# The Chemistry of Pyrazine and Its Derivatives. VIII. Diketones Derived from the Monoacylation of 2-Methyl-6-(acylmethyl)pyrazines and the Diacylation of 2,6-Dimethylpyrazine[1]

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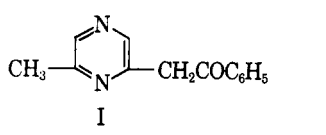
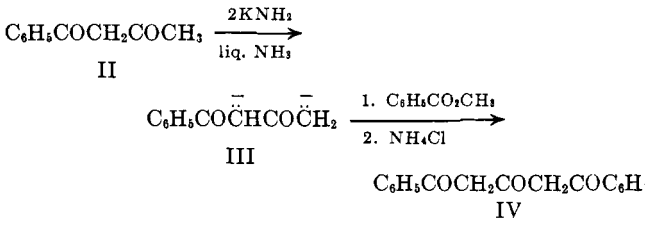
2,6-Bis(acylmethyl)pyrazines have been synthesized by (A) the monoacylation of 2-methyl-6-acylmethylpyrazines and (B) the direct lateral diacylation of 2,6-dimethylpyrazine using sodium amide in liquid ammonia as the condensing agent. Method A gives diketones in which the acylmethyl groups may be the same or different depending on the acylating ester while both of the acylmethyl groups in the diketones prepared by method B must be identical. When the same product is produced by both routes, method A gives the higher yield.

It has been demonstrated in these laboratories that 2-methyl-6-pyrazylmethylsodium, prepared by the reaction of 2,6-dimethylpyrazine with sodium amide in liquid ammonia, can be acylated[3] with esters to give 2-methyl-6-acylmethylpyrazines, alkylated[3] with alkyl halides to give 2-methyl-6-alkylpyrazines, and condensed with aldehydes and ketones[4] to give 2-methyl-6-pyrazylmethylcarbinols.

2-Methyl-6-phenacylpyrazine (I) is a typical 2-methyl-6-acylmethylpyrazine. It is structurally analogous to a β-diketone except that it contains an azomethine function of the ring in place of one of the carbonyl groups of the β-diketone. Hauser, *et al.*,[5,6] have shown that the β-diketones, acetylacetone and benzoylacetone, can be acylated with esters at a terminal methyl group by using *two equivalents* of potassium amide in liquid ammonia as the condensing agent for *each equivalent of β-diketone*. These workers envision the reactions as involving a dianion intermediate, *e.g.*, III. The benzoylation of benzoylacetone (II) to give the triketone (IV) illustrates this work.



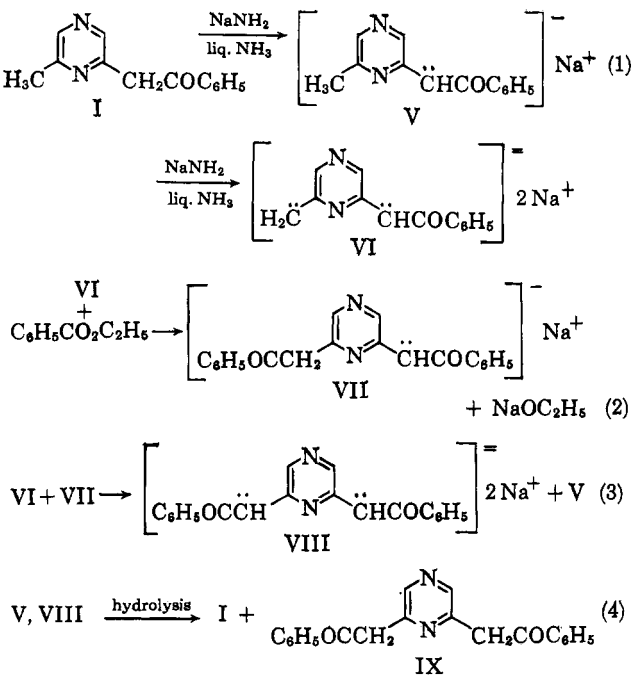
I



II III IV

It was, therefore, of interest to determine whether it would be possible to acylate 2-methyl-6-phenacylpyrazine (I) at its methyl group. In this compound the methyl hydrogen atoms may be considered as being activated by an azomethine function of the pyrazine ring towards anionic attack in much the same way that the methyl hydrogen atoms of benzoylacetone are activated by the adjacent carbonyl group. Both of these compounds may be regarded as fitting the general formula, $CH_3ZCH_2COR$, where R is the phenyl group and Z is the pyrazine ring or the carbonyl group.

