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The Chemistry of Pyrazine and its Derivatives. XII. The Reaction of Acetonylpyrazine with Phenyllithium in the Presence and Absence of Methyl Benzoate

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The reaction of acetonylpyrazine with phenyllithium in the absence and presence of methyl benzoate gives (a) 2-phenyl-6-acetonylpyrazine (IV) and (b) a mixture of IV and 3-(2-phenyl-6-pyrazyl)-4-phenylbutane-2,4-dione (V, VI), respectively. Evidence in support of the structures of the products has been presented and comments on their formation are made.

Hauser and Harris (2) have benzoylated the dianions of the β-diketones, acetylacetone (Ia) and benzoylacetone (Ib), at their terminal methyl groups

$$RCH_2COCH_2COR'$$

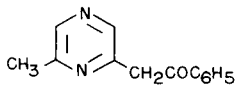
Ia: R = H, R' = CH_3 Ic: R = C_6H_5CO, R' = CH_3

Ib: R = H, R' = C_6H_5 Id: R = C_6H_5CO, R' = C_6H_5

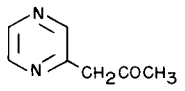
with ethyl benzoate using potassium amide in liquid ammonia as the condensing agent to give the triketones, Ic and Id, respectively.

Using the idea that the pyrazine ring of 2-methyl-6-phenacylpyrazine, II, might be expected to labilize the hydrogen atoms of the 2-methyl group in much the same way that a carbonyl group in Ia and Ib activates the hydrogen atoms of an adjacent methyl moiety to attack by a basic reagent, Kamal and Levine (3) found that the dianion of II can be acylated to give the corresponding 2-acylmethyl-6-phenacylpyrazines in good to high yields. More recently we have found (4) that the dianions of several acylmethyltrimethylpyrazines can be acylated to give good yields of 2,6-diacylmethyl-3,5-dimethylpyrazines. Additionally, Dimmig and Levine (5) have acylated the methyl group of 2-methyl-6-phenacylpyridine with a variety of aliphatic, aromatic and heterocyclic esters. Based on this earlier work and the facts that acetonylpyrazine, III, gives both an enol test with alcoholic iron(III) chloride solution (6) and a copper chelate with copper(II) acetate (6), it appears reasonable to compare III in a purely formal sense to a 1,3-dicarbonyl system. It was therefore of interest (1) to determine whether III can be acylated with an ester such as methyl benzoate under basic conditions and (2) to determine, if acylation occurred, where the benzoyl moiety was introduced into III. It should be pointed out that an attempt (3) to use methyl benzoate to acylate the monoanion of II, presumably formed by the abstraction of a proton from its methylene group by sodium amide in liquid ammonia which was used as the condensing agent, failed, probably among other reasons, because this anion is too weak a base to displace the alkoxide ion from the ester molecule. However, II was benzoylated at its methyl group in 81% yield via its dianion (3).

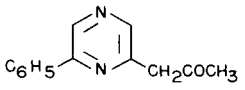
In the present study no acylation product was obtained from the interaction of a 2:1:1 molar ratio of sodium amide in liquid ammonia to III to methyl



