SYNTHESIS AND REACTIONS OF FURO[3,2-*c*]PYRIDINE DERIVATIVES*

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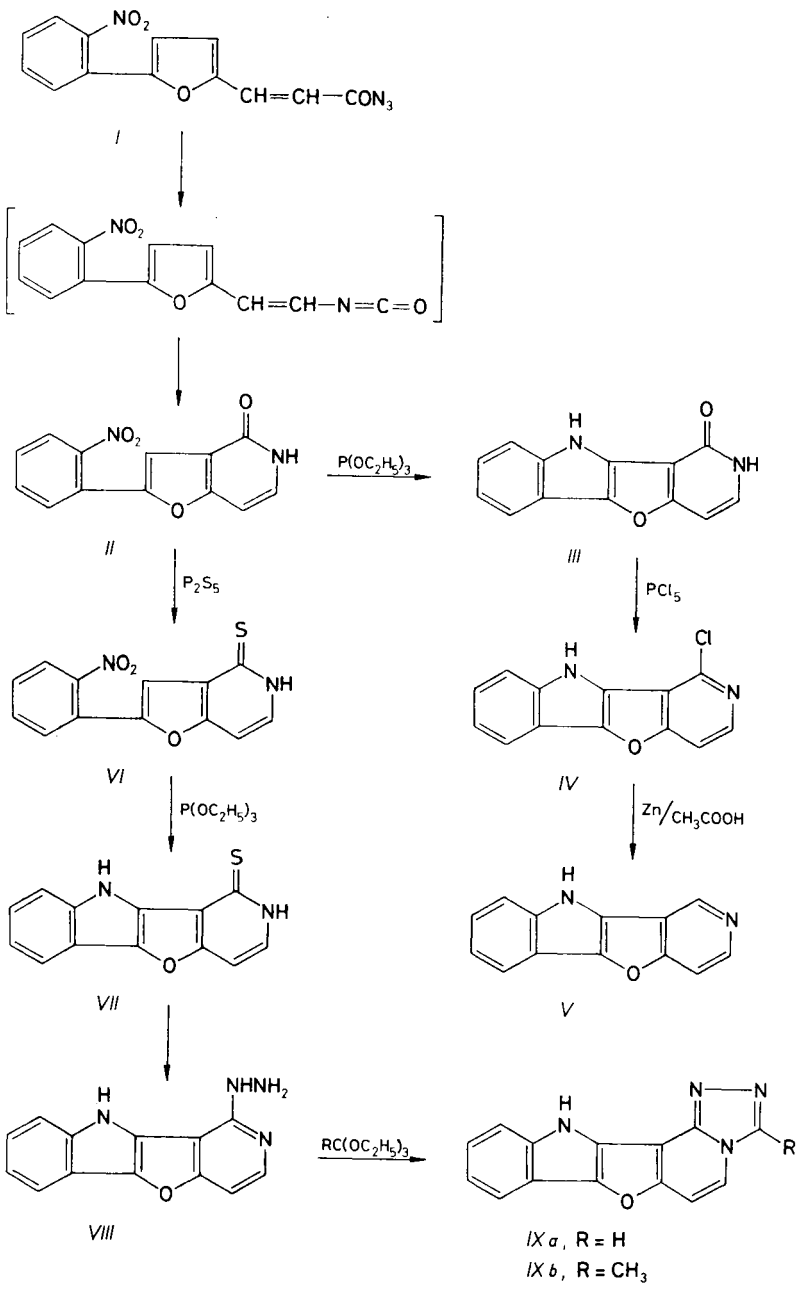
The synthesis of a new type of condensed hetrocycle pyrido[3',4' : 4,5]furo[3,2-*b*]indole (*V*) and 1,2,4-triazolo[4'',3'' : 1',2']pyrido[3',4' : 4,5]furo[3,2-*b*]indoles (*IX*) is described and the substitution nucleophilic reaction with 2-(2-nitrophenyl)-4-chlorofuro[3,2-*c*]pyridine (*X*) is presented.