As an orienting reaction, the benzoylation of 2-methyl-6-phenacylpyrazine (I) with ethyl benzoate was studied using sodium amide in liquid ammonia as the condensing agent. This reaction failed when a 1:1:1 molar ratio of sodium amide:I:ester was employed and most of the ester and ketone were recovered. However, when a 2:1:1 molar ratio of sodium amide:I:ester was used, an 81.0% yield of 2,6-diphenacylpyrazine (IX) was obtained assuming the reaction follows the course shown in the accompanying scheme. In addition, 49.5% of I was recovered.



I V (1)

V VI (2)

VI + C6H5CO2C2H5 → VII + NaOC2H5

VI + VII → VIII + V (3)

V, VIII → I + IX (4)

It is suggested that, in step 1, I and sodium amide react to give the dianion VI, with monoanion V as an intermediate. Then, in step 2, VI is acylated at its methylene carbanion to give the monoanion VII of the diacylated product. Apparently monoanion V, which would be the expected product, *vide supra*, from the interaction of equivalents of I and sodium amide (since the methylene hydrogen atoms of I are more acidic than its methyl hydrogen atoms) is not sufficiently basic to displace an alkoxide ion from an ester molecule. Hence, V is not acylated, *vide infra*, to give 2-dibenzoyl-

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(2) This paper is based on part of a thesis presented by M. R. Kamal to the graduate faculty of the University of Pittsburgh in partial fulfillment of the requirements of the Ph.D. degree.

(3) M. R. Kamal and R. Levine, *J. Org. Chem.*, **27**, 1355 (1962).

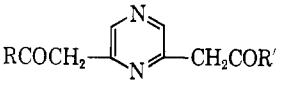
(4) M. R. Kamal and R. Levine, *ibid.*, **27**, 1360 (1962).

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

(6) R. J. Light and C. R. Hauser, *J. Org. Chem.*, **25**, 538 (1960).

