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CONDENSED 1,3,5-TRIAZEPINES—III[1]

DERIVATIVES OF 4,5-DIHYDRO-[1,3,5]TRIAZEPINO[1,2-*a*]BENZIMIDAZOLE

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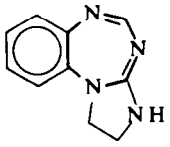
Abstract—Methods have been developed for the synthesis of 2-amino-1-(2-aminoethyl)-benzimidazoles **10**. By ring closures with the aid of suitable C_1-components, derivatives **11a–c**, **13–15** of the novel [1,3,5]triazepino[1,2-*a*] benzimidazole ring system have been obtained.

In part II[1] the synthesis of derivatives of the novel 2,3 - dihydro - 1*H* - imidazo - [1,2-*a*][1,3,5] - benzotriazepine system **1** was described. We now report the synthesis of derivatives of the isomeric 4,5 - dihydro - [1,3,5] - triazepino - [1,2-*a*] - benzimidazole system **2** (3*H*-form shown).



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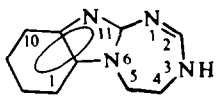
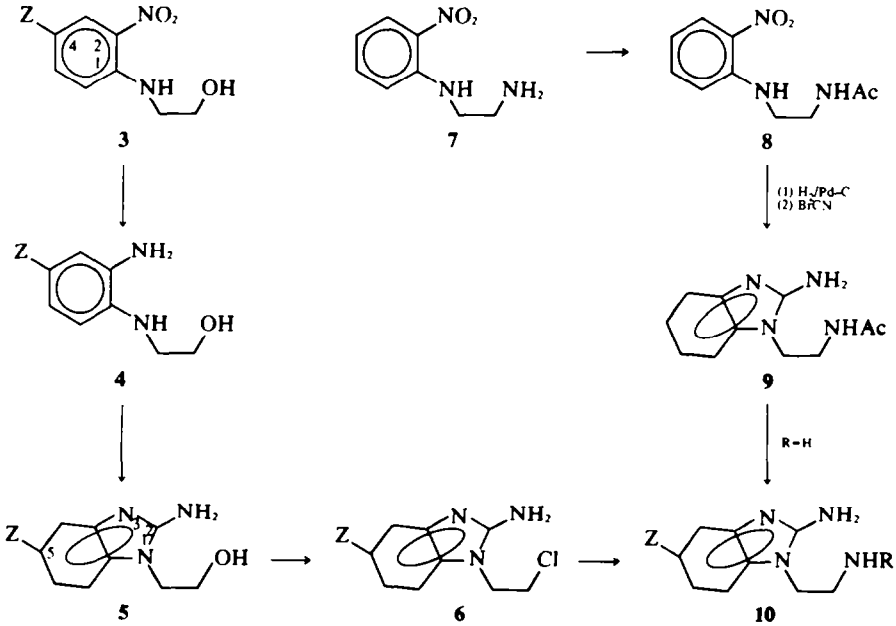


2

2-Amino-1-(2-aminoethyl)-benzimidazoles **10**, starting materials for the synthesis, were obtained starting either with 2-(2-nitranilino)-ethanols **3** or with *N*-(2-nitrophenyl)-ethylenediamine **7** as shown in Scheme 1. The compounds **3** were reduced and treated with cyanogen bromide to yield the benzimidazoles **5**, which were transformed into the compounds **6** and **10**. Successive treatment of **4** (Z = H) with MeNCS and MeI furnished the *N*-methyl amino analogue of **5** (Z = H). Compound **7** was acetylated and the resulting products **8** were reduced, treated with cyanogen bromide and deacetylated to yield, via **9**, the corresponding compounds **10** (R = H). [For the formation of compounds **10** by thermally induced rearrangements of 1 - (2 - aminophenyl) - 2 - iminoimidazolidines, see Ref. 1]. The 2-aminoimidazole derivatives **5**, **6**, **9** and **10** are potentially tautomeric; see Ref. 2 for their actual tautomeric structures.

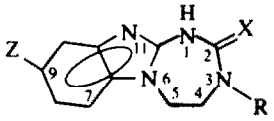
Since, in the 2,3 - dihydro - 1*H* - imidazo - [1,2-*a*][1,3,5] - benzotriazepine series phosgene proved to be a less satisfactory ring closure reagent than 1,1'-carbonylidi-imidazole,[1] only the latter was used for the conversion of compounds **10** into the oxo derivatives **11a**. In contrast to the 2,3 - dihydro - 1*H* - imidazo - [1,2-*a*][1,3,5] - benzotriazepine series, the conversions **10**→**11b** could not be effected with CS_2. The inner salts **12** were obtained instead of the expected products. While **12** (R = H) was transformed into **11b** (Z = R = H) by heating, all attempts to effect similar ring closure of **12** (R = n-Bu) failed. Treatment of **10** (Z = H, R = n-Bu) with $CSCl_2$ also failed to furnish **11b** (Z = H, R = n-Bu). The conversion of **10**



Scheme 1.

