Naphthyridine Chemistry: Ring Enlargement to a Pyrido[2,3-*b*]azepine

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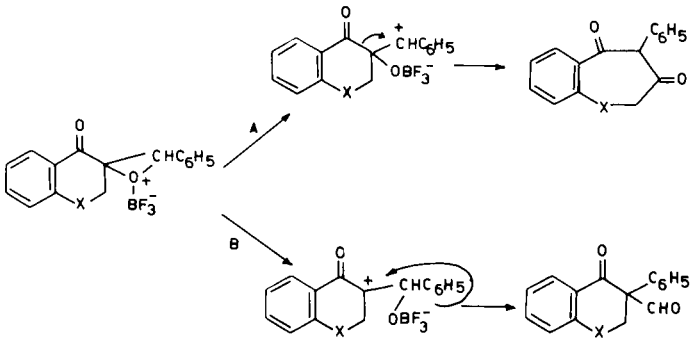
The boron trifluoride-catalyzed rearrangement of the epoxide derived from 3-benzylidene-7-methyl-2,3-dihydro-1,8-naphthyridin-4-(1*H*)one (II) is described. The structure of the obtained 8-methyl-4-phenyl-1,2,3,4-tetrahydro-5*H*-pyrido[2,3-*b*]-azepin-3,5-dione (X) has been elucidated with aid of chemical and spectral evidence.

It was shown that the boron trifluoride-catalyzed rearrangement of 2-benzalcycloalkanone epoxides, proceeds usually *via* benzoyl migration to give ring expanded β-diketones (1). This reaction was also applied successfully in the case of epoxides derived from α-tetralone and from some heterocyclic analogs (2,3,4) (path A). On the other hand the literature records some examples of boron trifluoride-catalyzed phenyl migration with formation of ring unexpanded β-ketoaldehydes (2,3,5) (path B).

Pursuing our interest in 1,8-naphthyridines (6) we have examined the reaction between a 1,8-naphthyridine keto oxide system and boron trifluoride in order to obtain a pyrido[2,3-*b*]azepine derivative.

Compounds of this type appear to be of particular



interest since they can be related to products having action on the central nervous system [benzodiazepines and pyridodiazepines (7)].

The route employed for the synthesis of the target compound was essentially the same as described by Hofmann and Westernacher for the preparation of some benzoxepindiones and benzothioepindiones (4).

Thus 7-methyl-2,3-dihydro-1,8-naphthyridin-4(1*H*)one (I) (8) was allowed to react with benzaldehyde in ethanol according to the procedure reported by Dann and Hofmann (9). The benzylidene derivative II was obtained as yellow needles melting at 150°. It was found that in alkaline solution compound II is readily converted into the isomer III (m.p. 253°), as shown by their nmr spectra (see Table I). This last compound was also obtained in 76% yield by treating I with benzaldehyde in aqueous alcoholic alkaline solution. Additional support for the above structures was obtained by converting II into the *N*-acetyl derivative V and III into the *N*-ethyl derivative IV whose infrared spectrum (nujol) showed a carbonyl band at 1640 cm^{-1} (nmr data, see Table I).

The above mentioned benzylidene-ketonaphthyridine II was changed into the related epoxide VI by reaction with hydrogen peroxide and 2*N* sodium hydroxide in methanolic suspension. Treatment of the oxide VI with boron trifluoride etherate in chloroform solution yielded the diketone X, the product expected from the preferential migration of the nicotinoyl group.

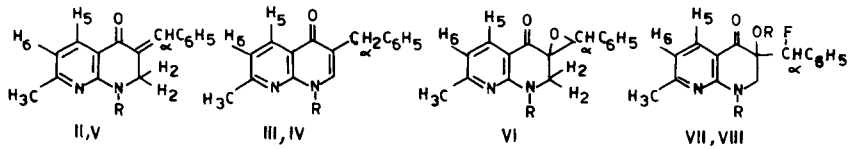
When benzene was employed as the medium for the rearrangement, fluorohydrin VII was produced, as evidenced by elemental analysis, nmr spectrum (see Table I) and by its conversion into the acetyl derivative VIII.