Many derivatives of furo[3,2-*c*]pyridines are biologically active; thus, *e.g.* 2,4,6-trimethylfuro[3,2-*c*]pyridines are analgesics, antipyretics and drugs with antiinflammatory effects[1,2]. The condensed furo[3,2-*c*]pyridines are used for curing ill anaemic cells[3]. Substances prepared by N-alkylation of furo[3,2-*c*]pyridines and reduction of their quaternary salts[4] reveal antiinflammatory, anticoagulatory and vasodilatatory properties[5,6]. In continuation of our preceding papers[7-9] we present herewith the synthesis of substituted furo[3,2-*c*]pyridine derivatives and the examination of their reactions.

Thermal decomposition of 3-[5-(2-nitrophenyl)]-2-furylpropenoic acid azide (*I*), obtained from the corresponding chloride[10] in a high-boiling solvent[11] *via* 2-(2-nitrophenyl)-4,5-dihydrofuro[3,2-*c*]pyridin-4-one (*II*); the latter reacted with triethyl phosphite under conditions of a deoxygenative cyclization to give 1,2-dihydropyrido[3',4' : 4,5]furo[3,2-*b*]indole-1-one (*III*). Upon reaction with phosphorus pentachloride compound *III* aromatized to afford 1-chloropyrido[3',4' : 4,5]furo[3,2-*b*]indole (*IV*) the reduction of which led to a new type of condensed heterocycle pyrido[3',4' : 4,5]furo[3,2-*b*]indole (*V*).

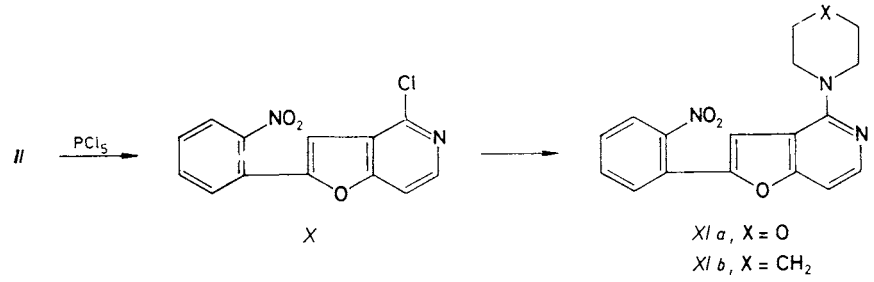
Treatment of 2-(2-nitrophenyl)-4,5-dihydrofuro[3,2-*c*]pyridin-4-one (*II*) with phosphorus pentasulfide afforded the corresponding 2-(2-nitrophenyl)-4,5-dihydrofuro[3,2-*c*]pyridine-4-thione (*VI*); its cyclization with triethyl phosphite gave 1,2-dihydropyrido[3',4' : 4,5]furo[3,2-*b*]indole-1-thione (*VII*). Reaction of the latter with hydrazine hydrate yielded the corresponding 1-hydrazinopyrido[3',4' : 4,5]furo[3,2-*b*]indole (*VII*, not isolated in pure state), which furnished 1,2,4-triazolo[4'',3'' : 1',2']pyrido[3',4' : 4,5]furo[3,2-*b*]indole (*IXa*) and its 3-methyl derivative (*IXb*) with triethyl orthoformiate and triethyl orthoacetate, respectively, Scheme 1.

* This paper should be considered as Part CCXVI in the series Furan Derivatives.


NO2
CH=CH—CON3
I
CH=CH—N=C=O
II
P(OC2H5)3
III
P2S5
PCl5
VI
IV
Zn/CH3COOH
VII
V
NHNH2
VIII
RC(OC2H5)3
IX a, R = H
IX b, R = CH3

SCHEME 1

Treatment of *II* with phosphorus oxychloride gave 2-(2-nitrophenyl)-4-chlorofuro-[3,2-*c*]pyridine (*X*), which afforded with nucleophiles the corresponding 4-substituted 2-(2-nitrophenyl)furo[3,2-*c*]pyridines (*XIa*, *b*) (Scheme 2).



SCHEME 2

The IR spectra of these compounds showed an absorption band at 3 170 to 3 110 cm^{-1} (ν(C—H_{arom})), the carbonyl group of *I*—*III* absorbed at 1 640 to 1 680 cm^{-1}. The wave numbers of N—H bonds varied within 3 210—3 250 cm^{-1}, those of C=S and C—Cl bonds within 1 570—1 575 and 790 cm^{-1}, respectively. Compounds *I*, *II*, *VI* and *X*—*XI* were characteristic of $\nu_{as}(NO_2)$ and $\nu_s(NO_2)$ bands at 1 515—1 530 and 1 330—1 360 cm^{-1}, respectively. Electronic spectra of compounds *I*—*VII* displayed an intense band at 308—360 nm and a weaker one at 218—287 nm. The relatively high λ_{max} values are subject to the extension of the conjugated system.

