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Received May 18, 1978

Ring transformation of 6-methyl-3,4-dihydro-2*H*-1,3-oxazine-2,4-dione (Ia) and its *N*-substituted derivatives, such as 3-methyl (Ib), 3-ethyl (Ic), and 3-benzyl (Id) derivatives is described. Reaction of Ia with hydrazine hydrate gave 1-amino-6-methyluracil (II), while Id reacted with hydrazine hydrate to give 3-hydroxy-5-methylpyrazole (III). Reaction of Ia,b,d with ethyl acetoacetate in ethanol in the presence of sodium ethoxide afforded ethyl 3-acetyl-6-hydroxy-4-methyl-2(1*H*)pyridone-5-carboxylate derivatives (IVa,b,d). On the other hand, reaction of Ib,c,d with ethyl acetoacetate in tetrahydrofuran in the presence of sodium hydride did not give IV, but gave 3-acetyl-1-alkyl-5-(*N*-alkylcarbamoyl)-6-hydroxy-4-methyl-2(1*H*)pyridone (VIb,c,d). Mechanisms for the formation of compounds IV and VI are discussed.

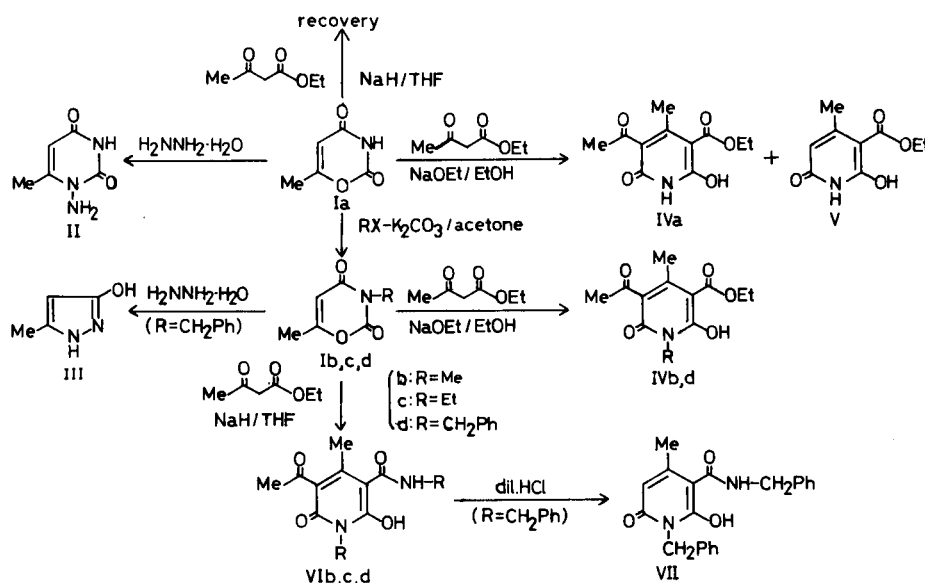
J. Heterocyclic Chem., 15, 1475 (1978)