As expected, the reaction of the fluorohydrin VII with boron trifluoride in chloroform solution afforded the expanded diketone X. This result is in agreement with that reported in the literature (1,10). Furthermore it may be suggested that compound VII is an intermediate in the isomerization of the keto-oxide VI to X.

Verification of the diketone structure X was gained from the nuclear magnetic resonance spectrum which shows an AB geminal system at 3.7 and 4.2 δ, due to the H_2 protons (J = 18.0 cps), a singlet at 5.82 δ assigned to H_4 and a NH signal (broad doublet) at 6.06 δ (see Table II). It is noteworthy that the H_2 protons couple differently with NH (J = 6.0 cps and J = 1.5 cps).

A further confirmation was obtained by treatment of X with acetic anhydride to yield the triacetyl derivative IX, and mainly by its alkaline cleavage to XIa. With regard to

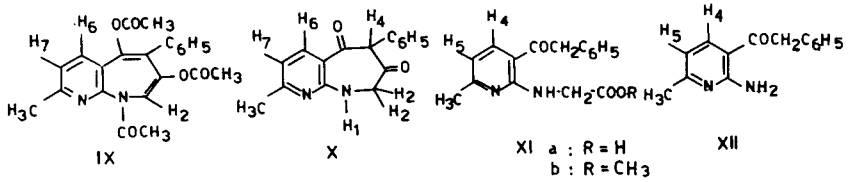
Table I



II,V III,IV VI VII,VIII

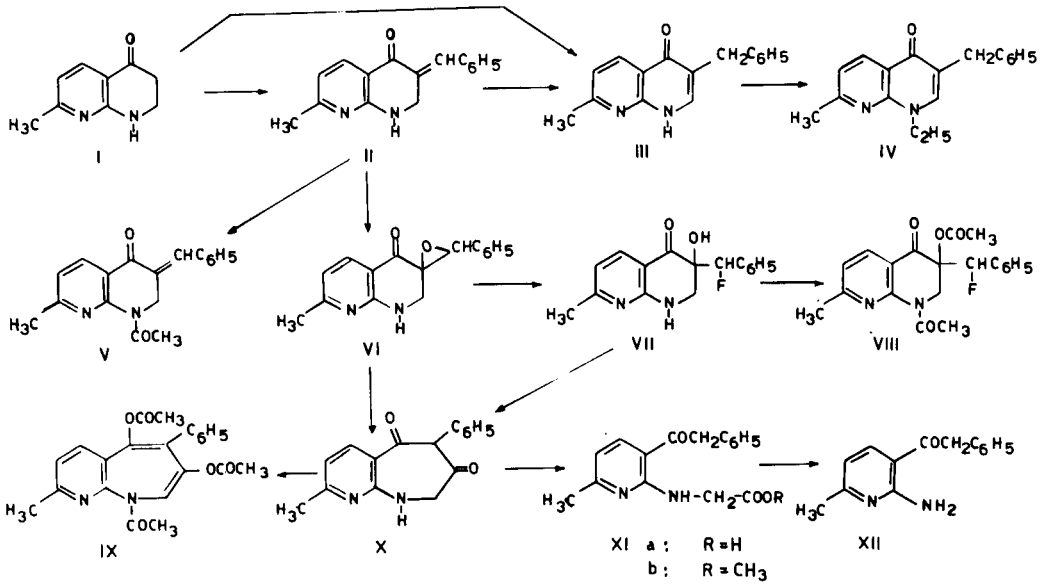
Compound	R	Chemical Shifts (δ) H_1	H_2	H_5	H_6	7-CH_3	H α	C_6H_5	Other Protons	Coupling Const. cps $J_{1\,2}$	$J_{2\,2}$	$J_{2\,\alpha}$	$J_{5\,6}$	J_{HF}	Solvent
II	H_1	5.96	4.72	8.20	6.63	2.42	7.88	7.44		2.0		2.4	8.2		deuteriochloroform
V	$COCH_3$		5.28	8.38	7.20	2.54	7.95	7.58	$COCH_3$ (2.62)			2.1	8.2		deuteriochloroform
III	H_1	12.1	7.82	8.44	7.28	2.60	3.82	7.32					8.2		DMSO-d_6
IV	C_2H_5		7.45	8.70	7.22	2.66	3.98	7.38	CH_3 (1.38); NCH_2 (4.40)				8.2		deuteriochloroform
VI	H_1	6.24	3.26 3.85	8.10	6.60	2.22	4.50	7.40		3.4 1.0	13.5		8.0		deuteriochloroform
VII	H_1	7.62	3.06	7.98	6.65	2.40	5.74	7.45	OH (5.98)	3.4	13.0		8.0	45.0	DMSO-d_6
VIII	$COCH_3$		4.22 5.05	8.15	7.02	2.48	5.88	7.25	$NCOCH_3$ (2.20); $OCOCH_3$ (2.14)		13.5		8.0	45.0	deuteriochloroform