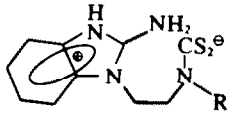
(Z = Cl, R = n-Bu) into the corresponding **11b** could, however, be effected with the aid of 1,1'-thiocarbonyldiimidazole.

Methylation of **11b** (Z = R = H) with MeI furnished the hydriodide of **13** (Z = R = H). The close similarity of its UV spectrum with those of compounds **14** and **15** (Z = Cl, R = n-Bu), in which the double bond is fixed between N-1 and C-2, appears to prove that in the case of **13** (Z = R = H) the tautomeric equilibrium is considerably shifted towards the 3*H*-form.

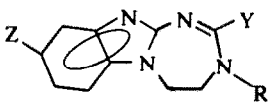


11

a: X = O
b: X = S
c: X = N—$SO_2C_6H_4Me$-*p*



12



13: Y = SMe
14: Y = NH_2
15: Y = H

Attempts to prepare compounds **14** by ammonolysis and morpholinolysis of **13** failed. **14** (Z = Cl, R = n-Bu) was therefore synthesised by allowing to react **10** (Z = Cl, R = n-Bu) with BrCN or $(MeS)_2C{=}NH{\cdot}HI$; the former proved to be the better reagent.

Similarly, when **10** (Z = R = H) was allowed to react with $(MeS)_2C{=}N$-Tos, the tetrahydro derivative **11c** (Z = R = H) was obtained which is potentially tautomeric and which has been formulated with a semicyclic C=N bond on the basis of results obtained with related systems.[3] By refluxing **10** (Z = Cl, R = N-Bu) with triethyl orthoformate ring closure to yield **15** (Z = Cl, R = n-Bu) was effected.

EXPERIMENTAL

2-(2-Aminoanilino)ethanols **4**

Compound **4** (Z = H) has been obtained by Na_2S_x treatment[4,5] or catalytic reduction,[6] compound **4** (Z = Cl) by Na_2SO_3 reduction[7] or catalytic[5] reduction of the corresponding nitranilino derivatives. We have found the $Na_2S_2O_4$ reduction of the latter to be more convenient. Thus, the warm methanolic (60 ml) solns of the nitro compounds **3** (Z = H, Cl) (0·05 mole) were added at 60° under continuous stirring to the aq soln (200 ml) of $Na_2S_2O_4$ (35 g; 0·2 mole) at a rate at which the orange colour of the nitro compounds just disappeared. The MeOH was distilled off, and 40% aq NaOH was added (pH ≈ 8). The products separated on cooling. **4** (Z = H), 55%, m.p. and lit.[4] m.p. 105–6° (from benzene). **4** (Z = Cl), 65%, m.p. and lit.[7] m.p. 122° (from benzene).

2-(2-Amino-1-benzimidazolyl)ethanols **5**

Ethanolic (40 ml) solns of compounds **4** (Z = H, Cl) (30 mmole) were refluxed with BrCN (3·3 g; 31 mmole) for 1 hr. The solvent was distilled off, and the residues were dissolved in hot water (50 ml) and made slightly alkaline (pH ≈ 8) with 40% aq NaOH. The products separated on cooling. **5** (Z = H),† 60%, m.p. 180° (from H_2O). Found: C, 60·88; H, 6·24; N, 23·86. Calc. for $C_9H_{11}N_3O$: C, 61·00; H, 626; N, 23·72%. **5** (Z = Cl), 80%, m.p. 170° (From H_2O). Found C, 51·22; H, 4·91; N, 19·71. Calc. for $C_9H_{10}ClN_3O$: C, 51·07; H, 4·76; N, 19·85%. UV (EtOH): 217 (4·58); 252 (3.78); 294 (3·98).

