

PYRIDYL AND N,N-DIMETHYLANILYLTRIFLUOROMETHYLKETONES FORMING STABLE *gem*-DIOLS

R. L. SALVADOR* and M. SAUCIER†

Contribution from the Medicinal Chemistry Section of the Faculty of Pharmacy
of the University of Montreal

(Received in USA 14 August 1970; Received in the UK for publication 7 October 1970)

Abstract—A series of six aryltrifluoromethylketones have been synthesized: 2,3 and 4-pyridyl and N,N-dimethylanilyl-2,3 and 4-trifluoromethylketones. Four of these six aryltrifluoromethylketones form stable *gem*-diols. It is proposed that the unusual stability of these *gem*-diols is not solely accounted for by the inductive effects of the trifluoromethyl radical, but also by the stabilization effects of H-bond formation between the acidic OH groups of the diols and their basic N atoms.

INTRODUCTION

ALDEHYDES and ketones add water reversibly, forming *gem*-diols. It is known that the *gem*-diols are stable enough to be isolated only when the CO compound is heavily substituted with electron withdrawing groups. A classical example is the case of trifluoroacetaldehyde whose CO is submitted to the inductive effects of the trifluoromethyl radical.¹

Although many trifluoromethylketones are described in the literature, and it is generally accepted that they exist as *gem*-diols in aqueous solutions,² very few trifluoromethylketone *gem*-diols have been isolated. The *gem*-diol of thenoyltrifluoroacetone (TTA.H₂O)‡ constitutes a rare example of a trifluoromethylketone *gem*-diol isolated in the pure state.³

In this paper we describe a new series of trifluoromethylketones which are the three isomers of pyridyltrifluoromethylketone (Ia, b, c) and of N,N-dimethylanilyl-trifluoromethylketone (IIa, b, c). Among these new trifluoromethylketones, four form crystalline *gem*-diols (IIIa, b, c, and IVa) whose stability is of interest.