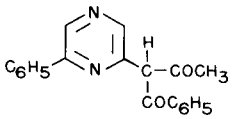
II



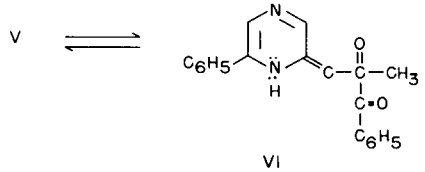
III



IV



V



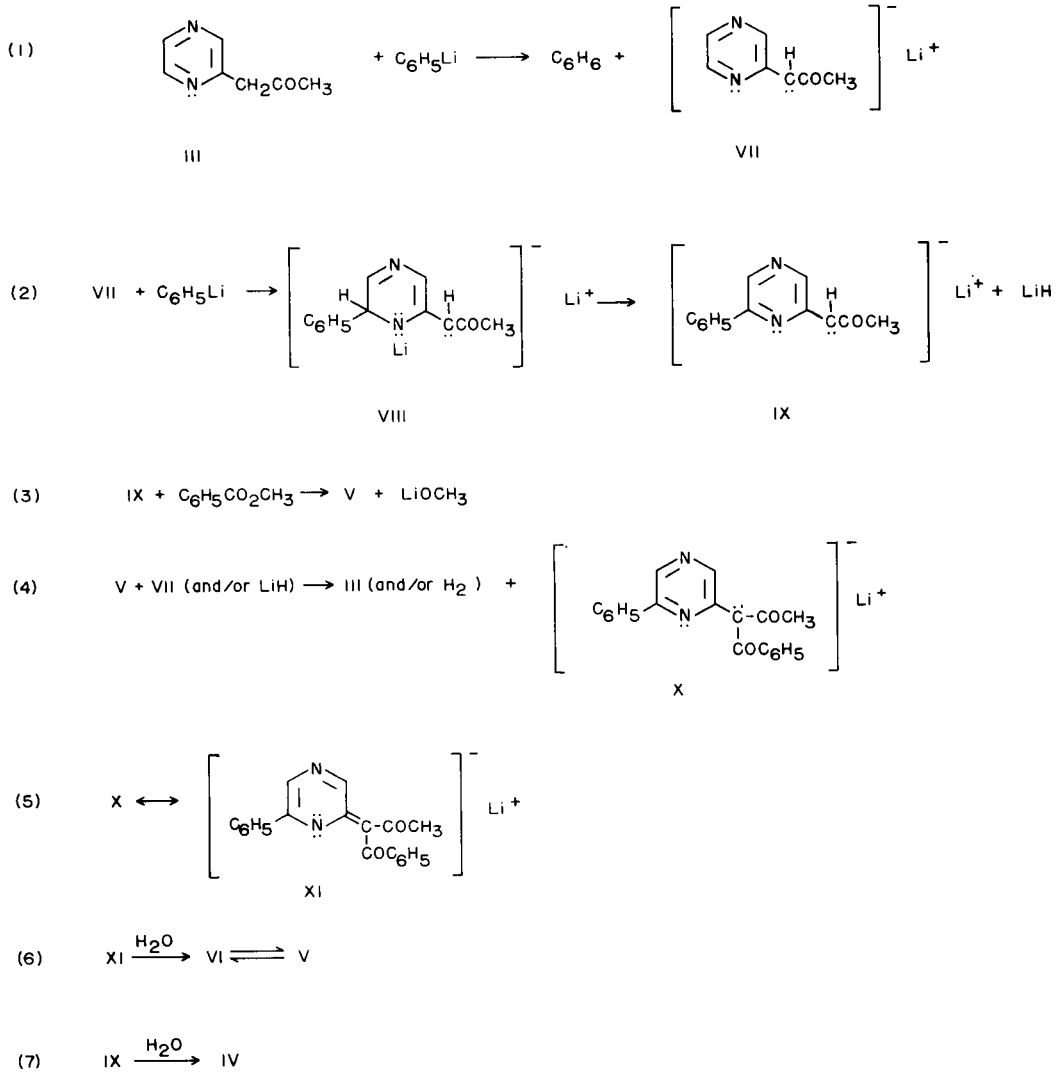
VI

benzoate. The monoketone (III, 77.0%), ester (32.4%) and benzamide (57.0%) were isolated. Because such a large amount of benzamide was formed and since we have found that methyl benzoate is not readily ammonolyzed by liquid ammonia alone, it appears that under the reaction conditions employed, the dianion of III is not formed to an appreciable extent and the excess sodium amide reacts with the ester to give benzamide. Under similar reaction conditions 2-acetonylpyridine (78%) was recovered and at least 69% of the ester was converted to benzamide.

