophorone (152 g, 1.1 mol), 124 g (1.32 mol) of aniline, and 50 mL of toluene were refluxed together at 153 °C, and the water was collected as it formed. In 9 h, 90% of the theoretical amount of water was collected. GC of the mixture showed that only isophorone anil had formed. Distillation gave 173 g (74%) of isophorone anil, bp 123–125 °C (1.8 mm), and 7 g of pot residues.

***N*-(3,5,5-Trimethyl-2-cyclohexenylidene)cyclohexylamine.** Cyclohexylamine (131 g, 1.32 mol), 75 mL of toluene, and 20 mL of concentrated HCl were refluxed, and the water was collected in a Dean-Stark trap. Isophorone (152 g, 1.1 mol) was added and the mixture refluxed for 10 h to give the theoretical amount of water. GC showed that no dimer **1** was present. The mixture was neutralized with 10 g of Na_2CO_3 in 150 mL of water, washed with water, rotovaped, and distilled to give 181 g (83%) of imine: bp 94–96 °C (0.4 mm); IR 1620 cm^{-1} (C=N); NMR ($CDCl_3$) δ 0.95 and 0.98 (two s, 6 H, CH_3), 1.17–2.22 (m, 23 H, CH_2, CH_3), 3.05–3.83 (broad, 1 H, CH), 5.97 and 6.23 (two m, 1 H, C=CH). The NMR spectrum is consistent with a mixture of syn and anti isomers of the imine.

Anal. Calcd for $C_{15}H_{25}N$: C, 82.21; H, 11.49; N, 6.39. Found: C, 82.32; H, 11.61; N, 6.33.

3-[(3,5,5-Trimethylcyclohexenylidene)methyl]-5,5-dimethyl-2-cyclohexen-1-one. *N*,*N*-Dimethylaniline (149 g, 1.2 mol), 20 mL (0.2 mol) of concentrated HCl, and 50 mL of toluene were refluxed together to remove the water. Isophorone (152 g, 1.1 mol) was added, and the mixture was refluxed at 156–159 °C for 6 h to give 5 mL (0.28 mol) of water. GC showed that no isophorone dimer was present. The acid was neutralized with 10 g of Na_2CO_3 in 150 mL of water, and the organic layer was separated, rotovaped to remove the toluene, and distilled to give 22 g (10%) of a yellow oil: bp 138–140 °C (0.7 mm); IR 1630 and 1610 cm^{-1} (O=CC=C–); NMR ($CDCl_3$) δ 0.97 and 1.10 (two s, 12 H, CH_3), 1.82 (s, 3 H, $=CCH_3$), 1.97 and 2.08 (two s, 2 H, $O{=}CCH_2$), 2.28 and 2.32 (two s, 2 H, $C{=}CCH_2$), 5.55–6.40 (m, 3 H, C=CH); mass spectrum, *m/e* 258 (M^+).

Anal. Calcd for $C_{18}H_{26}O$: C, 83.66; H, 10.14. Found: C, 83.58; H, 10.11.

N,N-Dimethylaniline (15 g, 0.12 mol) 2 mL of concentrated HCl and 15 mL of xylene were refluxed to remove the water. The mixture was cooled, and 15 g (0.1 mol) of isophorone dimer was added. The mixture was refluxed at 158 °C for 20 h; no water formed, and GC showed that no reaction had occurred.

Dimer 1 and Aniline. Isophorone dimer (126 g, 0.46 mol), 85 g (0.91 mol) of aniline, 24 g (0.18 mol) of aniline hydrochloride, and 75 mL of toluene were refluxed, and the water was collected as it formed in a Dean-Stark trap. In 5 h, only 30% of the theoretical amount of water had collected. GC showed the presence of dimer **1**, isophorone anil, and product **2**. In 15 h, 90% of the theoretical amount of water had formed. The reaction was worked up in the usual way to give 170 g of crude product from which 70 g (53%) of **2** was obtained by recrystallization from hexane (by mixture melting point and IR). Isophorone dimer (20 g, 0.07 mol) and 80 g (0.86 mol) of aniline were stirred and heated at 160 °C for 6 h. GC showed that no reaction had occurred.

