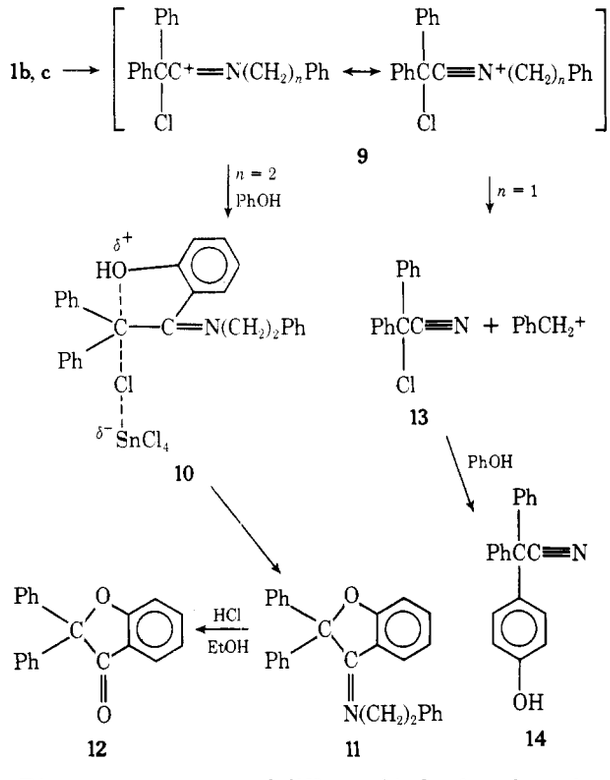
of stannic chloride at room temperature, 2,3-dihydro-2,2-diphenyl-3-(2-phenylethyl)iminobenzo[*b*]furan (**11**) was obtained in 39% yield. By the treatment of an ethanolic solution of **11** with hydrochloric acid solution at reflux temperature, 2,3-dihydro-2,2-diphenylbenzo[*b*]furan-3-one (**12**) was obtained in 55% yield.

A similar reaction of **1b** with phenol in the presence of stannic chloride in benzene afforded the noncyclic compound α-(*p*-hydroxyphenyl)-α,α-diphenylacetonitrile (**14**) in 43% yield. Considering the results of intramolecular cyclization of the *gem*-dichloroaziridines (**1a–c**) under acidic conditions and solvolyses of 1,3-diphenyl-2,2-dichloroaziridine as described above, the following reaction mechanism was tentatively proposed.



Divergent processes and different kinds of products from **1b** and **1c** may be attributed to the difference in nature of the group on the nitrogen atom. Stable carbonium ion forming groups such as a benzyl group would favor the von Braun type of degradation to give the nitrile **13**, which reacts subsequently with phenol to give **14**. The intermediate imidoylcarbonium ion **9** from **1c**, having a 2-phenylethyl group on the nitrogen, would attack phenol at the ortho position to form **11**. It is interesting to note that the alkylation of phenol with **1b** occurs at the para position while that with **1c** occurs at the ortho position. This seems to add an example to the known experimental criteria that secondary carbonium ions predominantly attack the ortho position of phenol while tertiary carbonium ions attack the para position.[8] Alternatively, the ortho substitution by **9** may be favored by the formation of cyclic intermediate **10** in the presence of $SnCl_4$. The reaction of **1c** with phenol is expected to serve as a general method for the synthesis of 2,3-dihydro-2,2-diphenylbenzo[*b*]furan-3-ones.

Experimental Section

Infrared spectra were obtained in KBr disks on a Jasco IRA-2 spectrometer, and NMR spectra were taken on a Hitachi R-20A spectrometer. Mass spectra were recorded on a Hitachi RMU-7M spectrometer. Combustion analyses were performed on a Perkin-Elmer 240 analyzer.