The last two reactions were repeated using phenyllithium in ether in place of sodium amide in liquid ammonia as the condensing agent. Again, the attempted acylation of 2-acetonylpyridine failed. However, two products were isolated from the acetonylpyrazine reaction, *i.e.* (a) an azomethine addition product, 2-phenyl-6-acetonylpyrazine (IV, 26.4%) and (b) the azomethine addition-acylation product, the diketone, 3-(2-phenyl-6-pyrazyl)-4-phenylbutane-2,4-dione (V, 21.5%). Also, the reaction of III with phenyllithium in the absence of methyl benzoate gave IV in 22.6% yield.

In addition to making use of elemental analysis, the structure of IV was established partly from spectral data (*viz.*, its infrared spectrum indicates

SCHEME I



the presence of an acetyl group and its n.m.r. spectrum shows the presence of methyl, methylene and phenyl groupings with the disappearance of one pyrazine ring hydrogen atom) and partly from the fact that position-6 in a monosubstituted pyrazine is the most reactive site for nucleophilic attack (7) ---- the reaction which is involved in the azomethine addition of phenyllithium to III.

Spectral data and elemental analysis were also used in elucidating the structure of the diketone, V. Its infrared spectrum has bands at 1630 cm^{-1} and 1650 cm^{-1} which suggest the presence of a 1,3-dicarbonyl system and a band of medium intensity at 1350 cm^{-1} which suggests the presence of an acetyl group. Its ultraviolet spectrum is similar to that of phenacylpyrazine with shifts to longer wave lengths from 247 mμ to 257 mμ and from 360 mμ to 370 mμ. These shifts are expected from the extension of conjugation by phenyl substitution at the pyrazine ring as well as from conjugation in the enol form of the 1,3-diketone. The bands at 247 mμ and 360 mμ have been assigned (8) to the π-π^* transitions in phenacylpyrazine and its enol form, respectively.

However, the assignment of structure V to the diketonic product is not in complete agreement with the n.m.r. data. Although, the ratio of the integrated peak areas of the methyl hydrogen atoms to the phenyl hydroge atoms is 3:9.96 (which is very close to the expected value of 3:10 for V) and the signals for α-methylene hydrogen atoms (τ = 6.08–6.14 p.p.m.) were missing, the signals for the pyrazine ring hydrogen atoms (τ = 1.5-1.7 p.p.m.) were also missing in the spectrum. Instead, three more signals in the low field region (τ = 3.80, 4.18 and 4.68 p.p.m.) with a ratio of the integrated peak areas nearly 1:1:1 (*viz.*, 1.0:0.996:0.85) were observed. Taken together all the spectral data suggest that (1) the diketone, V, is in equilibrium with the tautomeric structure VI and (2) the diketone exists probably predominantly in form VI as shown by the equation V ⇌ VI.

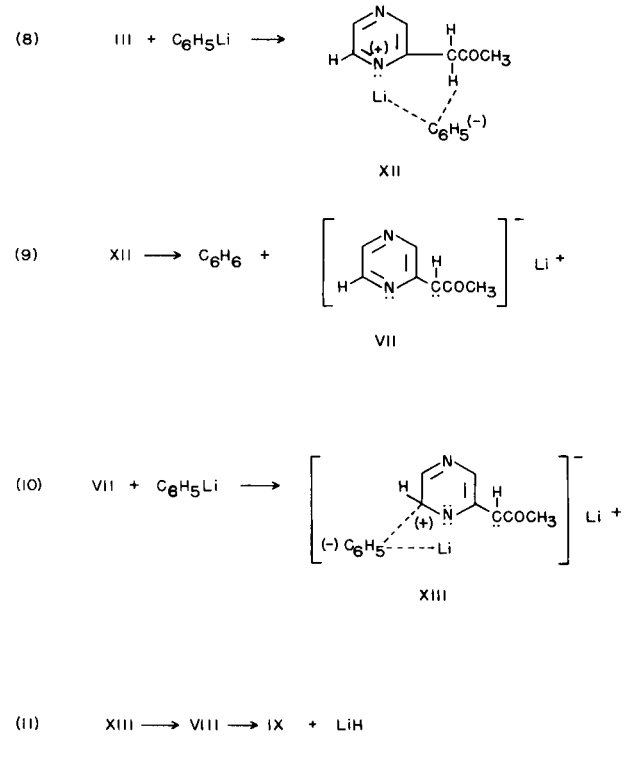
Assuming that the diketone consists of the tautomeric structures (V, VI) and recalling, *vide supra*, that IV was isolated from the reaction of III with phenyllithium in the absence of methyl benzoate, Scheme I is suggested for the formation of IV and (V, VI).