TABLE I

2,6-BIS(ACYLMETHYL)PYRAZINES OF THE TYPE

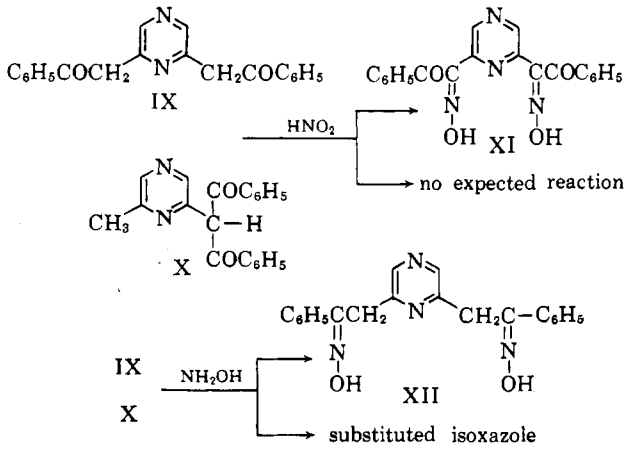


| Compound | R | R′ | Yield, % | M.p. or b.p. (mm.), °C. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|
| 1 | $C_6H_5$ | $C_6H_5$ | 81.0[a,b] 38.5[c,d] | 141–142[e] | $C_{20}H_{16}N_2O_2$ | 75.39 | 76.02 | 5.07 | 5.51 |
| 2 | $C_2H_5$ | $C_2H_5$ | 75.4[a,f] | 64.6–65.4[g] | $C_{12}H_{16}N_2O_2$ | 65.43 | 65.76 | 7.32 | 7.62 |
| 3 | $i$-$C_3H_7$ | $i$-$C_3H_7$ | 42.0,[a,h] 0.6[c,i] | 154–156 (0.9) | $C_{14}H_{20}N_2O_2$ | 67.71 | 67.44 | 8.12 | 8.15 |
| 4 | $t$-$C_4H_9$ | $t$-$C_4H_9$ | 19.8,[a,j] 21.0[a,k,l] | 146–147 (0.4) | $C_{16}H_{24}N_2O_2$ | 69.53 | 69.59 | 8.75 | 9.06 |
| 5 | $t$-$C_4H_9$ | 4-$C_5H_4N$[m] | 97.6[a,n,o] | 113.6–114.6[p] | $C_{17}H_{19}N_3O_2$ | 68.67 | 69.22 | 6.44 | 6.64 |
| 6 | $C_2H_5$ | $t$-$C_4H_9$ | 47.0[a,n,q] | 146–149 (0.5) | $C_{14}H_{20}N_2O_2$ | 67.70 | 67.14 | 8.12 | 8.31 |
| | | | | Dioximes | | | | | |
| 1a | | | | 171.5–172.2 | $C_{20}H_{18}N_4O_2$ | 69.34 | 68.90 | 5.24 | 5.44 |
| 2a | | | | 102.6–103.2 | $C_{12}H_{18}N_4O_2$ | 57.58 | 57.79 | 7.25 | 7.36 |
| 3a | | | | 106.2–106.6 | $C_{14}H_{22}N_4O_2$ | 60.41 | 60.67 | 7.97 | 8.19 |
| 4a | | | | 166.4–167.0 | $C_{16}H_{26}N_4O_2$ | 62.71 | 62.37 | 8.55 | 8.73 |
| 5a | | | | 177–178 | $C_{17}H_{21}N_5O_2$ | 21.50[r] | 21.52 | | |
| 6a | | | | 109.8–110.6 | $C_{14}H_{22}N_4O_2$ | 20.13[r] | 20.01 | | |

[a] Starting with the 2-methyl-6-(acylmethyl)pyrazine. [b] 49.5% of 2-methyl-6-phenacylpyrazine (A) was recovered. [c] Starting with 2,6-dimethylpyrazine. [d] 25.4% of A, m.p. 50–52° (see ref. 3), also was isolated. [e] Recrystallized from an acetone–water mixture. [f] 40.3% of 2-methyl-6-(propionylmethyl)pyrazine, b.p. 82–88° at 0.7 mm. (see ref. 3), was recovered. [g] Recrystallized from an ether–pentane mixture. [h] 45.0% of 2-methyl-6-(isobutyrylmethyl)pyrazine (B), b.p. 92–96° at 0.9 mm. (see ref. 3), and 33.3% of isobutyramide (C), m.p. 127–128°, alone and when mixed with an authentic sample, also were isolated. [i] 36.2% of B and 41.9% of C also were isolated. [j] 53.7% of 2-methyl-6-(pivalylmethyl)pyrazine (D), b.p. 102–106° at 1.0 mm. (see ref. 3), and 4.2 g. (46.0%) of pivalamide (E), m.p. 153–154°, alone and when mixed with an authentic sample, also were isolated. [k] Three hours were allowed for converting the starting pyrazine compound to its anion. In all other cases, a one-half hour anion time was used. [l] 73.5% of D and 33.6% of E also were isolated. [m] 4-$C_5H_4N$ = 4-pyridyl radical. [n] Starting with D. [o] 32.8% of D was recovered. [p] Recrystallized from a benzene–pentane mixture. [q] 60.8% of D was recovered. [r] Nitrogen analysis.

methyl-6-methylpyrazine (X), an isomer of the product, 2,6-diphenacylpyrazine (XI), during the interaction of equivalents of the reactants. In step 3, VI reacts with VII to form the dianion VIII of the diacylated product and the monoanion V of the starting material. Finally, on hydrolysis (step 4) the monoketone I and the diketone IX are formed. Thus, one-half of I is regenerated in steps 3 and 4 and only one-half a mole of diketone can be obtained from each mole of starting ketone.