Reaction of 2,2-Dichloro-3,3-diphenyl-1-(2-phenylethyl)-aziridine (1c) with Phenol. To a solution of 3.68 g (0.01 mol) of **1c** in 30 mL of benzene was added slowly a solution of 5.21 g (0.02 mol) of stannic chloride and 1.88 g (0.02 mol) of phenol in 30 mL of benzene. The mixture was stirred at room temperature for 36 h and then poured into water. The organic layer was separated, washed with aqueous sodium hydrogen carbonate and then with water, and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was chromatographed on a silica gel column using benzene as an eluent to give pure 2,3-dihydro-2,2-diphenyl-3-(2-phenylethyl)iminobenzo[*b*]furan (**11**) in 39% yield: mp 109–110 °C; IR 1650 cm^{-1} (C=N); NMR ($CDCl_3$) δ (ppm) 3.10 (t, 2, CH_2Ph), 4.17 (t, 2, CH_2N=C), 7.30 (m, 19, Ph); MS 389 (M^+), 298, 284, 270, 165, 105.

Anal. Calcd for $C_{28}H_{23}NO$: C, 86.34; H, 5.95; N, 3.60. Found: C, 86.09; H, 5.94; N, 3.52.

Hydrolysis of 2,3-Dihydro-2,2-diphenyl-3-(2-phenylethyl)-iminobenzo[*b*]furan (11). A solution of 0.2 g (0.51 mmol) of **11** in 11 mL of ethanol was treated with 1 mL of 12 M hydrochloric acid under reflux for 2 h. The acidic solution was neutralized with an ethanolic sodium hydroxide solution, and the sodium chloride that precipitated was removed. After evaporation of the solvent, the residue was chromatographed on a silica gel plate using carbon tetrachloride as an eluent. Isolation of the product band and extraction with acetone followed by evaporation of the solvent gave pure 2,3-dihydro-2,2-diphenylbenzo[*b*]furan-3-one (**12**): mp 91–92 °C (lit.[6] mp 90 °C); IR 1710 cm^{-1} (C=O); NMR ($CDCl_3$) δ (ppm) 7.3 (m, Ph); MS 286 (M^+), 258, 257, 181, 165, 109, 77, 76.

Anal. Calcd for $C_{20}H_{14}O_2$: C, 83.90; H, 4.93. Found: C, 83.14; H, 4.97.

Reaction of 1-Benzyl-2,2-dichloro-3,3-diphenylaziridine (1b) with Phenol. To a solution of 3.54 g (0.01 mol) of **1b** in 30 mL of benzene was added slowly a solution of 5.21 g (0.02 mol) of stannic chloride and 1.18 g (0.02 mol) of phenol in 30 mL of benzene. The mixture was stirred for 36 h at room temperature and worked up by a similar method to that described for the reaction of **1c**. The yield of α-(*p*-hydroxyphenyl)-α,α-diphenylacetonitrile (**14**) was 43%: mp 194.5–195 °C (lit.[7] mp 191–192 °C); IR 3400 (OH), 2225 (C≡N) cm^{-1}; NMR ($CDCl_3$) δ (ppm) 6.5–7.2 (m, Ph); MS 285 (M^+), 208, 190, 181, 165, 153, 152.

Anal. Calcd for $C_{20}N_{15}NO$: C, 84.19; H, 5.30; N, 4.91. Found: C, 84.51; H, 5.33; N, 4.96.

Registry No.—**1b,** 31528-96-8; **1c,** 61123-19-1; **11,** 66749-69-7; **12,** 66479-70-0; **14,** 13343-54-9; phenol, 108-95-2.

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A Facile Synthesis of 2-(Trifluoromethyl)histamine and 2-(Trifluoromethyl)-L-histidine

Hiroshi Kimoto,[1] Kenneth L. Kirk, and Louis A. Cohen*

Laboratory of Chemistry, National Institute of Arthritis, Metabolism and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20014

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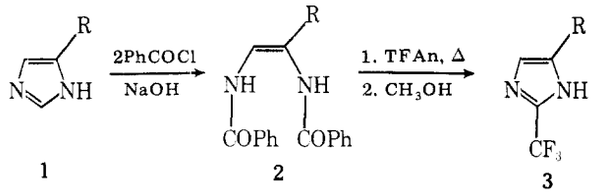
Our observations of the potent and selective biological activities of 2-fluoro-L-histidine[2] and 2-fluorohistamine[3] stimulated efforts to prepare and test additional analogues of metabolically significant imidazoles, particularly those with other electronegative groups at C-2. The more obvious synthetic approaches begin with a preformed 2-substituted imidazole, followed by elaboration of the histidine or histamine side chain.[4] There are, however, significant advantages to the