First, an acid base reaction occurs (equation 1) between III and phenyllithium to give VII, which reacts with more phenyllithium (equation 2) to give the anion of the azomethine addition product, IX, via VIII. Then, IX is benzoylated (equation 3) to give the diketone, V, which is converted to its anion, X, by reaction (equation 4) with part of VII and/or lithium hydride with the concomitant formation of some of III and/or hydrogen. The diketone anion, which is a resonance hybrid of X and XI (equation 5) is converted on hydrolysis (equation 6) to the tautomeric system (V, VI). The anion, IX, is hydrolyzed (equation 7) to the azomethine addition product, IV.

The question arises as to why acetonylpyrazine, III, undergoes azomethine addition when treated with phenyllithium in refluxing ether and 2-acetonylpyridine does not give an azomethine product when treated similarly. A more detailed examination of the probable course of the reaction between III and phenyllithium (Scheme II) may aid in shedding light on this point.

First, III is envisioned (equation 8) as reacting with phenyllithium to give the cyclic complex, XII, which loses benzene (equation 9) to give the anion, VII. This reaction appears reasonable because of the well known coordinating properties of the potential lithium cation of phenyllithium and the high acidity of the methylene hydrogen atoms of III. A similar reaction no doubt occurs between phenyllithium and acetonylpyridine. Then, phenyllithium reacts with VII to give XIII (equation 10). This complex gives the azomethine intermediate, VIII, which loses lithium hydride to give the anion of the azomethine product, IX, (equation 11). It appears that as complex formation occurs between phenyllithium and VII to give XIII, the positive charge which has developed at carbon-6 as a result of the polarization of the -C=N- bond of the pyrazine ring is intensified sufficiently in an inductive manner by the meta-nitrogen atom so that the potential phenyl anion of phenyl-

SCHEME II



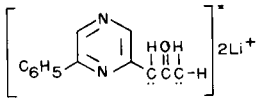
lithium forms a covalent bond with carbon-6 to give VIII. Then, VIII restores the aromaticity of the pyrazine ring with the concomitant loss of lithium hydride and gives IX. Apparently in the comparable reaction involving 2-acetonylpyridine, carbon-6 is not sufficiently electron deficient for the pyridine analogue of XIII to be formed to an appreciable extent and hence none of the pyridine analogue of IX (via the pyridine analogue of VIII) is formed under the relatively mild reaction conditions, *i.e.*, in refluxing ether for three hours. In this connection it is of interest to note that in order to obtain 2-phenylpyridine (40-49% yield), the azomethine addition product of phenyllithium to pyridine, the reaction is effected under more drastic reaction conditions, *viz.*, in toluene at 110° for eight hours (9). However, 2,5-dimethylpyrazine undergoes azomethine addition under considerably milder conditions, *i.e.*, its reaction with phenyllithium gives 2,5-dimethyl-6-phenylpyrazine (25.2% yield) at ice-bath temperature (10).

It is now necessary to attempt to explain why the diketonic product (V, VI) arises from the introduction of a benzoyl function at the methinyl carbon of IX (equation 3) rather than at the methyl group since it is conceivable that part of the phenyllithium which is present or the lithium hydride (from equation 2) could form the dianion, XIV, from IX. If XIV is indeed formed, it can be argued, *â priori*, that acylation might be expected to occur at the more basic terminal carbon atom to give XV rather than (V, VI).