Table II



IX X XI a : R = H b : R = CH_3 XII

Compound	Chemical Shifts (δ) H_1	H_2	H_4	H_5	H_6	H_7	CH_3	C_6H_5	Other Protons	Coupling Const. cps $J_{1\,2}$	$J_{2\,2}$	$J_{4\,5}$	$J_{6\,7}$	J_{NHCH_2}	Solvent
IX		6.84			7.96	7.35	2.64	7.46	$OCOCH_3$ (1.72; 1.95) $NCOCH_3$ (2.18)				8.2		deuteriochloroform
X	6.06	3.70 4.20	5.82		8.13	6.86	2.53	7.38		6.0 1.5	18.0		8.1		deuteriochlorofrom
XIa			8.15	6.58			2.45	7.38	$COCH_2$ (4.25); NCH_2 (4.32) COOH (8.42); NH (9.45)			8.2		6.0	deuteriochloroform
XIb			8.05	6.48			2.38	7.32	$COCH_2$ (4.21); NCH_2 (4.32) $COOCH_3$ (3.75); NH (9.35)			8.2		5.8	deuteriochloroform
XII			8.05	6.52			2.40	7.35	$COCH_2$ (4.23); NH_2 (7.25)			8.2			deuteriochloroform



this last reaction, although the ir and the nmr data were in agreement with structure XIa (nmr data, see Table II), we could not exclude the possibility of a cleavage at C_4-C_5 with formation of the isomeric product having the carboxyl group in C_3 of the pyridine nucleus.

Therefore in an attempt at decarboxylation compound XIa was refluxed with Dowtherm A in presence of copper chromite. However, under these conditions an unusual cleavage occurred and the ketoamino derivative XII was isolated (nmr data, see Table II). The formation of this latter confirmed the structure XIa. In addition mass spectra were performed both on the methyl ester of XIa (XIb) and on XII. The mass spectrum of XIb showed a parent peak at m/e 298 with 59% relative intensity. The main fragmentation resulted by elimination of methoxycarbonyl, benzyl and phenylacetyl radicals (see Experimental). The mass spectrum of XII showed a parent peak at m/e 226 with 32% relative intensity and intense ions at m/e 135, 107 and 80. These fragment ions correspond to sequential loss of a benzyl radical, carbon monoxide and hydrogen cyanide.

A wide range screening was carried out with the compounds II, IV, VI, VII and X in collaboration with the Carlo Erba Laboratories, Milan (Italy), in order to assay the microbiological and pharmacological properties of such compounds. Only compound X displayed a weak sedative action.

EXPERIMENTAL

All melting points were determined on a Kofler apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Infracord Model 137 spectrophotometer in nujol mulls. The nmr spectra of all the products described were obtained on a Jeol Model C 60 HL spectrometer. Mass measurements were carried out on a C H 7 Varian MAT mass spectrometer.

3-Benzylidene-7-methyl-2,3-dihydro-1,8-naphthyridin-4(1*H*)one (II).

Anhydrous hydrogen chloride was bubbled into a chilled solution of 2.0 g. of I (8) and 1.4 ml. of benzaldehyde in 120 ml. of absolute ethanol. After saturation, the solution was allowed to stand at room temperature overnight and concentrated to a small volume at reduced pressure. The separated solid was then filtered, treated with dilute ammonia and collected (2.2 g., 64.8%). Crystallization from ethanol gave pure II as yellow needles, m.p. 150° dec.

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.80; H, 5.61; N, 11.15.

3-Benzyl-7-methyl-1,8-naphthyridin-4(1*H*)one (III).