use of L-histidine or histamine as starting materials: (1) ready availability; (2) shorter synthetic sequences; and (3) direct entry into the L-amino acid series. These advantages were realized in the syntheses of 2-amino-L-histidine and 2-aminohistamine[5] and in their subsequent conversions to the 2-fluoro[6] and 2-chloro[7] analogues. The trifluoromethyl group, because of its strong electronegativity, was of particular interest to us; however, the only documented synthesis of 2-trifluoromethylimidazoles involves condensation of α-diketones with trifluoroacetaldehyde and ammonia,[8] a method limited in both scope and yield, and not entirely suitable for our purposes.

A few 2-alkylimidazoles have been obtained by condensation of *cis*-1,2-dibenzamido-1-alkenes (**2**), the products resulting from Bamberger cleavage of imidazoles, with appropriate carboxylic anhydrides at high temperature (140–180 °C).[9] Substituents introduced at C-2 by this method include methyl, ethyl, phenyl, and benzyl. We considered the possibility that an analogous ring closure (**3**) might be achieved with trifluoroacetic anhydride and anticipated the need for sealed tubes to achieve the high reaction temperatures. To our surprise and gratification, the condensation occurred readily in solvent trifluoroacetic anhydride at reflux (40 °C) and provided good yields (70%) of α-*N*-benzoyl-2-trifluoromethylhistamine (**3c**) and α-*N*-benzoyl-2-trifluoromethyl-L-histidine methyl ester (**3e**). Attempted removal of the benzoyl blocking groups by alkaline hydrolysis resulted in concomitant breakdown of the trifluoromethyl group,[10] but acid hydrolysis was successful and led to 2-trifluoromethylhistamine (**3d**) and



1 2 3

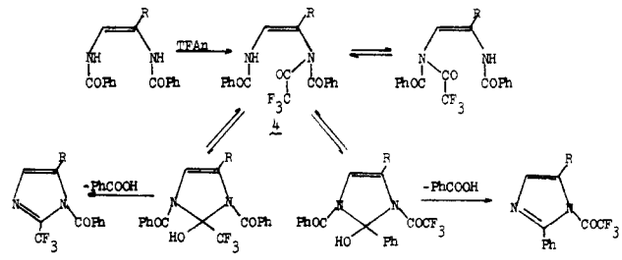
a, R = H
b, R = CH_3
c, R = $CH_2CH_2NHCOPh$
d, R = $CH_2CH_2NH_2$
e, R = $CH_2CH(NHCOPh)COOCH_3$
f, R = $CH_2CH(NH_2)COOH$

2-trifluoromethyl-L-histidine (**3f**). In their classical synthesis of histidine via **2e** and 2-mercaptohistidine, Ashley and Harington[11] had demonstrated the absence of racemization at any step in the sequence. In the reaction of **2e** with trifluoroacetic anhydride, azlactone formation (the only remaining source of racemization) cannot occur because the carboxyl group is protected as its ester. Consequently, we tentatively assume the optical rotations observed for **3e** and **3f** to represent those of the essentially unracemized L-amino acid.

Encouraged by these results, we then applied the cyclization method to the simpler dibenzamidoalkenes **2a** and **2b.** The expected products, **3a** and **3b,** were obtained, but in considerably lower yield than **3c** or **3e.** In the case of **2a,** the major fraction consisted of a complex mixture of materials much more polar than **3a;** with **2b,** however, the principal products consisted of two (or more) relatively nonpolar, crystalline compounds with molecular weights above 550. The structures of these products have not yet been elucidated. We assume that the more favorable results with **2c** and **2e** are related to the steric bulk of their side chains in promoting cyclization and/or maintaining the cis geometry of the olefin in the acidic medium.