Structure of the synthesized compounds was corroborated by ^{1}H NMR spectroscopy. Compound *I* is the *E* isomer, since the coupling constant between protons H_A and H_B $^3J_{A,B}$ = 15·7 Hz. The absence of the $C_{(3)}$—H signal, when compared with that of the starting *I*, was in favour of structure *II*. Structures of compounds *III* and *VI* were proved by the absence of the $C_{(2)}$—H signal originally present in the respective starting compounds *II* and *III*. Replacement of oxygen for sulfur in compounds *II* and *III* was associated with a downfield shift of furopyridine proton signals. The position of pyridine ring protons was also downfield shifted by aromatization of *IV*, *V*, *X*, *XI*. The structure of compound *V* was backed by the presence of a $C_{(1)}$—H signal, its chemical shift value is in the interval reported for the fundamental skeleton[11-13]. Formation of 1,2,4-triazine derivatives *IX* was corroborated by the presence of $C_{(3)}$—H or $C_{(3)}$—CH_3 protons.

Compounds *II*—*XI* revealed in the ^{1}H NMR spectrum coupling constant ^3J = = 8·00—5·6 Hz, compounds *II*, *VI*, *X*, *XI* displayed a long-range coupling constant between $C_{(7)}$—H of the pyridine system and $C_{(3)}$—H of the furan ring $^5J_{3,7}$ = = 0·76—0·70 Hz.

EXPERIMENTAL

3-[5-(2-Nitrophenyl)-2-furyl]propenoic Acid Azide (*I*)

A solution of 3-[5-(2-nitrophenyl)-2-furyl]propenoic acid chloride[10] (2·78 g, 10 mmol) in dioxane (10 ml) was added to sodium azide (1·26 g, 20 mmol) dissolved in water–dioxane (14 ml, 1 : 1) at 0°C; the mixture was kept at 5°C for 10 min, poured on crushed ice and the precipitate was filtered off. Yield 2·57 g (90·6%), m.p. 89–90°C (benzene). For $C_{13}H_8N_4O_4$ (284·2) calculated: 54·94% C, 2·84% H, 19·72% N; found: 54·82% C, 2·70% H, 20·02% N. IR spectrum ν_{max}, cm^{-1}: 2 120 (N_3), 1 680 (C=O), 1 525 ($(NO_2)_{as}$), 1 357 ($(NO_2)_s$). UV spectrum, λ_{max}, nm (log ε, $m^2 . mol^{-1}$): 245 (3·19), 365 (3·35). ^{1}H NMR spectrum, δ, ppm: 6·28 (1 H, d, $C_{(A)}$—H), 7·65 (1 H, d, $C_{(B)}$—H), 7·10 (1 H, d, $C_{(3)}$—H), 7·00 (1 H, d, $C_{(4)}$—HN, 8·04–7·70 (4 H, m, H_{arom}), $J_{A,B}$ = 15·7 Hz, $J_{3,4}$ = 4·0 Hz.

2-(2-Nitrophenyl)-4,5-dihydrofuro[3,2-*c*]pyridine-4-one (*II*)

A solution of *I* (4 g, 14 mmol) in benzene (300 ml) was added to the mixture of diphenyl ether (10 ml) and tributylamine (2·59 g, 14 mmol) heated to 230–235°C at such a rate as the lower-boiling solvent continuously distilled. After benzene had been removed, the mixture was coled and the precipitate was filtered off. Yield 2·70 g (75%), m.p. 235°C (water). For $C_{13}H_8N_2O_4$ (256·2) calulated: 60·95% C, 3·15% H, 10·94% N; found (61·03% C, 3·21% H, 10·74% N. IR spectrum ν_{max}, cm^{-1}: 1 640 (C=O), 1 530 ($(NO_2)_{as}$), 1 360 ($(NO_2)_s$). UV spectrum λ_{max}, nm (log ε, m^2 mol^{-1}): 218 (3·16), 308 (3·09). ^{1}H NMR spectrum, δ, ppm: 7·36 (1 H, d, $C_{(6)}$—H), 6·62 (1 H, dd, $C_{(7)}$—H), 7·34 (1 H, d, $C_{(3)}$—H), 7·98–7·56 (4 H, m, H_{arom}), $J_{6,7}$ = 7·8 Hz, $J_{3,7}$ = 0·76 Hz. Mass spectrum, *m/z* (relat. intens., %): 256 (80·7), 226 (48), 211 (38·5), 187 (48), 184 (34·6), 143 (100), 115 (34·6), 113 (34·6), 70 (73), 53 (34·6).