From II.

To a suspension of 0.5 g. of II in 20 ml. of ethanol was added 1 ml. of 10% sodium hydroxide solution. After 30 minutes of refluxing, the ethanol was evaporated. The solution was then diluted with water (10 ml.) and neutralized with hydrochloric acid. The precipitated solid was collected (0.49 g., 98.0%) and crystallized from 50% aqueous methanol (m.p. 253°)

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.60; H, 5.45; N, 10.94.

From I.

A solution of 0.5 g. of I and 0.4 ml. of benzaldehyde in 5 ml. of 4% ethanolic potassium hydroxide was refluxed for 3 hours. Upon neutralization with hydrochloric acid there was obtained 0.59 g. of III (76.47%).

3-Benzyl-1-ethyl-7-methyl-1,8-naphthyridin-4(1*H*)one (IV).

To a solution of 1.5 g. of III in 20 ml. of ethanol was added 20 ml. of 10% potassium hydroxide solution and 7 ml. of ethyl iodide. After about 10 hours of refluxing, the ethanol was removed by evaporation at reduced pressure and the reaction mixture extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and evaporated to dryness to give 1.250 g. of IV (74.9%). Crystallization from methanol afforded analitically pure IV as white plates, m.p. 147-149°; ir (nujol): 1640 cm^{-1} (C=O).

Anal. Calcd. for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.07. Found: C, 77.82; H, 6.48; N, 9.87.

1-Acetyl-3-benzylidene-7-methyl-2,3-dihydro-1,8-naphthyridin-4-(1*H*)one (V).

A mixture of 0.10 g. of II and 4 ml. of acetic anhydride was refluxed for 40 minutes. The solution was diluted with water (20 ml.) and allowed to stand at room temperature until the acetic anhydride was completely decomposed. The solution was made basic with ammonium hydroxide and the resulting precipitate was collected (0.1 g., 90.9%). The product crystallized from 50% aqueous ethanol as pale yellow needles, m.p. 112-115°.

Anal. Calcd. for $C_{18}H_{16}N_2O$: C, 78.23; H, 5.84; N, 10.14. Found: C, 78.12; H, 5.68; N, 10.23.

3-Benzyl-3,α-epoxy-7-methyl-2,3-dihydro-1,8-naphthyridin-4(1*H*)-one (VI).

To a suspension of 2.0 g. of the benzylidene derivative II in 120 ml. of methanol was added 1.2 ml. of 35% hydrogen peroxide and 4 ml. of 2*N* aqueous sodium hydroxide. After stirring at room temperature overnight, the solution was poured onto crushed ice and the resulting precipitate collected (1.6 g., 75.2%). Recrystallization from benzene-light petroleum gave yellow crystals, m.p. 140-142°.

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.39; H, 5.24; N, 10.40.

3-(α-Fluorobenzyl)-3-hydroxy-7-methyl-2,3-dihydro-1,8-naphthyridin-4(1*H*)one (VII).

A stirred solution of 1.0 g. of VI in 100 ml. of benzene was treated with 6.0 ml. of boron trifluoride etherate. After stirring at room temperature for 15 minutes, the suspension was washed repeatedly with saturated sodium bicarbonate solution. The organic layer was then dried over magnesium sulfate and evaporated. The residue (0.9 g., 83.7%) was crystallized from ethanol: m.p. 212-215°.

Anal. Calcd. for $C_{16}H_{15}N_2O_2F$: C, 67.12; H, 5.28; N, 9.78; F, 6.63. Found: C, 67.31; H, 5.36; N, 9.67; F, 6.81.

3-Acetoxy-1-acetyl-3-(α-fluorobenzyl)-7-methyl-2,3-dihydro-1,8-naphthyridin-4(1*H*)one (VIII).

A mixture of 0.2 g. of fluorohydrin VII, acetic anhydride (1.5 ml.) and anhydrous pyridine (1.5 ml.) was heated at 90° for 20 hours. The solution was then diluted with water (10 ml.) and allowed to stand at room temperature for several hours. The resulting precipitate was collected (0.24 g., 93.0%) and crystallized from ethanol to give white plates, m.p. 156-158°.