The conversion of **2** to **3** probably involves the pathway shown in Scheme I. This scheme suggests 2-phenylimidazoles as alternative products of cyclization; although such products have not been detected in the present work, they do occur as minor products in the reaction of **2** with trichloroacetic anhydride.[12] Cyclization of **2c** has not been detected up to 110 °C in the absence of acid anhydride, and a triacylated species

Scheme I



is presumed to be a requisite intermediate. The facility of the reaction with trifluoroacetic anhydride may be due, therefore, to its high reactivity as an acylating agent,[13] and/or the high electrophilic reactivity of the trifluoroacetyl carbonyl group in **4.**

In view of the biological activity found for 2-fluorourocanic acid,[14] the trifluoromethyl analogue also became a goal of synthesis. It was already known that imidazoles with electronegative substituents at C-4 (or C-5) fail to undergo the Bamberger cleavage reaction.[15] Consistent with this property, urocanic acid (or its esters) did not undergo cleavage with benzoyl chloride, thus precluding synthesis by direct introduction of the trifluoromethyl group. In an alternative approach, we considered use of 4-hydroxymethylimidazole, but this compound also failed to undergo Bamberger cleavage.

The NMR spectra of ring protons in the trifluoromethylimidazoles are displaced downfield to an extent qualitatively consistent with the effect of a strong electronegative substituent. As expected, the substituent also reduces the values of pK_1 and pK_2 for the imidazole ring, to the extent predicted by Hammett correlations.[16]

Experimental Section[17]

2-Trifluoromethylimidazole (3a). A solution of 2.8 g (0.01 mol) of **2a**[18] in 80 mL of trifluoroacetic anhydride was stirred and refluxed for 2 h, during which time the solution developed a reddish yellow color and a colorless precipitate separated. Another portion of 2.8 g of **2a** was then added and refluxing was continued for 5 h. The solvent was removed by distillation and 100 mL of methanol was added to the residue. The solution was refluxed for 1 h and stored overnight at room temperature. A colorless precipitate was filtered off (1.2 g) which proved to be starting material (**2a**). The solvent was evaporated and the tarry residue (9.7 g) was applied to a column of silica gel 60 (250 mL). Elution with ether–petroleum ether (1:1) gave 0.55 g of Pauly-positive material. This fraction was sublimed (1 mm, 50–70 °C bath) to give 0.13 g (4.8%) of **3a** as a colorless powder. Recrystallization from chloroform afforded needles: mp 145–146 °C; NMR (acetone-d_6) δ 7.29 (2, s, H-4,5).

Anal. Calcd for $C_4H_3F_3N_2$ (136.1): C, 35.31; H, 2.22; F, 41.88; N, 20.59. Found: C, 35.39; H, 2.21; F, 41.93; N, 20.66.

Further elution of the column with ethyl acetate gave ca. 5 g of a complex mixture of Pauly-negative materials, none of which have yet been identified. Numerous variations in procedure failed to improve the yield of **3a.**

4(or 5)-Methyl-2-trifluoromethylimidazole (3b). A solution of 1.4 g (5 mmol) of **2b**[19] in 80 mL of trifluoroacetic anhydride was stirred and refluxed. The starting material dissolved within a few minutes and a new, colorless product began to separate. Three additional portions (1.4 g each) of **2b** were added at 1-h intervals and, after a total of 6 h of reflux, the solvent was distilled. The reddish yellow residue was dissolved in 100 mL of methanol and the solution was refluxed for 1 h. The solution was stored overnight at room temperature and a colorless, Pauly-negative precipitate (2.0 g) was separated. This material crystallized from ethyl acetate as needles (mp 220–222 °C, *m/e* 569). The methanol filtrate was evaporated and the yellow residue (11.2 g) was applied to a column of silica gel 60 (150 mL). Elution with ether–petroleum ether (1:1) first gave 2.2 g of a Pauly-negative material which crystallized from ethyl acetate (mp 121–122 °C, *m/e* 578). Continued elution gave 1.9 g of benzoic acid and, finally, 0.50 g of Pauly-positive material. The latter fraction was sublimed (1 mmHg, 50–70 °C bath) to give 0.113 g (3.8%) of **3b** as a colorless powder. Recrystallization from water gave plates: mp 103–105 °C; NMR (acetone-d_6) δ 2.26 (3, s, CH_3), 6.96 (1, s, H-4 or 5).