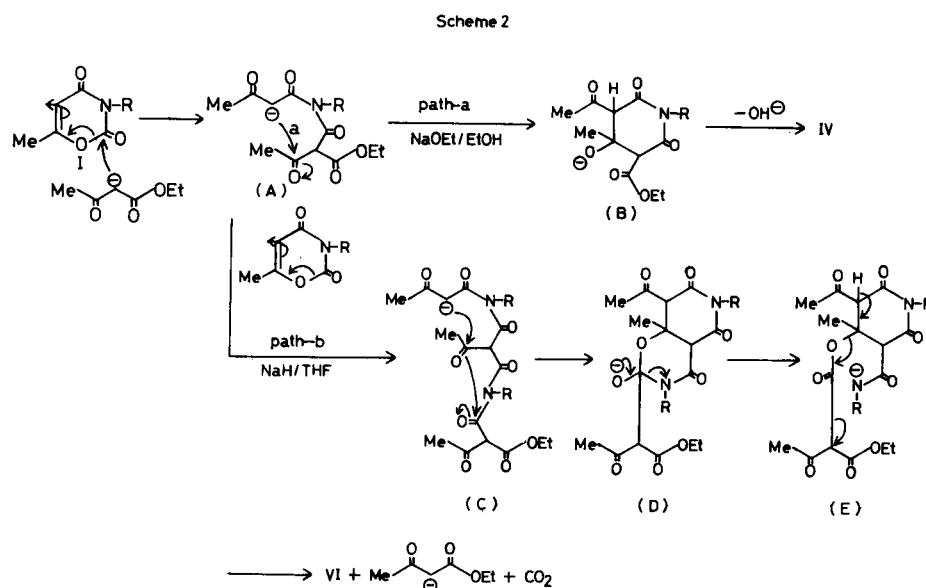
In connection with our continuing interests in 1,3-oxazine chemistry (2,3) and with studies directed toward the synthesis of heterocyclic compounds (4,5,6), we wish to report the ring transformation reaction of the 3,4-dihydro-2*H*-1,3-oxazine-2,4-diones to give pyridone, pyrimidone, and pyrazole derivatives. The oxazines used in this reaction were 6-methyl-3,4-dihydro-2*H*-1,3-oxazine-2,4-dione (Ia), and its *N*-substituted derivatives, such as the 3-methyl (Ib), 3-ethyl (Ic), and 3-benzyl (Id) derivatives. Compounds Ib, Ic and Id were obtained by *N*-alkylation of compound Ia, which was prepared by the reaction of diketene with urethane followed by cyclization with concentrated sulfuric acid.

When compound Ia was allowed to react with an equimolar amount of hydrazine hydrate in ethanol, 1-amino-6-methyluracil (II) was obtained in 33% yield. The similar reaction of the *N*-alkyl derivatives, such as compound Id, did not give the corresponding uracil, but gave 3-hydroxy-5-methylpyrazole (III) in 24% yield.

When compound Ia was allowed to react with ethyl acetoacetate in ethanol in the presence of sodium ethoxide, two products of m.p. 215-216° (IVa) and m.p. 175-176° (V) were obtained. On the basis of elemental analyses and spectral data detailed in the experimental section, they were characterized as ethyl 3-acetyl-6-hydroxy-4-methyl-2(1*H*)pyridone-5-carboxylate (IVa) and ethyl 6-hydroxy-4-methyl-2(1*H*)pyridone-5-carboxylate (V), respectively. The similar reaction of the 3-methyl (Ib) and 3-benzyl-oxazine (Id) with ethyl acetoacetate under the same conditions as above gave rise to ethyl 3-acetyl-1,4-dimethyl-6-hydroxy-2(1*H*)pyridone-5-carboxylate (IVb) and the 1-benzyl derivative (IVd), respectively. On the other hand, when the reaction was carried out in tetrahydrofuran (THF) in the presence of sodium hydride in place of sodium ethoxide, compounds Ib, Ic and Id were not converted to the esters IV, but were converted to the amide derivatives VIb, VIc and VIId, respectively. The same amides were obtained using diethyl malonate instead of

Scheme 1





ethyl acetoacetate. Elemental and mass analyses suggested an empirical formula of $2 \times \text{Ib} \sim d - \text{CO}_2$. However, the amides (VI) could not be obtained in the absence of ethyl acetoacetate. Since Ia was not soluble in THF, its reaction in THF resulted in recovery of the starting materials.

On treatment with hydrochloric acid in ethanol, compound VI_d was deacetylated to give compound VII in quantitative yield.

Although details of the mechanism of the formation of these products still remains obscure, a likely pathway is shown in Scheme 2. Addition of ethyl acetoacetate anion to the 2-position of the oxazines (I) would form an intermediate A, which could cyclize to give the products (IV) *via* the intermediate B (path-a). The formation of the amides (VI) can be elucidated as follows: that is, the intermediate A adds to the another mole of the oxazines (I) giving the intermediate C. The subsequent stage might involve cyclization to give the bicyclic intermediate D. Fission of the oxazine ring of the intermediate D accompanied with the elimination of carbon dioxide and ethyl acetoacetate would give the amides (VI) *via* the intermediate E (path-b).