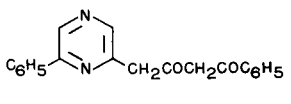
This point is particularly important since as has been mentioned, *vide supra*, the monoanion of 2-methyl-6-phenacylpyrazine (formed at the methylene group) is not benzoylated by methyl benzoate but the dianion is benzoylated at the 6-methyl group to give XVI (3).

If one looks at structures (V, VI) which arise from the benzoylation of IX at the methinyl carbon atom, it can be seen that VI is highly stabilized by extended cross conjugation between the $CH_3COC=$ and the $C_6H_5COC=$ functions and the phenylated dihydropyrazine ring. In addition, two enol forms (XVII and XVIII) involving the methinyl hydrogen atom of V can be envisioned. These are also stabilized by cross conjugation. However, had benzoylation occurred at the terminal methyl group of IX, *i.e.*, at the methylene group of XIV to give XV, then although XV can be conjugatively stabilized by three enolic structures and a tautomeric structure analogous to VI, none of these is extensively conjugated or cross conjugated and hence might be expected to be less stable than (V, VI).

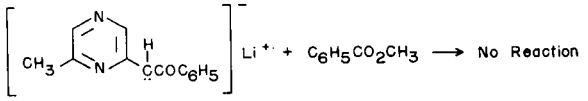
A somewhat similar argument can be presented to suggest why 2-methyl-6-phenacylpyrazine is benzoylated at its methyl group to give XVI rather than at its methylene group to give XIX. It can be seen that both of the enolic sights in the dienol of XVI can be stabilized by conjugation with the pyrazine ring. Also, although the monoenol of XIX can be stabilized by cross conjugation one might argue that the extent of this stabilization should probably be less than that which would be expected from the dienol of XVI. Thus, on the basis of the arguments which have been presented, the facts that 2-methyl-6-phenacylpyrazine is benzoylated at its methyl group to give XVI, m.p. 142-143° (3); and its isomer, 2-phenyl-6-acetonylpyrazine, is benzoylated at its methylene group to give (V, VI), m.p. 204-207°, can be rationalized.

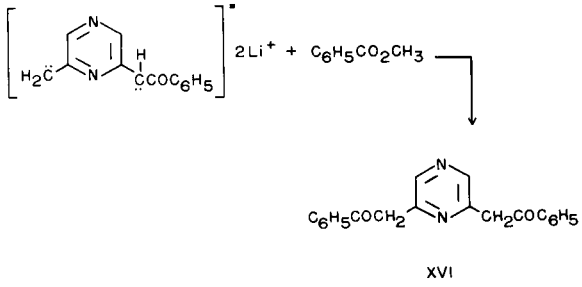


XIV

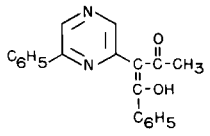


XV

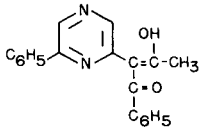




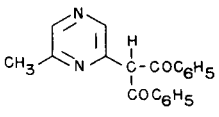
XVI



XVII



XVIII



XIX

EXPERIMENTAL

2-Phenyl-6-acetonylpyrazine, IV.

