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SYNTHESIS OF FUSED TETRACYCLES FROM THE NITRATION PRODUCTS OF BENZO[*b*]THIENO[2,3-*c*]PYRIDINES

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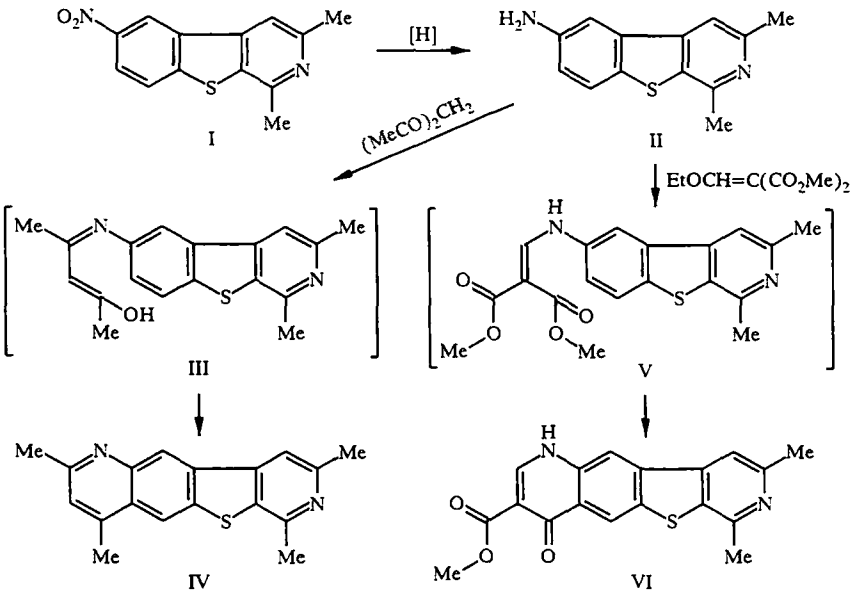
The nitration products of benzo[b]thieno[2,3-c]pyridines were used in the synthesis of new fused tetracyclic heterocyclic systems, which are structural analogs of natural ellipticine and olivicine alkaloids. Closure of the pyridine ring gives products only with linear ring fusion. This behavior was explained using the steric strain–stability principle and complete optimization of the structure of these products with a PCMODEL program and MMX force field in conjunction with the π-electron approximation.

In previous communications, we presented results on the electrophilic substitution in benzo[*b*]thieno[2,3-*c*]pyridines in the case of nitration and acylation [1, 2]. The nitration products are convenient intermediates for the synthesis of new fused tetracyclic systems, which may be seen as structural analogs of natural alkaloids such as ellipticine and olivicine, which hold interest in light of their anti-cancer activity [3]. Furthermore, the sulfur analog of ellipticine also displays high anti-cancer activity [4].

The Combe, Gold–Jacobs, and Knorr methods for quinone synthesis and the Leimgruber–Batcho method for indole synthesis were used for constructing the new ring. Amino derivatives of benzo[*b*]thieno[2,3-*c*]pyridines II and III obtained by the reduction of the corresponding nitro derivatives I and VII on Pd/C in methanol were used as starting materials for construction of the pyridine ring. The structures of amines II and VIII were supported by elemental analysis (Table 1) and IR and PMR spectral data (Table 2).