The above mechanism (path-b) can be supported by the experimental facts; namely, ethyl acetoacetate was recovered in almost quantitative yield. However, as mentioned above, transformation of the oxazines (I) to the amides (VI) did not occur in the absence of ethyl acetoacetate (or diethyl malonate).

EXPERIMENTAL (7)

3,6-Dimethyl-3,4-dihydro-2H-1,3-oxazine-2,4-dione (Ib).

A mixture of 6-methyl-3,4-dihydro-2H-1,3-oxazine-2,4-dione (Ia) (8) (2.5 g., 0.02 mole), methyl iodide (3.4 g., 0.024 mole),

and potassium carbonate (8.3 g., 0.06 mole) in acetone (40 ml.) was refluxed for 3 hours. The mixture was filtered. The filtrate was condensed. The residue was purified by recrystallization from petroleum ether giving colorless needles, m.p. 108° (lit. m.p. (8) 108-109°), yield 2.68 g. (95%); ir (chloroform): ν max cm^{-1} 1770, 1695; nmr (deuteriochloroform): 2.20 (3H, s, 6-CH₃), 3.33 (3H, s, N-CH₃), 5.80 (1H, s, 5-H).

3-Ethyl-6-methyl-3,4-dihydro-2H-1,3-oxazine-2,4-dione (Ic).

Following the same procedure used for compound Ib, Ia (2.54 g., 0.02 mole) was allowed to react with ethyl iodide (9.36 g., 0.06 mole) in acetone (40 ml.) in the presence of potassium carbonate (8.3 g., 0.06 mole) for 18 hours giving 2.2 g. (71%) of Ic, m.p. 68-70° (lit. m.p. (9) 69-70°).

3-Benzyl-6-methyl-3,4-dihydro-2H-1,3-oxazine-2,4-dione (Id).

Following the same procedure described above, the oxazine (Ia) (2.54 g., 0.02 mole) reacted with benzyl bromide (4.1 g., 0.024 mole) to give 3.43 g. (79%) of the product as colorless needles from petroleum ether, m.p. 94-95° (lit. m.p. (8) 93°).

1-Amino-6-methyluracil (II).

A solution of 80% hydrazine hydrate (0.25 g., 0.004 mole) and the oxazine (Ia) (0.63 g., 0.005 mole) in ethanol (8 ml.) was refluxed for 3 hours. After cooling, the crystals which separated were collected by suction. Recrystallization from methanol gave 0.23 g. (33%) of II, m.p. 245-246° (lit. m.p. (10) 242-244° dec.).

3-Hydroxy-5-methylpyrazole (III).

A mixture of the oxazine (Id) (0.54 g., 0.0025 mole) and 80% hydrazine hydrate (0.15 g., 0.0025 mole) in ethanol (8 ml.) was refluxed for 1 hour. The reaction mixture was condensed, and the residue was washed with ethyl acetate. The insoluble residue was purified by recrystallization from ethanol to give 0.06 g. (24%) of III, m.p. 222° (lit. m.p. (11) 219°).

Ethyl 3-Acetyl-6-hydroxy-4-methyl-2(1H)pyridone-5-carboxylate (IVa) and Ethyl 6-Hydroxy-4-methyl-2(1H)pyridone-5-carboxylate (V).

To a sodium ethoxide solution in ethanol prepared from sodium metal (0.13 g., 0.0057 g. atom) and absolute ethanol (10 ml.), was

added ethyl acetoacetate (0.65 g., 0.005 mole). The mixture was stirred at room temperature. After 30 minutes compound Ia (0.65 g., 0.005 mole) was added, and the mixture was refluxed for 2 hours. The mixture was evaporated and the residue was acidified with 10% hydrochloric acid. The crystals which separated were collected and recrystallized from ethanol to give 0.06 g. (5%) of the product IVa as pale purple needles, m.p. 175-176°, and 0.05 g. (5%) of the product V as prisms, m.p. 215-216° (lit. m.p. (12) 218°); ir (potassium bromide): ν max cm^{-1} 3280-2400, 1700, 1655 (sh), 1640; nmr (trifluoroacetic acid): 1.47 (3H, t, J = 7.5 Hz), 2.73 (6H, s, COCH₃ and 4-CH₃), 4.58 (2H, q, J = 7.5 Hz).