1,2-Dihydropyrido[3′,4′ : 4,5]furo[3,2-*b*]indole-1-one (*III*)

Compound *II* (1·28 g, 5 mmol) was refluxed in triethyl phosphite (6·64 g, 40 mmol) in a nitrogen atmosphere. The unreacted triethyl phosphite was distilled off under reduced pressure and the solid residue was crystallized. Yield 0·78 g (69·2%), m.p. 327–329°C (methanol). For $C_{13}H_8N_2O_2$ (224·2) calculated: 69·64% C, 3·60% H, 12·49% N; found: 69·83% C, 3·52% H, 12·31% N. IR spectrum ν_{max}, cm^{-1}: 1 650 (C=O). UV spectrum λ_{max}, nm (log ε, m^2 mol^{-1}): 235 (3·16), 360 (3·00). ^{1}H NMR spectrum: 7·35 (1 H, d, $C_{(3)}$—H), 6·81 (1 H, d, $C_{(4)}$—H), 7·75–7·18 (4 H, m, H_{arom}), $J_{3,4}$ = 8·0 Hz. Mass spectrum, *m/z* (relat. intens., %): 224 (100), 135 (8·6), 168 (11·6), 140 (11·4), 112 (14·3).

1-Chloropyrido[3′,4′ : 4,5]furo[3,2-*b*]indole (*IV*)

A mixture of *III* (2·24 g, 10 mmol) and phosphorus pentachloride 2·08 g, 10 mmol) was refluxed in phosphorus oxychloride (10 ml) for 4 h. The mixture was cooled, poured onto crushed ice and the separated solid was filtered off. Yield 1·94 g (80·0%), m.p. 225–227°C (chloroform). For $C_{13}H_7ClN_2O$ (242·7) calculated: 64·34% C, 2·91% H, 14·60% Cl, 11·54% N; found: 64·13% C, 2·98% H, 14·73% Cl, 11·49% N. IR spectrum ν_{max}, cm^{-1}: 790 (C—Cl). UV spectrum λ_{max}, nm (log ε, m^2 mol^{-1}): 254 (3·04), 320 (3·26). ^{1}H NMR spectrum, δ, ppm: 8·27 (1 H, d, $C_{(3)}$—H), 7·76 (1 H, d, $C_{(4)}$—H), 7·79–7·18 (4 H, m, H_{arom}), $J_{3,4}$ = 5·5 Hz. Mass spectrum, *m/z* (relat. intens., %): 242 (100), 179 (20·3), 151 (15·6), 121 (9·4), 76 (20·3), 28 (18·8).

Pyrido[3',4' : 4,5]furo[3,2-*b*]indole (*V*)

Zinc (0·84 g, 12·8 mmol) was added to *IV* (0·5 g, 2·1 mmol) dissolved in formic acid (5 ml) and the mixture was refluxed for 7 h. The solvent was distilled off, the residue was neutralized and the precipitate was filtered off. Yield 0·23 g (52·5%),m.p. 240—242°C (tetrahydrofuran). For $C_{13}H_8N_2O$ (208·2) calculated: 75·00% C, 3·87% H, 13·46% N; found: 74·89% C, 3·74% H, 13·20% N. ^{1}H NMR spectrum, δ, ppm 9·07 (1 H, s, $C_{(1)}$—H), 8·52 (1 H, d, $C_{(3)}$—H), 7·44 (1 H, d, $C_{(4)}$—H), 7·76—7·23 (4 H, m, H_{arom}), $J_{3,4}$ = 5·6 Hz.