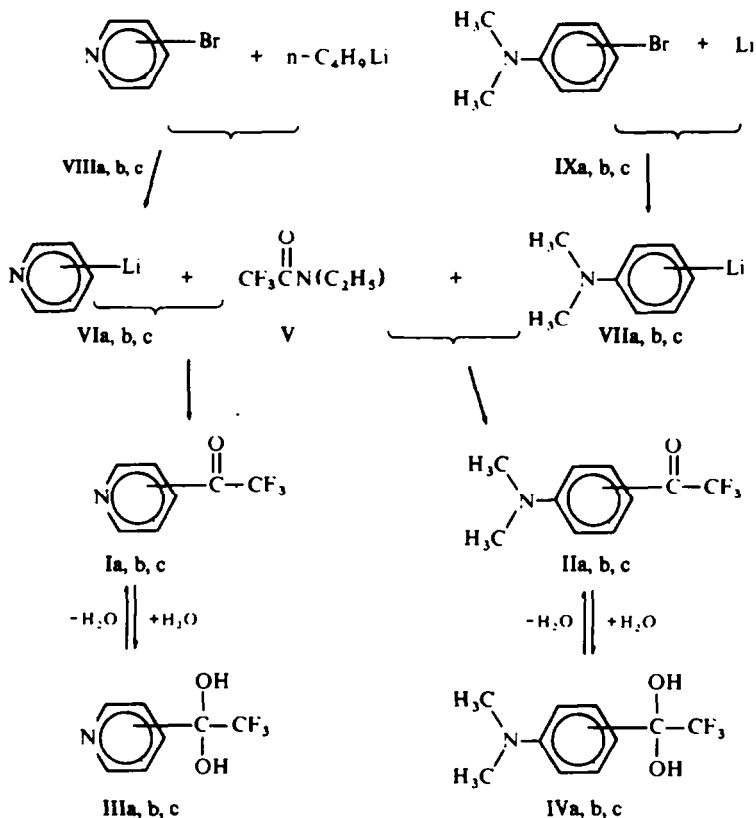
Syntheses

The syntheses were achieved according to Scheme I, by a method already described.⁴ Thus N,N-diethyl trifluoroacetamide (V) was reacted with an ethereal solution of the appropriate lithium derivatives at -70° (VIa, b, c, and VIIa, b, c). The lithium derivatives were themselves obtained from the corresponding bromopyridines (VIIIa, b, c) and bromo-N,N-dimethylanilines (IXa, b, c). The structures of the new compounds have been confirmed by IR and NMR spectroscopy, as well as by elemental analyses.

* To whom correspondence should be addressed

† Holder of a predoctoral scholarship of the National Research Council of Canada

‡ See Fig 1 for structural formula



SCHEME I

The letters a, b, and c correspond to ortho, meta, and para positions.

DISCUSSION

The *gem*-diols described in this paper are particularly stable. For instance, compounds IIIa and IIIc are recrystallizable from anhydrous solvents. Compound IIIc can be sublimed at 120° without loss of water. We believe that such a stability is not solely accounted for by the inductive effects of the trifluoromethyl radical. Middleton and Lindsey⁵ have shown that fluoroalcohols form with electron-rich atoms extremely strong H-bonds (6 kcal/mole). This property of fluoroalcohols allows them to form stable 1-1 complexes with bases such as dioxan, tetrahydrofuran, pyridine, and tetrahydrothiophene. The stability of these complexes is in fact a function of the acidity of the alcohols and the basicity of the involved bases. Like the fluoroalcohols, the OH functions of some trifluoromethylketone *gem*-diols have been estimated² to be quite acidic, and they should thus form strong H-bonds with basic atoms.

This susceptibility of the trifluoromethylketone *gem*-diols to form strong H-bonding interactions could explain the stability of TTA · H₂O, as well as that of the new *gem*-diols. In fact these *gem*-diols all contain basic atoms susceptible to intra- and intermolecular H-bonds with their hydroxylic hydrogens. TTA · H₂O would thus be stabilized by H-bonding with its CO group, whereas the new trifluoromethyl-

ketone *gem*-diols would be stabilized by similar bonding with their basic N atom (Fig 1).

Among the pyridyl *gem*-diols (III), compounds IIIa and IIIc are more stable than IIIb—as expected, because of the mesomeric effects of the pyridine ring. In the aniline series, the mesomeric effects of the anilyl radical compensate the inductive effects of the trifluoromethyl radical, and also reduce the basicity of the dimethylamino group. For that reason, the anilyltrifluoromethylketones (IIa, b, c) would not be expected to form stable *gem*-diols. In spite of this fact, the ketone IIa forms a crystalline *gem*-diol IVa. It is well known that a bulky *ortho*-substituent on an N,N-dimethylaniline

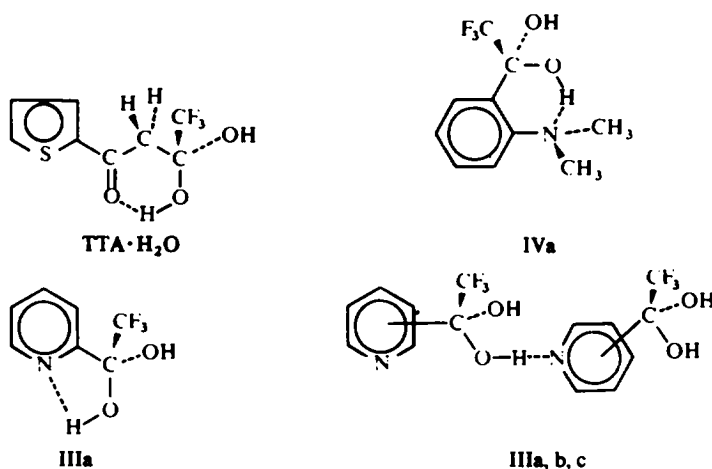


FIG 1. *gem*-Diols intra- and intermolecular H-bonding stabilization

increases its basicity because it twists the amino group out of plane, and thus reduces the mesomeric effects.⁶ A scale model of trifluoromethylketone (IVa) favours an out-of-plane position for its dimethylamino group whose enhanced basicity would then permit strong enough H-bonding in the *gem*-diol to allow its isolation in the pure state.