That the compound formed by the benzoylation of I is indeed IX and not its isomer X was shown by (1) nitrosating the product and obtaining 2,6-bis(1-oximinophenacyl)pyrazine[7] (XI) and (2) converting a sample of the product to its dioxime (XII) by reaction with hydroxylamine. These two reactions would not be expected to take place if the product were X since such a $\beta$-diketone could not be dinitrosated readily and it would be expected to give a substituted isoxazole when treated with hydroxylamine.[8]




Five other 2,6-bis(acylmethyl)pyrazines (Table I) of the general formula, 2-RCOCH$_2$PzCH$_2$COR′-6 (where Pz = the pyrazine ring) also were prepared. Three of these diketones (compounds 2–4) like 2,6-diphenacylpyrazine (compound 1) are symmetrical, *i.e.*, R = R′. The remaining two diketones (compounds 5 and 6) are unsymmetrical, *i.e.*, R $\neq$ R′. These two diketones, *viz.*, 2-(pivalylmethyl)-6-(isonicotinylmethyl)-pyrazine and 2-(propionylmethyl)-6-(pivalylmethyl)-pyrazine, were obtained in 97.6% and 47.0% yields, respectively, by the acylation of 2-methyl-6-pivalylmethylpyrazine with methyl isonicotinate and methyl propionate.

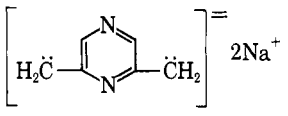
It was also of interest to determine whether the symmetrical diketones can be prepared by the direct diacylation of 2,6-dimethylpyrazine as well as by the acylation of the previously prepared[8] and isolated monoketones, *i.e.*, the 2-methyl-6-acylmethylpyrazines. Thus, from the interaction of a 1:3:2 molar ratio of 2,6-dimethylpyrazine:sodium amide:ethyl benzoate there was obtained a mixture of 2-methyl-6-phenacylpyrazine (I, 25.4%) and 2,6-diphenacylpyrazine (IX, 38.5%) as compared with the 81.0% yield of IX which was obtained by the benzoylation of I. Finally, the attempted diacylation of 2,6-dimethylpyrazine with ethyl isobutyrate gave a mixture of isobutyramide (41.9%), 2-methyl-6-(isobutyrylmethyl)pyrazine (36.2%), and 2,6-di(isobutyrylmethyl)pyrazine (0.6%) as compared with the 42.0% yield of this diketone which was obtained by the acylation of 2-methyl-6-isobutyrylmethylpyrazine. That such a low yield of diacylated product was obtained in the attempted diisobutyrylation of 2,6-dimethylpyrazine may be due to the probability that

(7) A sharp melting point was not obtained for XI. This may be due to the probability that a mixture of geometrical isomers of the dioximino compound was formed.

(8) V. Migrdichian, "Organic Synthesis," Vol. II, Reinhold Publishing Corp., New York, N. Y., 1957, p. 1366.

the ethyl isobutyrate reacts preferentially with the large amount of sodium amide which is present to give isobutyramide, rather than with the anion of 2,6-dimethylpyrazine to give the desired product.

Although it is tempting to assume that in the sodium amide-effected direct diacylation of 2,6-dimethylpyrazine a dianion (XIII) is formed which then can give rise to the mono- and diacylated products, no



XIII

conclusive data in support of its existence are available at the present time. The formation of the ketonic products may be explained also by envisioning that one equivalent of sodium amide converts one equivalent of 2,6-dimethylpyrazine to its monoanion which is then acylated to give the monoketone. Part of this monoketone may then react further as indicated in the reaction scheme described previously to give the diketone. More work must be done before a decision can be made as to which of these two alternative paths is followed when symmetrical 2,6-diacylmethylpyrazines are formed by the direct diacylation of 2,6-dimethylpyrazine.

## Experimental[9]

**A. Synthesis of 2,6-Diphenacylpyrazine by the Direct Benzoylation of 2,6-Dimethylpyrazine.**—This reaction illustrates the preparation of the symmetrical diacylated products *via* the direct acylation of 2,6-dimethylpyrazine. To 0.45 mole of sodium amide,[10] prepared from sodium (10.4 g., 0.45 g.-atom), in 500 ml. of anhydrous liquid ammonia was added over a 15-min. period, 2,6-dimethylpyrazine (16.2 g., 0.15 mole) dissolved in 50 ml. of anhydrous ether. The reaction mixture, which became deep red in color, was stirred for 30-min. Then ethyl benzoate (45.0 g., 0.30 mole) dissolved in an equal volume of anhydrous ether was added over a 20-min. period and the reaction mixture was stirred for 90 min. Ammonium chloride (27.0 g.) was added to quench the reaction and the liquid ammonia was replaced by ether. The mixture was then carefully poured onto ice and was made slightly acidic with dilute hydrochloric acid. There was precipitated 18.5 g. (38.5%) of 2,6-diphenacylpyrazine, m.p. 141–142°, from an acetone–water mixture. In addition, 8.1 g. (25.4%) of 2-methyl-6-phenacylpyrazine, m.p. 50–52°,[3] was isolated.