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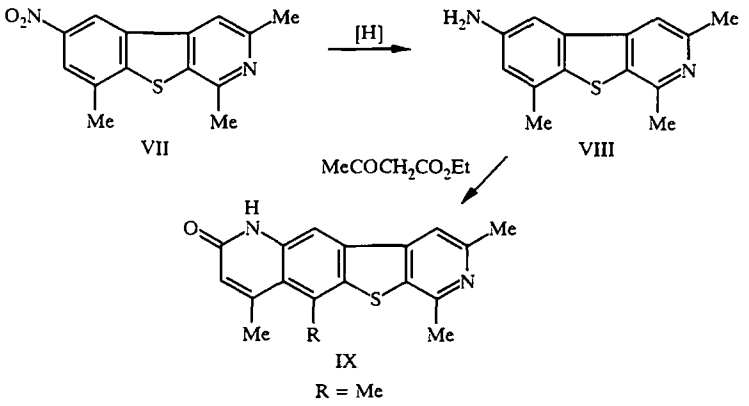
The Combe cyclization involved condensation of 1,3-dimethyl-6-aminobenzo[*b*]thieno[2,3-*c*]pyridine II with acetylacetone and subsequent cyclization of anil (III) without separation by the action of sulfuric acid to give 2,4,7,9-tetramethyldipyrido[3,4-*b*:2,3-*f*]benzo[*b*]thiophene IV in 47% yield.

2,4-Dimethyl-8-carbomethoxydipyrido[3,4-*b*:2,3-*f*]benzo[*b*]thiophen-7-(10H)-one VI was obtained in 27% yield by the Gold–Jacobs condensation of amine III with the methyl ester of ethoxymethylenemalonic acid and the subsequent thermal cyclization of condensation product V with separation of the latter. 2,4,6,7-Tetramethyldipyrido-[3,4-*b*:2,3-*f*]benzo-[*b*]thiophen-9(10H)-one IX was obtained in the Knorr synthesis in 40% yield by heating 1,3,6-trimethyl-6-aminobenzo-[*b*]thieno[2,3-*c*]pyridine (VIII) with ethyl acetoacetate at reflux in the presence of sulfuric acid.



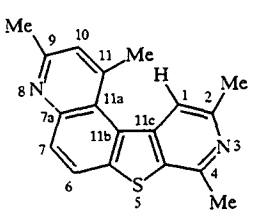
IX

R = Me

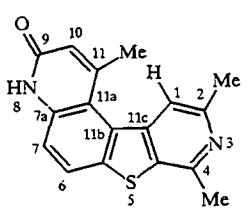
The cyclization by these methods was expected to lead to the formation of products with linear and angular ring fusion (closure of the pyridine ring at positions 7 and 5, respectively). However, we found that only linear pyridines IV, VI, and IX formed. The finding of two singlets for benzene ring protons in the PMR spectrum indicated this ring fusion (Table 2). In the case of angular fusion, the benzene ring protons would appear as doublets. The formation of α-pyridone IX is indicated since the IR band for the carbonyl group in this compound is in the vicinity of 1625 cm^{-1}, which corresponds to an amide structure.

The formation of only linear structures IV, VI, and IX is probably related to steric hindrance to formation of products with angular ring fusion X-XII. Hence, we carried out complete structural optimization of these pyridines using the PCMODEL program [5] and the MMX force field in conjunction with the π-electron approximation.

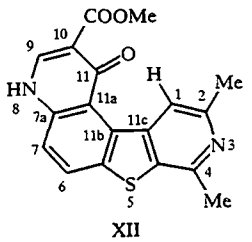
These calculations indicated that IV has 39.8 kJ/mole less steric energy than possible isomer X, while pyridine IX (R = H) has 33.02 kJ/mole less steric energy than possible isomer XI. Such a significant energy difference indicates the high probability for cyclization only to give compounds with linear ring fusion, which is observed experimentally. We note that the greatest contribution to the difference in the steric energies of isomeric linear and angular compounds (ΔE_{st}) is made by the torsional component (ΔE_{tor} = 29.4 for IV and possible isomer X and 32.89 kJ/mole for IX (R = H) and possible isomer XI) These differences reflect the marked breakdown in the planar structure of the aromatic skeleton due to steric repulsion between the methyl group at $C_{(11)}$ and hydrogen atom at $C_{(1)}$ in X–XII.