Spectroscopy

IR spectra. The IR spectra (nujol) of the four new *gem*-diols all showed strong and broad absorptions in the OH stretching region (3400 to 2500 cm⁻¹), which is suggestive of a strong association state of the OH groups.

The pyridyl *gem*-diol IIIa was soluble enough in chloroform for IR spectroscopy. In this solvent, the *gem*-diol is perfectly stable (i.e. no CO absorption was detectable). The pyridyl *gem*-diols IIIb and IIIc could not be dissolved in chloroform.

The anilyl *gem*-diol IVa is not stable in non-acceptor solvents such as carbon tetrachloride. In that solvent, no OH stretching vibrations were observed, but instead a strong CO band at 1695 cm⁻¹. However, this *gem*-diol is stabilized in an acceptor solvent such as THF, where its IR shows a broad OH absorption at

* The IR spectra were obtained with a Perkin-Elmer 257 IR Spectrophotometer

3250 cm^{-1} , and no CO absorption. This observation suggests that H-bonding of the OH groups of the new *gem*-diols with a strong acceptor atom such as their own basic nitrogen contributes largely to their stability.

*NMR spectra.** The NMR spectra of the new *gem*-diols were run either in acetone or in THF (Table 1).

TABLE I. POSITION OF NMR OH-ABSORPTION OF THE GEM-DIOLS

Compound	Solvent	p.p.m. from TMS
III a	acetone	6.95 (s)†
b	acetone	—
b	THF	7.38 (s)
c	THF	7.16 (s)
IV a	THF	9.1 (s) and 2.77 (s)

* 15% concentration

† (s) = singlet

In the pyridyl series, the OH functions of the *gem*-diols all showed as singlets, which rules out the possibility of strong intramolecular interactions such as presented in Fig 1 for IIIa, but which favours intermolecular interactions. The less stable *gem*-diol IIIb is stable in THF, but loses its mole of water in acetone, a fact which points out the importance of the stabilization-effect of H-bonding in the new *gem*-diols.

The only stable anilyl *gem*-diol (IVa) shows two nonequivalent OH groups suggesting an intramolecular interaction of one of its OH groups with the dimethyl-amino group, as shown in Fig 1.

EXPERIMENTAL

N,N-Diethyltrifluoroacetamide⁴

(b.p. 74–75° (43 mm), n_D^{25} 1.3795) was obtained by reacting diethylamine with trifluoroacetylchloride,⁷ which was prepared from benzoylchloride and trifluoroacetic acid. The yield of the amide was 48% (calculated from the starting trifluoroacetic acid).

2-Pyridyltrifluoromethylketone *gem*-diol

n-BuLi (0.15 mole in 100 ml ether) was prepared in a 500 ml 3-neck flask according to the procedure of Gilman *et al.*⁸ A soln of 2-bromopyridine (16 g, 0.1 mole in 100 ml ether) was then added to the BuLi soln according to the procedure of Wibaut *et al.*⁹ to afford a soln of 2-lithiopyridine. *N,N*-diethyltrifluoroacetamide (16 g, 0.1 mole) was then added dropwise (over 1 hr) to the mixture (cooled to –70°) and stirred for 2 additional hr at that temp. The content of the flask was then poured onto a mixture of conc HCl and crushed ice. The aqueous phase was separated and extracted twice with ether. It was then cooled and basified with 20% NaOH aq. The soln was then transferred into a liquid-liquid extractor and extracted with ether for 24 hr. The ethereal extract was concentrated and the residue distilled under reduced pressure. We thus obtained 2-pyridyltrifluoromethylketone, b.p. 92–102° (68 mm). Its IR spectrum (CCl_4) showed a CO band at 1735 cm^{-1} . The 2-pyridyltrifluoromethylketone was rapidly transformed into its *gem*-diol by absorption of atmospheric moisture. The 2-pyridyltrifluoromethylketone *gem*-diol (12 g for 62% yield) was recrystallized from *n*-hexane, m.p. 64–66°; IR (Nujol) broad absorption at 3225 cm^{-1} for OH. (Found: C, 43.30; H, 3.46; N, 7.46. Calcd for $\text{C}_7\text{H}_6\text{O}_2\text{NF}_3$: C, 43.53; H, 3.13; N, 7.25%).