Anal. Calcd for $C_5H_5F_3N_2$ (150.1): C, 40.01; H, 3.36; N, 18.66; F,

37.97. Found: C, 39.77; H, 3.43; N, 18.93; F, 37.78.

α-N-Benzoyl-2-trifluoromethylhistamine (3c). A solution of 4.13 g (0.01 mol) of **2c** (mp 198–199 °C)[20] in 80 mL of trifluoroacetic anhydride was stirred and refluxed for 1 h. A second portion of **2c** (4.13 g) was added and refluxing was continued for 5 h. The solvent was distilled and a solution of the residue in 100 mL of methanol was refluxed for 1 h. The solution was stored overnight at room temperature and a colorless, Pauly-negative precipitate (1.46 g) was separated. This material crystallized from ethanol (mp 261 °C dec, *m/e* 492). Evaporation of the methanol filtrate gave a tarry residue which was chromatographed on 200 mL of silica gel 60. Elution with ether gave 3.9 g (68.8%) of **3c** as pale yellow crystals. Recrystallization from benzene–tetrahydrofuran gave colorless plates: mp 179–180 °C; NMR ($CDCl_3$) δ 2.95 (2, t, J = 7 Hz, β-CH_2), 3.67 (2, t, J = 7 Hz, α-CH_2), 7.07 (1, s, H-4 or 5), 7.4–8.0 (5, m, C_6H_5).

Anal. Calcd for $C_{13}H_{12}N_3F_3O$ (283.3): C, 55.13; H, 4.27; N, 14.83; F, 20.12. Found: C, 55.23; H, 4.42; N, 14.50; F, 19.98.

2-Trifluoromethylhistamine Dihydrochloride (3d). A solution of 2.13 g (7.5 mmol) of **3c** in 200 mL of 3 N hydrochloric acid and 15 mL of ethanol was heated on steam for 24 h. The reaction mixture was evaporated to dryness under reduced pressure. The residual material was freed of benzoic acid by trituration, twice with ether and twice with 2-propanol, giving 1.56 g (82.5%) of **3d**·2HCl. Recrystallization from ethanol gave colorless needles: mp 210–212 °C; NMR (D_2O) δ 3.14, 3.26 (4, q, A_2B_2, J = 6.0 Hz, α and β CH_2's), 7.52 (1, s, H-4 or 5).

Anal. Calcd for $C_6H_8N_3F_3$·2HCl (252.1): C, 28.59; H, 4.00; N, 16.67; F, 22.61. Found: C, 28.36; H, 4.35; N, 16.42; F, 22.88.

α-N-Benzoyl-2-trifluoromethyl-L-histidine Methyl Ester (3e). A suspension of 4.71 g (0.01 mol) of **2e**[21] in 80 mL of trifluoroacetic anhydride was stirred and refluxed for 2 h (solution was complete after 0.5 h). An additional 4.71 g of **2e** was added and refluxing was continued for 5 h. The solvent was removed by distillation and a solution of the residual material in 100 mL of methanol was refluxed for 0.5 h. The solvent was evaporated and the residual material was chromatographed on 200 mL of silica gel 60. Elution of the column with ether gave benzoic acid, followed by **3e.** The Pauly-positive fractions were pooled and concentrated to give 4.8 g (70.3%) of light yellow crystals. Recrystallization from benzene gave **3e** as colorless plates: mp 157–159 °C; NMR ($CDCl_3$) δ 3.25 (2, d, J = 5.8 Hz, β-CH_2), 3.70 (3, s, OCH_3), 5.05 (1, t, J = 5.8 Hz, α-CH), 6.95 (1, s, H-4 or 5), 7.4–8.0 (5, m, C_6H_5); $[\alpha]^{20}_D$ −37.7° (*c* 0.5, CH_3OH).

Anal. Calcd for $C_{15}H_{14}F_3N_3O_3$ (341.3): C, 52.79; H, 4.14; N, 12.31; F, 16.70. Found: C, 52.53; H, 4.17; N, 12.04; F, 16.29.