Anal. Calcd. for $C_{20}H_{19}N_2O_4F$: C, 64.85; H, 5.17; N, 7.56; F, 5.13. Found: C, 64.72; H, 5.28; N, 7.54; F, 5.31.

8-Methyl-4-phenyl-1,2,3,4-tetrahydro-5*H*-pyrido[2,3-*b*]azepin-3,5-dione (X).

From VI.

A solution of 1.0 g. of epoxide VI in 200 ml. of chloroform was heated to 40° and 5 ml. of boron trifluoride etherate was added. The resulting mixture was stirred at room temperature for 30 minutes and then washed repeatedly with saturated sodium bicarbonate solution. The organic layer was dried over magnesium sulfate and evaporated to dryness. The residue (1.0 g., 100%) was crystallized from benzene to give pale yellow crystals, m.p. 180-182°.

The ir spectrum showed main bands at 3380, 1740, 1660, 1595, 1230, 1120, 778, 740, 700 cm^{-1}.

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.28; H, 5.29; N, 10.39.

From VII.

The title compound was obtained in 100% yield by treating fluorohydrin VII with boron trifluoride under the same conditions used for the conversion of VI into X.

1-Acetyl-3,5-diacetoxy-8-methyl-4-phenyl-pyrido[2,3-*b*]azepine (IX).

A misture of 0.25 g. of X, acetic anhydride (2 ml.) and anhydrous pyridine (2 ml.) was heated at 90° for 15 hours. The solution was then worked up as described earlier for the preparation of VIII. The yield of IX, purified by crystallization from 40% aqueous methanol, was 0.13 g. (35.2%), white needles with m.p. 163-165°.

Anal. Calcd. for $C_{22}H_{20}N_2O_5$: C, 67.33; H, 5.14; N, 7.14. Found: C, 67.19; H, 5.02; N, 7.03.

N-[6-Methyl-3-phenylacetyl-2-pyridyl]glycine (XIa).

A solution of 1.0 g. of X and 6.0 ml. of 6*N* aqueous sodium hydroxide in 30 ml. of ethanol was boiled under reflux for 45 minutes. After evaporation of ethanol the solution was diluted with water, acidified (*p*H 5) with hydrochloric acid and extracted with chloroform. The extract was dried over magnesium sulfate and evaporated to dryness to give 0.55 g. (51.5%) of crude product. The pure amino acid crystallized from benzene as white needles, m.p. 130-131°.

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.52; H, 5.46; N, 9.89.

Methyl *N*-[6-methyl-3-phenylacetyl-2-pyridyl]glycinate (XIb).

Esterification of XIa was worked up in the usual manner by diazomethane. The obtained crude product (100% yield) was crystallized from methanol to give white plates, m.p. 103-105°; mass spectrum, m/e (relative abundance) 298 (59, M^+), 239 (38, M-$COOCH_3$), 207 (54, M-$CH_2C_6H_5$), 179 (83, M-$COCH_2C_6H_5$), 147 (100, $C_8H_7N_2O^+$).

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.32; H, 6.12; N, 9.50.

2-Amino-6-methyl-3-phenylacetylpyridine (XII).

A mixture of XIa (0.3 g.) and copper chromite (0.3 g.) in Dowtherm A (10 ml.) was refluxed for 1 hour. The catalyst was then removed by filtration and the solution was extracted with dilute hydrochloric acid (50 ml.). The aqueous layer was washed with ethyl ether, basified with concentrated ammonium hydroxide and extracted with five 50-ml. portions of chloroform. The combined extracts were dried over magnesium sulfate and evaporated to dryness at reduced pressure to give 0.125 g. (52.3%) of XII. The analytical sample was obtained by crystallization from ligroin, pale yellow crystals with m.p. 150-152°.

The ir spectrum showed main bands at 3450, 3150, 1655, 1625, 1220, 1200, 992, 776, 738, 726 cm^{-1}; mass spectrum, m/e (relative abundance) 226 (32, M^+), 135 (100, M-$CH_2C_6H_5$), 107 (30, M-$COCH_2C_6H_5$), 80 [14, (M-$COCH_2C_6H_5$)-HCN].

Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.08; H, 6.02; N, 12.22.

Acknowledgment.

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