X



XI



XII

Thus, dihedral angles $C_{(1)}C_{(11c)}C_{(11b)}C_{(11a)}$ = 14.54°, $C_{(11)}C_{(11a)}C_{(11b)}C_{(11c)}$ = 23.97° for pyridine X and $C_{(1)}C_{(11c)}C_{(11b)}C_{(11a)}$ = 14.86° and $C_{(11)}C_{(11a)}C_{(11b)}C_{(11c)}$ = 24.75° for pyridone XI. Furthermore, the methyl group at $C_{(11)}$ in X is extruded from the plane by 18.4°, while this group is extruded by 20.45° in XI. Such deviation from planar structure leads to breakdown in the sp^2-hybridization of $C_{(1)}$, $C_{(11c)}$, $C_{(11b)}$, $C_{(11a)}$, and $C_{(11)}$ and the destabilization of these molecules.

The above situation holds fully for pyridone VI and its possible isomer XII, where ΔE_{st} = 48.3 kJ/mole and ΔE_{tor} = 20.74 kJ/mole. The benzene fragment in XII is considerably deformed: $C_{(2)}C_{(1)}C_{(11c)}C_{(11b)}$ = 177.25° and

TABLE 1. Physical Indices for II, IV, VI, VIII, IX, XIV, and XV

Compound	Chemical formula	Found, %				Calculated, %				mp, °C	R_f	TLC system†	Yield, %
		C	H	N	S	C	H	N	S				
II	$C_{13}H_{12}N_2S$	68,3	5,4	12,3	14,1	68,4	5,3	12,3	14,1	—*	0,25	1:1 Benzene–chloroform	77
IV	$C_{18}H_{16}N_2S$	74,3	5,5	9,5	10,8	73,9	5,5	9,6	11,0	164...167	0,64	10:1 Benzene–ethyl acetate	47
VI	$C_{18}H_{14}N_2O_3S$	64,2	4,3	8,4	9,4	64,0	4,2	8,3	9,5	160...162	0,94	10:1 Benzene–ethanol	27
VIII	$C_{14}H_{14}N_2S$	69,6	5,9	11,6	13,1	69,4	5,8	11,6	13,2	—	0,51	1:1 Benzene–chloroform	65
IX	$C_{18}H_{16}N_2OS$	70,0	5,1	9,2	10,5	70,1	5,2	9,1	10,4	151...154	0,82	6:1 Benzene–ethanol	40
XIV	$C_{17}H_{17}N_3O_2S$	62,3	5,2	12,7	9,8	62,4	5,2	12,8	9,8	261...263	—	—	95
XV	$C_{15}H_{12}N_2S$	71,6	4,9	11,0	12,5	71,4	4,8	11,1	12,7	136...138	0,63	6:1 Benzene–ethyl acetate	68

*Oil.

†On Silufol UV-254 for IV and on Alufol for the other compounds.