Anal. Calcd. for C₁₁H₁₃NO₅ (IV): C, 55.23; H, 5.48; N, 5.86. Found: C, 54.85; H, 5.54; N, 5.87.

Ethyl 3-Acetyl-6-hydroxy-1,4-dimethyl-2(1H)pyridone-5-carboxylate (IVb).

To a sodium ethoxide-ethanol solution prepared from sodium metal (0.46 g., 0.02 g. atom) and absolute ethanol (60 ml.), was added ethyl acetoacetate (1.95 g., 0.015 mole) with stirring. After 30 minutes, the oxazine (Ib) (2.1 g., 0.015 mole) was added, and the reaction mixture was stirred at room temperature for 3 hours. The mixture was condensed, and the residue was neutralized with 10% hydrochloric acid. The mixture was extracted with ethyl acetate. The ethyl acetate soluble fraction gave IVb, as colorless needles (from petroleum ether), m.p. 60-61°, yield 1.1 g. (30%); ir (chloroform): ν max cm^{-1} 3000, 1725, 1660, 1640 (sh); nmr (deuteriochloroform): 1.39 (3H, t, J = 7.5 Hz, -CH₂-CH₃), 2.39 (3H, s, 4-CH₃), 2.60 (3H, s, COCH₃), 3.46 (3H, s, N-CH₃), 4.45 (2H, q, J = 7.5 Hz, -CH₂CH₃), 18.85 (1H, br, OH).

Anal. Calcd. for C₁₂H₁₅NO₅ (IVb): C, 56.91; H, 5.97; N, 5.53. Found: C, 56.86; H, 5.92; N, 5.51.

Ethyl 3-Acetyl-1-benzyl-6-hydroxy-4-methyl-2(1H)pyridone-5-carboxylate (IVd).

According to the same procedure described above, Id (1 g., 0.005 mole) was allowed to react with ethyl acetoacetate (0.65 g., 0.005 mole) in sodium ethoxide-ethanol solution prepared from sodium metal (0.14 g., 0.006 g. atom) and absolute ethanol (30 ml.) to give 0.5 g. (30%) of the product, colorless needles (from petroleum ether), m.p. 86-87°; ir (chloroform): ν max cm^{-1} 3000, 1725, 1660, 1640 (sh); nmr (deuteriochloroform): 1.37 (3H, t, J = 7.5 Hz, -CH₂CH₃), 2.37 (3H, s, 4-CH₃), 2.57 (3H, s, COCH₃), 4.43 (2H, q, J = 7.5 Hz, CH₂CH₃), 5.27 (2H, s, CH₂Ph), 7.42 (5H, m, ring-H), 18.90 (1H, br, OH).

Anal. Calcd. for C₁₈H₁₉NO₅ (IVd): C, 65.64; H, 5.82; N, 4.25. Found: C, 65.70; H, 5.78; N, 4.33.

3-Acetyl-1,4-dimethyl-6-hydroxy-5-(N-methylcarbamoyl)-2(1H)pyridone (VIb).

Ethyl acetoacetate (1.9 g., 0.015 mole) was added to a suspension of sodium hydride (50% oil, 0.9 g., 0.02 mole) in THF (60 ml.). After stirring at room temperature for 30 minutes, Ib (2.1 g., 0.015 mole) was added and the mixture was refluxed for 2 hours. The mixture was condensed and the residue was neutralized with 10% hydrochloric acid. Extraction with chloroform gave a crystalline substance, which was recrystallized from ethyl acetate to give 0.8 g. (45%) of VIb as colorless needles, m.p. 180-181°; ir (potassium bromide): ν max cm^{-1} 3280, 2920, 1660 (sh), 1640; nmr (trifluoroacetic acid): 2.52 (3H, s, 4-CH₃), 2.62 (3H, s, COCH₃), 2.97 (3H, d, J = 4.5 Hz, NH-CH₃), 3.38 (3H, s, 1-CH₃), 6.90 (1H, br, NH-), 18.85 (1H, br, OH); ms: m/e 238 (M⁺).