Acetonylpyrazine (6) (6.8 g., 0.05 mole in 25 ml. of anhydrous ether) was added to phenyllithium (prepared from lithium ribbon (1.4 g., 0.2 mole)) and bromobenzene (16.2 g., 0.1 mole in 200 ml. of anhydrous ether) over a 15-minute period and the reaction mixture was refluxed for 3 hours. The mixture was poured onto a slurry of ice and hydrochloric acid, neutralized with sodium bicarbonate and extracted with several portions of chloroform. The combined ether phase and chloroform extracts were dried over anhydrous sodium sulfate, the solvents were removed at atmospheric pressure and the residue was distilled in vacuum to give 2-phenyl-6-acetonylpyrazine (IV, 2.4 g., 22.6%, b.p. 133-135° at 0.5 mm., *Anal.* Calcd. for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70. Found: C, 73.53; H, 5.65) and 3.8 g. of tarry, non-distillable residue. The following spectral data on the product were obtained: (1) the infrared spectrum determined in chloroform shows bands at 1700 cm^{-1} (C=O stretching), 1600 cm^{-1} (C C in-the-plane vibration) and 1350 cm^{-1} (CH_3 deformation for $CH_3C=O$), (2) the n.m.r. spectrum determined in carbon tetrachloride using tetramethylsilane as an internal standard shows the presence of 3 α-CH_3 protons at τ = 7.92 p.p.m.; 2 α-CH_2 protons at τ = 6.14 p.p.m.; 2 pyrazine ring protons at τ = 1.50-1.65 p.p.m. and 5 protons of the phenyl group at τ = 2.50-2.70 p.p.m. For comparative purposes the n.m.r. spectrum of acetonylpyrazine was obtained similarly and indicated the presence of 3 α-CH_3 protons at τ = 7.84 p.p.m., 2 α-CH_2 protons at τ = 6.08 p.p.m. and 3 pyrazine ring protons at τ = 1.50-1.70 p.p.m.

The Mixture of IV and the Tautomeric Pair (V, VI).

The last experiment was repeated except that methyl benzoate (6.2 g., 0.05 mole in 25 ml. of anhydrous ether) was added after the initial 3-hour reflux period and the reaction mixture was stirred for 2 hours at 25-30°. Processing the reaction mixture gave: methyl benzoate (2.0 g., 32.0%, b.p. 73.0-75.0° at 9.0 mm.); acetonylpyrazine (3.0 g., 43.0%, b.p. 112.0-114.0° at 10 mm.); IV (0.8 g., b.p. 130.0-135.0° at 0.5 mm.) and 6.2 g. of a semi-solid residue. On recrystallization from absolute ethanol this semi-solid gave the tautomeric pair 3-(2-phenyl-6-pyrazyl)-4-phenylbutane-2,4-dione (V, VI) (3.4 g., 21.5%, m.p. 204-207°) and IV (2.0 g., b.p. 133-135° at 0.4 mm.). The total yield of IV is thus 2.8 g. (26.4%) and its infrared and n.m.r. spectra are identical with those of the material discussed in the last experiment. The diketone (V, VI) gave the following analytical data: *Anal.* Calcd. for $C_{20}H_{18}N_2O_2$: C, 75.93; H, 5.10. Found: C, 75.73; H, 5.18. Spectral data (see discussion section) were used in elucidating the structure of the diketone.

REFERENCES

(1) This work is based on part of the thesis presented by S.K.C. to the Graduate Faculty of the University of Pittsburgh in partial fulfillment of the requirements for the Ph.D. degree. Part of this work was done under Contract No. AT(30-1)-670 between the U. S. Atomic Energy Commission and the University of Pittsburgh.

(2) C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, 80, 6360 (1958).

(3) M. R. Kamal and R. Levine, *J. Org. Chem.*, 29, 191 (1964).

(4) S. K. Chakrabartty and R. Levine, *J. Heterocyclic Chem.*, 1, 196 (1964).

(5) D. A. Dimmig and R. Levine, Unpublished Observations, University of Pittsburgh.

(6) J. D. Behun and R. Levine, *J. Am. Chem. Soc.*, 81, 5157 (1959).

(7) This has been determined by molecular orbital calculations. These and a number of other calculations on other systems will appear in another paper.

(8) N. Naqvi, E. L. Amma, Q. Fernando and R. Levine, *J. Phys. Chem.*, 65, 218 (1961).

(9) J. C. W. Evans and C. F. H. Allen, *Org. Synth.*, Coll. Vol. II, p. 517.

(10) B. Klein and P. E. Spoerri, *J. Am. Chem. Soc.*, 72, 1844 (1950).

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