* PMR spectra were obtained with a Jeol 60 MHz spectrophotometer. Spectra were calibrated in terms of lower field displacement in p.p.m. from the proton resonance of TMS used as internal reference.

3-Pyridyltrifluoromethylketone gem-diol

A soln of 3-bromopyridine (16 g, 0.1 mole in 25 ml ether) was added to a soln of n-BuLi (0.15 mole in 100 ml ether) according to Wibaut *et al.*¹⁴ to give a soln of 3-lithiopyridine. This soln was cooled to -70° and N,N-diethyltrifluoroacetamide (16.9 g, 0.1 mole) was added dropwise for 1 hr. The reaction was then kept at that temp for 2 hr, hydrolyzed, and worked up as described. The 3-pyridyltrifluoromethylketone distilled at $98-100^{\circ}$ (68 mm). Its IR spectrum (CCl_4) showed a CO band at 1725 cm^{-1} . The free ketone was transformed into its gem-diol overnight, by absorption of atmospheric moisture. The 3-pyridyltrifluoromethylketone gem-diol thus obtained (13.4 g for 69.4% yield) is an amorphous solid, m.p. $93-96^{\circ}$. Its IR spectrum (Nujol) showed a broad absorption at 3480 cm^{-1} for OH. (Found: C, 43.26; H, 3.25; N, 7.60. Calcd. for $\text{C}_7\text{H}_6\text{O}_2\text{NF}_3$: C, 43.53; H, 3.13; N, 7.25%.)

4-Pyridyltrifluoromethylketone gem-diol

A soln of 4-bromopyridine¹⁰ (16 g, 0.1 mole in 200 ml ether) was added to a soln of n-BuLi (0.15 mole in 100 ml ether) according to Wibaut and Herringa¹¹ to obtain a soln of 4-lithiopyridine. N,N-diethyltrifluoroacetamide (16.9 g, 0.1 mole) was then added dropwise (for 2 hr) to the Li-derivative soln (cooled to -75°). The mixture was stirred at that temp for an additional 4 hr, hydrolyzed and extracted for 48 hr as described. The ethereal extract was concentrated to dryness, and the residue (11 g for 57% yield) consisted of the 4-pyridyltrifluoromethylketone gem-diol. It was purified either by sublimation at 120° or by recrystallization from EtOAc. Its IR spectrum (nujol) showed absorption bands at 3300 and 2500 cm^{-1} for OH. (Found: C, 43.59; H, 3.25; N, 7.47. Calcd. for $\text{C}_7\text{H}_6\text{O}_2\text{NF}_3$: C, 43.53; H, 3.13; N, 7.25%.)