Anal. Calcd. for C₁₁H₁₄N₂O₄ (VIb): C, 55.45; H, 5.92; N, 11.76. Found: C, 55.48; H, 5.89; N, 11.70.

3-Acetyl-1-ethyl-5-(N-ethylcarbamoyl)-6-hydroxy-4-methyl-2(1H)pyridone (VIc).

Employing the same procedure described above, Ic (1.5 g., 0.01 mole) was allowed to react with ethyl acetoacetate (1.3 g., 0.01 mole) in the presence of sodium hydride (50% oil, 0.96 g., 0.02 mole) in THF (40 ml.) to give 0.4 g. (30%) of VIc as needles (from ethyl acetate), m.p. 153-155°; ir (potassium bromide): ν max cm^{-1} 3330, 2970, 1660 (sh), 1640; nmr (deuteriochloroform): 1.23 (6H, t, J = 7 Hz, 1-CH₂CH₃ and NH-CH₂CH₃), 2.53 (3H, s, 4-CH₃), 2.64 (3H, s, COCH₃), 3.43 (2H, q, J = 7 Hz, NHCH₂CH₃), 4.11 (2H, q, J = 7 Hz, 1-CH₂CH₃), 6.90 (1H, br, -NHCH₂CH₃), 18.93 (1H, br, OH).

Anal. Calcd. for C₁₃H₁₈N₂O₄ (VIc): C, 58.63; H, 6.81; N, 10.52. Found: C, 58.43; H, 6.72; N, 10.51.

3-Acetyl-1-benzyl-5-(N-benzylcarbamoyl)-6-hydroxy-4-methyl-2(1H)pyridone (VIId).

1.

According to the same procedure described above, Id (1 g., 0.005 mole) was treated with ethyl acetoacetate (0.65 g., 0.005 mole) in THF (20 ml.) in the presence of sodium hydride (50% oil, 0.28 g., 0.006 mole) to give 0.78 g. (80%) of VIId as needles (from benzene), m.p. 180-181°; ir (potassium bromide): ν max cm^{-1} 3340, 3100, 1670, 1630; nmr (deuteriochloroform): 2.50 (3H, s, 4-CH₃), 2.56 (3H, s, COCH₃), 4.56 (2H, d, J = 6 Hz, NHCH₂Ph), 5.16 (2H, s, 1-CH₂Ph), 7.30 (11H, m, ring-H and NH) 18.70 (1H, br, OH); ms: m/e 390 (M⁺).

Anal. Calcd. for C₂₃H₂₂N₂O₄ (VIId): C, 70.75; H, 5.68; N, 7.18. Found: C, 70.64; H, 5.56; N, 7.02.

2.

Similar reaction of compound Id (1 g., 0.005 mole) with diethyl malonate (0.8 g., 0.005 mole) under the same condition gave 0.2 g. (20%) of VIId.

1-Benzyl-5-(N-benzylcarbamoyl)-6-hydroxy-4-methyl-2(1H)pyridone (VII).

A mixture of VIId (0.5 g., 0.0013 mole), 15% hydrochloric acid (25 ml.) and ethanol (15 ml.) was refluxed for 7 hours. After cooling, the crystals which separated were collected. Recrystallization from ethyl acetate gave VII as needles, m.p. 142-144°; ir (chloroform): ν max cm^{-1} 3480, 3000, 1660.

Anal. Calcd. for C₂₁H₂₀N₂O₃ (VII): C, 72.39; H, 5.79; N, 8.04. Found: C, 72.11; H, 5.84; N, 7.87.

Acknowledgment.

The authors are grateful to Mrs. C. Koyanagi and Miss. K. Mushiaki for elemental analysis, and Miss. H. Koizumi, Mrs. A. Sato and Mr. K. Kawamura for the spectral data.

A part of the expenses for this work was defrayed by the Grant-in-Aid for Scientific Research from the Ministry of Education, which is gratefully acknowledged.

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