2-(2-Nitrophenyl)-4,5-dihydrofuro[3,2-*c*]pyridine-4-thione (*VI*)

2-(2-Nitrophenyl)-4,5-dihydrofuro[3,2-*c*]pyridin-4-one (0·5 g, 2 mmol) and phosphorus pentasulfide (0·44 g, 2 mmol) was refluxed in pyridine (10 ml) for 4 h. The cooled mixture was poured on a crushed ice and the product was filtered off. Yield 0·45 g (82·0%), m.p. 221—222°C (ethanol). For $C_{13}H_8N_2O_3S$ (272·3) calculated: 57·34% C, 2·96% H, 10·28% N, 11·76% S; found: 57·12% C, 2·82% H, 10·07% N, 11·94% S. IR spectrum ν_{max}, cm^{-1}: 1 570 (C=S), 1 515 ($(NO_2)_{as}$) 1 330 ($(NO_2)_s$). ^{1}H NMR spectrum, δ, ppm: 7·64 (1 H, d, $C_{(6)}$—H), 7·13 (1 H, dd, $C_{(7)}$—H), 7·37 (1 H, d, $C_{(3)}$—H), 8·06—7·69 (4 H, m, H_{arom}), $J_{6,7}$ = 6·8 Hz, $J_{3,7}$ = 0·7 Hz.

1,2-Dihydropyrido[3',4' : 4,5]furo[3,2-*b*]indole-1-thione (*VII*)

Compound *VI* (1·36 g, 5 mmol) was refluxed with tirethyl phosphite (6·64 g, 40 mmol) in a nitrogen atmosphere. The unreacted triethyl phosphite was removed under diminished pressure and the residue was crystallized. Yield 0·78 g (65·1%), m.p. over 350°C. For $C_{13}H_8N_2OS$ (240·2) calculated: 65·00% C, 3·36% H, 11·66% N; found: 65·23% C, 3·45% H, 11·42% N. IR spectrum ν_{max}, cm^{-1}: 1 575 (C=S). UV spectrum λ_{max}, nm (log ε, m^2 mol^{-1}): 287 (3·02), 345 (3·05). ^{1}H NMR spectrum, δ, ppm: 8·31 (1 H, d, $C_{(3)}$—H), 7·44 (1 H, d, $C_{(4)}$—H), 7·78—7·11 (4 H, m, H_{arom}), $J_{3,4}$ = 6·0 Hz.

1-Hydrazinopyrido[3',4' : 4,5]furo[3,2-*b*]indole (*VIII*)

Compound *VII* (2·40 g, 10 mmol) was stirred with 94%-hydrazine hydrate (15 ml) at 90°C for 8 h. The mixture was cooled, poured on ice, the solid precipitate was filtered off and used for further reaction without any purificaion.

1,2,4-Triazolo[4'',3'' : 1',2']pyrido[3',4' : 4,5]furo[3,2-*b*]indole (*IXa*)

A mixture of *VIII* (1·19 g, 5 mmol) and triethyl orthoformiate (2 g, 14 mmol) was refluxed in dimethylformamide (10 ml) for 4 h, cooled and the crystalline product was filtered off. Yield 0·76 g (61%), m.p. 211—213°C (decomp. dimethylformamide). For $C_{14}H_8N_4O$ (248·2) calculated: 67·74% C, 3·25% H, 22·54% N; found: 67·57% C, 3·16% H, 22·31% N. ^{1}H NMR spectrum, δ, ppm: 7·35 (1 H, d, $C_{(5)}$—H), 7·31 (1 H, s, $C_{(3)}$—H), 6·60 (1 H, d, $C_{(6)}$—H), 7·99—7·49 (4 H, m, H_{arom}), $J_{5,6}$ = 8·0 Hz.

3-*Methyl*-1,2,4-*triazolo*[4'',3'' : 1',2']*pyrido*[3',4' - 4,5]*furo*[3,2-b]-*indole* (IXb) was prepared as *IXa* employing triethyl orthoacetate. Yield 58%, m.p. 225°C (decomp., dimethylformamide). For $C_{15}H_{10}N_4O$ (262·3) calculated: 68·69% C, 3·84% H, 21·36% N; found: 68·53% C, 3·72% H, 21·15% N. ^{1}H NMR spectrum, δ, ppm: 7·28 (1 H, d, $C_{(5)}$—H), 6·57 (1 H, d, $C_{(6)}$—H), 7·87 to 7·32 (4 H, m, H_{arom}), 2·76 (3 H, s, $C_{(3)}$—CH_3), $J_{5,6}$ = 7·9 Hz.