Xylene (50 mL), 13 g (0.12 mol) of *N*-methylaniline, and 2 mL of concentrated HCl were refluxed, and the water was removed in a Dean-Stark trap. Isophorone dimer (15 g, 0.1 mol) was added and the mixture refluxed at 144–148 °C for 24 h. GC showed that no reaction had occurred.

p-Toluenesulfonic acid (2 g) and 50 mL of xylene were refluxed for 3 h, and the water was collected as it formed in a Dean-Stark trap. Isophorone dimer 1 (10 g, 0.036 mol) was added, and the mixture was refluxed for 10 h at 143 °C. Samples were taken every 2 h and analyzed by GC. Dimer 1 was found to be slowly but completely converted into a number of higher boiling materials. No isophorone was detected.

Acknowledgment. We would like to thank Charles P. Jacobs for assisting in the experiment work and K. Welch for the mass spectral work.

Registry No.—**1**, 6244-16-2; **2**, 68936-70-9; **2** reduction product, 68928-14-3; isophorone-*m*-toluidine condensation product, 68928-15-4; 3,5-dimethylcyclohexen-1-one–aniline condensation product, 68928-16-5; (*E*)-isophorone anil, 68928-17-6; (*Z*)-isophorone anil, 68928-18-7; (*E*)-*N*-(3,5,5-trimethyl-2-cyclohexenylidene)cyclohexylamine, 68928-19-8; (*Z*)-*N*-(3,5,5-trimethyl-2-cyclohexenylidene)-cyclohexylamine, 68928-20-1; 3-[(3,5,5-trimethylcyclohexenylidene)methyl]-5,5-dimethyl-2-cyclohexen-1-one, 68928-21-2; isophorone, 78-59-1; aniline, 62-53-3; isophorone anil, 36755-22-3; aniline hydrochloride, 142-04-1; *m*-toluidine, 108-44-1; 3,5-dimethylcyclohexen-1-one, 1123-09-7; cyclohexylamine, 108-91-8.

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Esterification of Carboxylic Acids with Trialkyloxonium Salts

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Received August 25, 1978

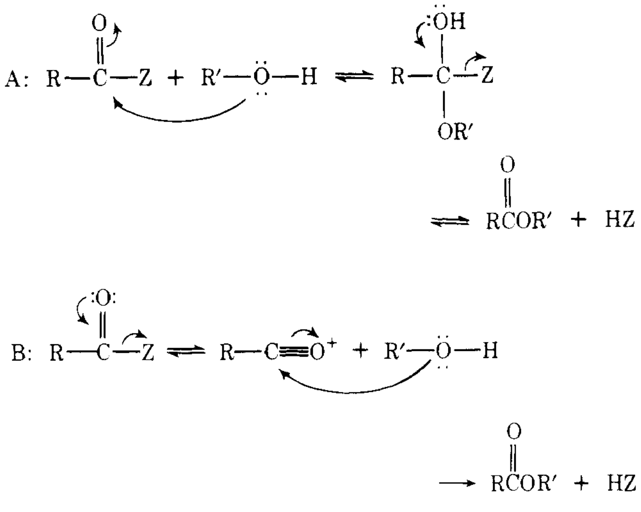
The preparation of methyl and ethyl esters of a variety of carboxylic acids using trimethyl- and triethyloxonium tetrafluoroborate has been explored. This method has been found to be successful for a broad series of carboxylic acids including sterically hindered and polyfunctional carboxylic acids. Mild conditions are employed and the reaction is quite rapid in the absence of steric hindrance. Carboxylic acids can be esterified by this procedure in excellent yield to afford products with a high degree of purity.

Methods for effecting the synthesis of carboxylic acid esters from the corresponding acid can be envisioned in terms of two general schemes: nucleophilic attack on the *carboxyl carbon* atom of the carboxylic acid or on one of its derivatives by an alcohol (Scheme I); or alkylation of the *carboxyl oxygen* atom of a carboxylic acid or carboxylate anion by an appropriate alkylating agent (Scheme II).

The direct esterification of a carboxylic acid by an alcohol (Scheme IA, Z = OH) proceeds at a reasonable rate only in the presence of acid catalysts[1] and thus severe problems are usually encountered in the esterification of acid-sensitive compounds. Furthermore, this reaction is reversible, often exhibiting an unfavorable equilibrium constant.[2] Therefore, it is frequently necessary to remove water and/or use a large excess of alcohol in order to achieve reasonable yields of product.[3] Finally, sterically crowded carboxylic acids are not readily esterified by this procedure because of increased steric interaction in the tetrahedral intermediate.[4]

Conversion of a carboxylic acid to a more reactive derivative

Scheme I



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