2-Trifluoromethyl-L-histidine Dihydrochloride (3f). A solution of 2.05 g (6 mmol) of **3e** in 200 mL of 3 N hydrochloric acid and 20 mL of ethanol was heated on steam for 24 h. The reaction mixture was concentrated to 100 mL and was extracted with three 50-mL portions of ether to remove benzoic acid. The aqueous layer was evaporated to dryness to give **3f**·2HCl as a colorless powder, mp 237–238 °C. This material was triturated twice with ether and was dried overnight in vacuo at 50 °C. Crystallization of the salt or of the neutral amino acid could not be effected: NMR (D_2O) δ 3.32 (2, d, J = 7.0 Hz, β-CH_2), 4.32 (1, t, J = 7.0 Hz, α-CH), 7.44 (1, s, H-4 or 5); $[\alpha]^{20}_D$ −3.80° (*c* 0.6, H_2O, pH 1.9), −14.06° (*c* 5, H_2O, pH 7.2).

Anal. Calcd for $C_7H_8O_2N_3F_3$·2HCl (296.1): C, 28.40; H, 3.40; N, 14.19; F, 19.25. Found: C, 28.22; H, 3.32; N, 13.79; F, 19.08.

pK Determinations. pK values were obtained by titration in aqueous solution at 25 °C, calculations being based on 7–10 readings. For **3a:** pK_1 = 2.06 ± 0.03; pK_2 = 10.00 ± 0.05. For **3b:** pK_1 = 2.54 ± 0.02; pK_2 = 10.34 ± 0.06.

Registry No.—**2a,** 33511-28-3; **2b,** 66675-19-2; **2c,** 66675-20-5; **2e,** 66675-21-6; **3a,** 66675-22-7; **3b,** 66675-23-8; **3c,** 66675-24-9; **3d**·2HCl, 66675-25-0; **3e,** 66675-26-1; **3f**·2HCl, 66675-27-2.

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Acid-Catalyzed Rearrangements of the Dihydroxyacetone Side Chain in Steroids during Ketal Exchange

Kenneth B. Sloan,* Roy J. Little, and Nicholas Bodor*

INTERx Research Corporation, Lawrence, Kansas 66044

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Discussion

The synthesis of steroid derivatives often makes it necessary to protect the hydroxy groups that are present. One method of accomplishing this goal is by converting the substrate into a ketal or an ortho ester. Gardi et al.[2] reported that the reaction of hydrocortisone and prednisolone with 2,2-diethoxypropane gave not only the expected 17α,21-acetonides (**1** and **2,** respectively) but also the 17α,21-acetonide 11β-(1′-ethoxy-1′-methyl)ethyl ethers (**3** and **4,** respectively). Similarly, the reaction of hydrocortisone with triethyl orthoacetate gave 17α,21-(1′-ethoxy)ethylidenedioxy 11β-(1′,1′-diethoxy)ethyl ether (**5**) in addition to the expected 17α,21α-(1′-ethoxy)-ethylidenedioxy derivative (**6**).

The Italian workers[2,3] relied on relatively mild conditions which involved a brief distillation of benzene suspensions of the steroid in the presence of a ketal, acetal, or ortho ester and a trace of an acid catalyst. However, in our hands this procedure generally did not lead to the previously reported protected steroid by-products. Instead, ketal exchange yielded **10** and **11** which are formally the result of a Mattox[4] rearrangement although in one reaction the Mattox rearrangement product itself underwent exchange at the 11β position to yield **17.** Only if the 21 position of the dihydroxyacetone side chain was acylated was an 11β-ether obtained without rearrangement, and this required a much longer reaction time.[2] The Mattox rearrangement of a dihyroxyacetone side chain is commonly encountered whenever steroids come in contact with acidic media; however, this is its first observation during acetonide formation.[5]

The reaction of hydrocortisone with 2,2-dimethoxypropane consistently gave four products: a trace of 11β-hydroxy-3-methoxy-3,5-pregnadien-20-one 17α,21-acetonide (**9**),[6] 40–50% of hydrocortisone 17α,21-acetonide (**1**),[2] 12–15% of **10,** and 2–3% of **11. 10** and **11** had almost identical mass spectra and infrared spectra but their NMR spectra and TLC behavior were decidedly different. The mass spectra of **10** and **11** showed an M^+ at (*m/e*) 416 instead of at (*m/e*) 489 for the

0022-3263/78/1943-3405$01.00/0