2-(2-Nitrophenyl)-4-chlorofuro[3,2-*c*]pyridine (*X*)

Compound *II* (2·56 g, 10 mmol) and phosphorus oxychloride (2·50 g, 25 mmol) was refluxed for 4 h, cooled, poured on ice, the solid was filtered off and washed with 5%-sodium hydroxide. Yield 1·77 g, (64·7%), m.p. 139—141°C (ether). For $C_{13}H_7ClN_2O_3$ (274·7) calculated: 56·85% C, 2·57% H, 12·91% Cl, 10·20% N; found: 56·61% C, 2·38% H, 13·04% Cl, 10·06% N. IR spectrum ν_{max}, cm^{-1}: 1 528 ($(NO_2)_{as}$), 1 360 ($(NO_2)_s$), 790 (C—Cl). ^1H NMR spectrum, δ, ppm: 8·30 (1 H, d, $C_{(6)}$—H), 7·72 (1 H, dd, $C_{(7)}$—H), 7·49 (1 H, d, $C_{(3)}$—H), 8·10—7·65 (4 H, m, H_{arom}), $J_{6,7}$ = 6·0 Hz, $J_{3,7}$ = 0·75 Hz.

2-(2-Nitrophenyl)-4-morpholinofuro[3,2-*c*]pyridine (*XIa*)

Morpholine (0·87 g, 10 mmol) and *X* (0·55 g, 2 mmol) were refluxed in ethylene glycol monomethyl ether (10 ml) at 90°C for 48 h, the mixture was poured on ice and the precipitate was filtered off. Yield 0·38 g (58%), m.p. 118—120°C (ethanol). For $C_{17}H_{15}N_3O_3$ (325·3)calculated: 62·76% C, 4·65% H, 12·92% N; found: 62·52% C, 4·48% H, 12·81% N. IR spectrum ν_{max}, cm^{-1}: 1 525 ($(NO_2)_{as}$), 1 358 ($(NO_2)_s$). ^1H NMR spectrum, δ, ppm: 8·30 (1 H, d, $C_{(6)}$—H), 7·49, (1 H, d, $C_{(3)}$—H), 6·99 (1 H, dd, $C_{(7)}$—H), 8·02—7·6 (4 H, m, H_{arom}), 3·68 (4 H, s, N—CH_2), 3·38 (4 H, s, O—CH_2), $J_{6,7}$ = 6·0 Hz, $J_{3,7}$ = 0·7 Hz.

2-(2-*Nitrophenyl*)-4-*piperidinofuro*[3,2-c]*pyridine* (XIb) was obtained analogously as *XIa*. Yield 61%, m.p. 125—127°C (ethanol). For $C_{18}H_{17}N_3O_3$ (323·4) calculated: 68·86% C, 5·30% H, 13·00% N; found: 68·68% C, 5·19% H, 12·84% N. IR spectrum ν_{max}, cm^{-1}: 1 530 ($(NO_2)_{as}$), 1 357 ($(NO_2)_s$). ^1H NMR spectrum, δ, ppm: 8·29 (1 H, d, $C_{(6)}$—H), 7·50 (1 H, d, $C_{(2)}$—H), 6·86 (1 H, dd, $C_{(7)}$—H), 8·08—7·69 (4 H, m, H_{arom}), 3·27 (4 H, s, HN—CH_3), 1·55 (6 H, s, —CH_2—), $J_{6,7}$ = 6·0 Hz, $J_{3,7}$ = 0·7 Hz.

Spectral Measurements

The IR spectra were measured on a Specord 71 IR (Zeiss, Jena) spectrophotometer using KBr technique and 1 mg/100 mg KBr concentration. The electronic spectra of ethanol or dioxane solutions were taken with a Specord UV VIS (Zeiss, Jena) apparatus in the 200—800 nm range at room temperature and 5 . 10^{-5} mol l^{-1} concentration. The ^1H NMR spectra of hexadeuteriodimethyl sulfoxide solutions were recorded with a Tesla BS 487 C instrument, hexamethyldisiloxane being the reference. The mass spectra were run with an MS 902 S (AEI Manchester) spectrometer at 70 eV, 100 μA trap current and 115—225°C ion source temperature depending on the volatility of the respective derivative.

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