TABLE 2. Spectral Indices of II, IV, VI, VIII, IX, XIV, and XV

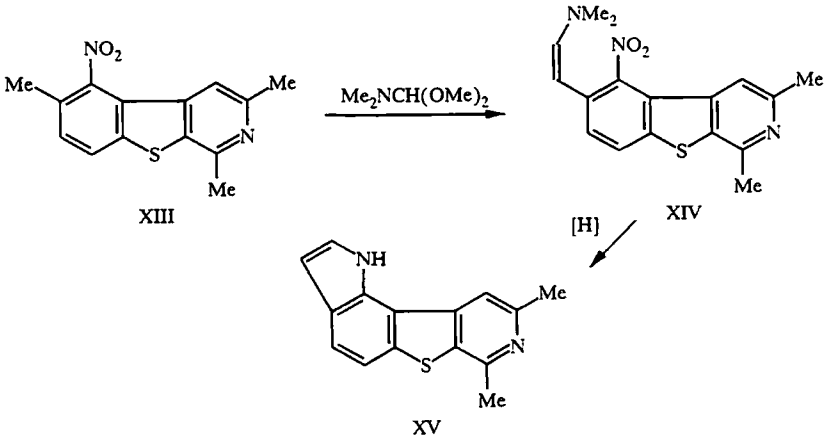
Compound	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm, coupling constant (J), Hz
II	3410, 3320 (N–H)*	2,58 (1H, s, 3-CH_3), 2,71 (1H, s, 1-CH_3), 4,25 (2H, s, 6-NH_2), 7,31 (1H, d.d, J = 7,5, 3,3, 7-H), 7,37 (1H, d, J = 7,5, 8-H), 7,59 (1H, s, 4-H), 7,92 (1H, d, J = 3,3, 5-H)
IV	–	2,34 (6H, s, 2,4-$(CH_3)_2$), 2,53 (1H, s, 7-CH_3), 3,14 (1H, s, 9-CH_3), 7,056 (1H, s, 1-H), 7,064 (1H, s, 8-H), 7,18 (1H, s, 6-H), 7,49 (1H, s, 11-H) †
VI	1690 (C=O), 1720 (O–C=O), 1610 (C=C)	2,68 (1H, s, 2-CH_3), 2,81 (1H, s, 4-CH_3), 3,91 (1H, s, 8-(CO_2CH_3)), 7,88 (1H, s, 1-H), 7,92 (1H, s, 6-H), 7,96 (1H, s, 9-H), 8,00 (1H, s, 11-H) †
VIII	3410, 3320 (N–H)*	2,57 (1H, s, 3-CH_3), 2,71 (1H, s, 1-CH_3), 2,76 (1H, s, 8-CH_3), 4,23 (2H, s, 6-NH_2), 7,34 (1H, d, J = 3,2, 7-H), 7,60 (1H, s, 4-H), 7,90 (1H, d, J = 3,2, 5-H)
IX	1625 (C=O), 3140 (N–H)	2,36 (1H, s, 2-CH_3), 2,71 (1H, s, 4-CH_3), 2,58 (1H, s, 6-CH_3), 2,68 (1H, s, 7-CH_3), 7,07 (1H, s, 1-H), 7,09 (1H, s, 8-H), 7,53 (1H, s, 11-H) †
XIV	1620 (C=C), 1210 (C–N)	2,48 (1H, s, 3-CH_3), 2,62 (1H, s, 1-CH_3), 3,51 (6H, s, 2′-$N(CH_3)_2$), 6,07 (1H, d, J = 6,6, 2′-H), 7,11 (1H, d, J = 6,6, 1′-H), 7,17 (1H, s, 4-H), 7,60 (1H, d, J = 8,2, 7-H), 8,61 (1H, d, J = 8,2, 8-H)
XV	3200 (N–H)	2,51 (1H, s, 2-CH_3), 2,67 (1H, s, 4-CH_3), 6,73 (1H, d, J = 5,4, 8-H), 7,06 (1H, d, J = 5,4, 9-H), 7,28 (1H, s, 1-H), 7,43 (1H, d, J = 6,6, 7-H), 7,51 (1H, d, J = 6,6, 6-H), 9,23 (1H, s, N–H)

*IR spectra taken in chloroform, other spectra taken in KBr pellets.

†PMR spectra taken in pyridine-d_5 (TMS), other spectra taken in $CDCl_3$ (TMS).

$C_{(7a)}C_{(11a)}C_{(11b)}C_{(11c)}$ = 166.26°. A large difference is observed in the heats of formation of pyridine VI (H_f = −61.1 kJ/mole) and its isomer XII (H_f = 15.8 kJ/mole). Hence, the formation of the isomer with linear fusion VI is much preferred.

The formation of the structure with angular ring fusion was achieved only when the pyrrole ring was added to 1,3,6-trimethyl-5-nitrobenzo[*b*]thieno[2,3-*c*]pyridine XIII in the Leimgruber–Batcho reaction.



This reaction involves the condensation of nitropyridine XIII with the dimethylacetal of dimethylformamide in DMF at reflux with subsequent formation of the pyrrole ring by reduction of intermediate enamine (XIV) on Pd/C in methanol in good yield to give 2,4-dimethylpyrido[3,4-*b*]pyrrolo[2,3-*e*]benzo[*b*]thiophene (XV).