**B. Synthesis of 2,6-Diphenacylpyrazine by the Benzoylation of 2-Methyl-6-phenacylpyrazine.**—This reaction illustrates the preparation of the symmetrical diacylated products *via* the acylation of a monoacylated 2,6-dimethylpyrazine. To sodium amide[10] (0.20 mole) in 200 ml. of anhydrous liquid ammonia was added 2-methyl-6-phenacylpyrazine[3] (21.2 g., 0.1 mole) over a 15-min. period. The red solution was stirred for 30 min. after which ethyl benzoate (15.0 g., 0.1 mole) was added over a 20-min. period. The reaction mixture was stirred for 90 min. and then was processed as in the previous reaction to give 12.9 g. (81.0%) of 2,6-diphenacylpyrazine, m.p. 141–142°, from an acetone–water mixture. In addition, 10.5 g. (49.5%) of 2-methyl-6-phenacylpyrazine, m.p. 50–52°,[3] was recovered.

When this reaction was performed using a 1:1:1 molar ratio of sodium amide:2-methyl-6-phenacylpyrazine:ethyl benzoate, none of the desired diketone was obtained and the starting materials were recovered.

**C. Synthesis of 2-(Pivalylmethyl)-6-(isonicotinylmethyl)pyrazine.**—This reaction illustrates the preparation of an unsymmetrically diacylated product *via* the acylation of a monoacylated 2,6-dimethylpyrazine. 2-Methyl-6-(pivalylmethyl)pyrazine[3] (19.2 g., 0.1 mole), sodium amide[10] (0.2 mole) in 200 ml. of anhydrous liquid ammonia, and methyl isonicotinate (0.1 mole, 13.7 g.) dissolved in an equal volume of anhydrous ether were allowed to react as described in reaction B and processed as described in reaction A to give 14.5 g. (97.6%) of 2-(pivalylmethyl)-6-(isonicotinylmethyl)pyrazine, m.p. 108–112°. Several attempts to recrystallize this material from the usual solvents did not give a sharp melting material. Finally, it was purified by dissolving it in benzene, adding a small amount of Florex, and shaking the mixture for 10 min. The Florex was removed by filtration. The addition of pentane to the filtrate caused the yellow crystalline product to precipitate. This material melted at 113–114° and on recrystallization from a benzene–pentane mixture, it melted at 113.6–114.6°.

**D. Reaction of 2,6-Diphenacylpyrazine with Aqueous Sodium Nitrite.**—Sodium nitrite (2.0 g., 0.028 mole) dissolved in 25 ml. of water, was added slowly (30 min.) to a stirred solution of 2.0 g. (0.006 mole) of 2,6-diphenacylpyrazine in 25 ml. of glacial acetic acid. The mixture was then stirred for 3 hr. with occasional cooling to maintain the reaction temperature at 25°. The addition of 50 ml. of water caused the precipitation of 0.4 g. of a yellow solid, which was removed by filtration and identified as 2,6-diphenacylpyrazine, m.p. 141–142°. The addition of 500 ml. of water to the filtrate resulted in the precipitation of 0.9 g. (40.3%) of 2,6-bis(1-oximinophenacyl)pyrazine, m.p. 100–110°. Several recrystallizations of this solid from an ethanol–water mixture failed to give a sharp melting material presumably due to the possibility that it consists of geometrical isomers. However, its elemental analysis agreed with the proposed structure.

*Anal.* Calcd. for $C_{20}H_{14}N_4O_4$: C, 64.17; H, 3.77; N, 14.97. Found: C, 63.69; H, 4.09; N, 14.70.

(9) The 2,6-dimethylpyrazine was supplied through the courtesy of Wyandotte Chemicals Corp.

(10) S. R. Harris and R. Levine, *J. Am. Chem. Soc.*, **70**, 3360 (1948).