N,N-Dimethylanilyl-2-trifluoromethylketone gem-diol

To a suspension of Li sand (0.20 mole) in 60 ml ether was added 5 ml of a soln of 2-bromo N,N-dimethylaniline¹² (20 g, 0.1 mole) in 75 ml ether. The resulting soln was then refluxed until a reaction was initiated, and this maintained by the controlled addition of the remaining halide soln. When all the halide had been added, the mixture was refluxed for an additional 2 hr. It was then cooled to -70° , and N,N-diethyltrifluoroacetamide added over a period of 2 hr. After this addition, the mixture was stirred at that temp for 3 hr, hydrolyzed, and extracted as described. The ethereal extract was concentrated to dryness, and the solid yellow residue yielded, after washing with ligroin, N,N-dimethylanilyl-2 trifluoromethylketone gem-diol (17.4 g for 74% yield), m.p. $74-76^{\circ}$. Its IR spectrum (nujol) showed a broad absorption band at 3215 cm^{-1} for OH. (Found: C, 50.81; H, 5.11; N, 6.15. Calcd. for $\text{C}_{10}\text{H}_{12}\text{O}_2\text{NF}_3$: C, 51.06; H, 5.14; N, 5.95%.)

N,N-dimethylanilyl-3-trifluoromethylketone

This compound was obtained in a 69.2% yield from 3-bromo-N,N-dimethylaniline¹² and N,N-diethyltrifluoroacetamide reacted under the same conditions and molar concentrations as for its isomer of position 2. N,N-dimethylanilyl-3-trifluoromethylketone is a yellow liquid, b.p. $74-76^{\circ}$ (1 mm), n_D^{25} 1.5259. Its IR spectrum (CCl_4) showed a CO band at 1715 cm^{-1} . It was characterized as its oxime derivative, m.p. $90-91^{\circ}$ (from n-hexane). (Found: C, 51.88; H, 5.12; N, 11.86. Calcd. for $\text{C}_{10}\text{H}_{11}\text{N}_2\text{OF}_3$: C, 51.72; H, 4.77; N, 12.06%.)

N,N-dimethylanilyl-4-trifluoromethylketone

This ketone was obtained in a 65% yield from 4-bromo-N,N-dimethylaniline and N,N-diethyltrifluoroacetamide under the conditions and molar concentrations as described for its isomers. N,N-dimethylanilyl-4-trifluoromethylketone is a yellow solid, m.p. $75-75.5^{\circ}$ (ligroin), its IR spectrum (CCl_4) showed a CO band at 1695 cm^{-1} . (Found: C, 55.46; H, 4.82; N, 6.50. Calcd. for $\text{C}_{10}\text{H}_{10}\text{ONF}_3$: C, 55.30; H, 4.64; N, 6.44%.)

REFERENCES

- 1 D. R. Husted and D. L. Ahlbrecht, *J. Am. Chem. Soc.* **74**, 5422 (1952)
- 2 R. Stewart and R. Van der Linden, *Canad. J. Chem.* **38**, 399 (1960)
- 3 E. L. King and W. H. Reas, *J. Am. Chem. Soc.* **73**, 1806 (1951)
- 4 N. A. Zaitseva, E. M. Panov and K. A. Kocheshkova, *Translation of Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk* **5**, 831 (1961)

- ⁵ W. J. Middleton and R. V. Lindsey Jr, *J. Am. Chem. Soc.* **86**, 4948 (1964)
- ⁶ G. Girault-Vexleaschi, *Bull. Soc. Chim. Fr* 589 (1956)
- ⁷ A. L. Henne, R. M. Alm and M. Smook, *J. Am. Chem. Soc.* **70**, 1968 (1948)
- ⁸ H. Gilman, J. A. Bell, C. G. Brannen, M. W. Bullock, G. E. Dunn and L. S. Miller, *J. Am. Chem. Soc.* **71**, 1499 (1949)
- ⁹ J. P. Wibaut, A. P. De Jonge, P. Ph. Van der Voort Otto and H. L. Otto, *Rec. Trav. Chim.* **70**, 1054 (1951)
- ¹⁰ A. Murray and R. H. Langham, *J. Am. Chem. Soc.* **74**, 6289 (1952)
- ¹¹ J. P. Wibaut and L. G. Hoering, *Rec. Trav. Chim.* **74**, 1003 (1955)
- ¹² H. Gilman and I. Banner, *J. Am. Chem. Soc.* **62**, 344 (1940)