EXPERIMENTAL

The PMR spectra were taken on a Gemini-200 spectrometer at 200 MHz in $CDCl_3$ for II, VIII, XIV, and XV and in pyridine-d_5 for VI, VI, and IX with TMS as the internal standard. The IR spectra were taken on a Specord M-80 spectrometer in chloroform for II and VIII and in KBr pellets for VI, IX, and XIV. The physical parameters of the products are given in Table 1, while the PMR and IR spectral data for these compounds are given in Table 2. The course of the reaction and purity and isomer composition of the products were monitored by thin-layer chromatography on Silufol UV-254 plates for IV and Alufol plates for the other compounds.

Samples of starting compounds I, VII, and XIII were prepared according to our previous procedure [1].

General Method for the Reduction of I and VII. The reductions of nitropyridines I and VII were carried out with hydrogen in methanol using 10% palladium on charcoal. After no further hydrogen was absorbed, the Pd/C sample was filtered off and the solvent was evaporated. The residue was subjected to chromatography on an alumina column using 1:1 benzene–chloroform as the eluent. The solvent was evaporated to give amines II and VIII as viscous yellow oils.

2,4,7,9-Tetramethyldipyrido[3,4-*b*:2,3-*f*]benzo[*b*]thiophene (IV). A mixture of 1.53 mmole amine II and 10 ml acetylacetone was heated at reflux for 90 min on an oil bath. After cooling, 0.5 ml concentrated sulfuric acid was added and the mixture was heated at reflux for an additional 30 min. After cooling, the mixture was poured into excess water and extracted with chloroform. The extract was washed with aqueous sodium bicarbonate and water and dried over magnesium sulfate. The solvent was evaporated and the residue of product IV was subjected to chromatography on a silica gel column using 10:1 benzene–ethyl acetate as the eluent, collecting the fraction with R_f 0.64. Product IV was recrystallized from benzene.

2,4-Dimethyl-8-carbomethoxydipyrido[3,4-*b*:2,3-*f*]benzo[*b*]thiophen-7-(10H)-one (VI). A mixture of 0.88 mmole amine II and 0.9 mmole methyl ester of ethoxymethylenemalonic acid in 5 ml toluene was heated at reflux for 4 h. The solvent was evaporated and 5 ml diphenyl ether was added to the residue and the mixture was heated at reflux for an additional 2 h. After cooling, the mixture was poured into 15 ml petroleum ether. The precipitate of pyridine VI was filtered off, washed with petroleum ether, dried in the air, and recrystallized from 2-propanol.

2,4,6,7-Tetramethyldipyrido[3,4-*b*:2,3-*f*]benzo[*b*]thiophen-9(10H)-one (IX). A mixture of 0.95 mmole amine VIII, 5 ml ethyl acetoacetate, and 0.5 ml concentrated sulfuric acid was heated at reflux for 30 min. After cooling, the mixture

was poured into excess water and made neutral by adding aqueous sodium bicarbonate. The precipitated residue of IX was filtered off, washed with water, dried in the air, and recrystallized from 2-propanol.

2,4-Dimethylpyrido[3,4-*b*]pyrrolo[2,3-*e*]benzo[*b*]thiophene (XV). A mixture of 1.1 mmole nitropyridine XIII and 1.3 mmole dimethyl acetal of dimethylformamide in 7 ml DMF was heated at reflux for 5 h. The excess solvent was distilled off at reduced pressure. The residue was poured into excess water and extracted with chloroform. The extract was washed with water and dried over magnesium sulfate. The solvent was evaporated and the residue, enamine XIV, was recrystallized from methanol.

The reduction of 1.05 mmole enamine XIV was carried out with hydrogen in methanol over palladium on charcoal as the catalyst. At the end of hydrogen absorption, the Pd/C catalyst was filtered off and the solvent was evaporated. The residue of XV was recrystallized from benzene–hexane.

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