2-(2-Methylamino-1-benzimidazolyl)ethanol

An anhydrous methanolic (30 ml) soln of MeNCS (7·3 g; 0·1 mole) was added at 0° within 5 min to the anhydrous methanolic (50 ml) soln of **4** (Z = H) (15·2 g; 0·1 mole). The mixture was allowed to stand for 4 hr at room temp., refluxed for 15 min and cooled. MeI (11·8 ml; 0·1 mole) was added. MeSH and heat were evolved, and the mixture started to boil. The mixture was kept for 2 hr at room temp. Dry Et_2O (100 ml) was added, precipitating an oil which gradually solidified. The solid was filtered off, washed with ether and, in order to complete ring closure, refluxed for 8 hr with n-BuOH (70 ml). A crystalline iodide (16 g) separated, when the mixture was kept overnight in a refrigerator. The aq soln of the product was made alkaline with 10% aq K_2CO_3 to precipitate colourless crystals (8·4 g; 44%) of the title compound, m.p. >200° (dec.; from EtOH). Found: C, 62·64; H, 6·91; N, 22·16. Calc. for $C_{10}H_{11}N_3O$: C, 62·80; H, 6·85; N, 21·98%.

2-Amino-1-(2-chloroethyl)benzimidazoles **6**

Compounds **5** (Z = H, Cl) (30 mmole) were refluxed with $SOCl_2$ (30 ml) for 30 min. The excess reagent was distilled off, and the residues were taken up in MeOH (50 ml). The solvent was distilled off, and the residues were dissolved in water (120 ml) and made slightly alkaline (pH ≈ 8) with 10% aq Na_2CO_3 to precipitate the title compounds in 90% yield. **6** (Z = H), m.p. 135° (from benzene). Found: Cl, 18·41; N, 20·82. Calc. for $C_9H_{10}ClN_3$: Cl, 18·12; N, 21·48%. **6** (Z = Cl), m.p. 147–9° (from benzene). Found: C, 47·32; H, 4·22; N, 18·31. Calc. for $C_9H_9Cl_2N_3$: C, 46·98; H, 3·94; N, 18·26%.

1-(2-Chloroethyl)-2-methylaminobenzimidazole

2-(2-Methylamino-1-benzimidazolyl)ethanol (2·0 g; 10·4 mmole) was treated with $SOCl_2$ (10 ml) at room temp. A green soln resulted which was evaporated to dryness in vacuo. The residue was triturated with acetone, until it crystallised, it was dissolved in warm water and treated with 10% aq K_2CO_3 to precipitate 1·06 g (49%) of the title compound, m.p. 145° (from EtOAc-light petroleum). Found: C, 57·53; H, 5·84; Cl, 16·68; N, 20·17. Calc. for $C_{10}H_{12}ClN_3$: C, 57·28; H, 5·77; Cl, 16·91; N, 20·04%.

N-Acetyl-N-(2-nitrophenyl)ethylenediamine **8**

A mixture of **7**' (20 g; 0·11 mole), benzene (100 ml) and Ac_2O (11–17 ml; 0·11–0·17 mole) was refluxed for 30 min. The solvents were either distilled off *in vacuo*, and the residue was triturated with water (100 ml) until it turned crystalline; otherwise light petroleum (200 ml) was added to the benzene soln to precipitate the product. Yield 16·4–18 g (73–80%), yellow crystals, m.p. 103° (from benzene-light petroleum). Found: C, 53·78; H, 5·96; N, 18·72. Calc. for $C_{10}H_{13}N_3O_3$: C, 53·80; H, 5·87, N, 18·83%. UV (EtOH) 236 (4·33); 280 (3·70); 423 (3·80).

N-[2-(2-Amino-1-benzimidazolyl)ethyl]acetamide hydrobromide (**9**·*HBr*)

The above nitro compound (16·4 g; 73·5 mmole) was hydrogenated in ethanolic (300 ml) soln at room temp. in the presence of a Pd–C catalyst. When the theoretical amount of H_2 was taken up, the catalyst was removed by rapid filtration, and BrCN (8·8 g; 80 mmole) was immediately added to the colourless filtrate. The mixture was refluxed for 1·5 hr (during which period it turned dark) and concentrated to about one third of its original volume. Et_2O (500 ml) was added to precipitate 20·5 g (96%) of the title compound which was filtered off and washed with acetone and cold i-PrOH. M.p. 205–6° (from EtOH–acetone–Et_2O). Found: C, 45·90; H, 4·79; Br, 27·78. Calc. for $C_{11}H_{15}BrN_4O$: C, 45·68; H, 5·23; Br, 27·63%. UV (EtOH): 208 (4·46); 250 (3·46); 284 (3·71).

†This compound and its preparation according to the method described have been mentioned without experimental detail in Ref. 5.

N-(2-Amino-1-benzimidazolyl)ethylenediamines **10**

(a) Mixtures of compounds **6** (Z = H, Cl) (0·01 mole) and n-$BuNH_2$ (10 ml) were refluxed for 6 hr. The excess amine was distilled off, and the residues were dissolved in water (25 ml) and made slightly alkaline (pH ≈ 9–10) with 10% aq NaOH to precipitate the crystalline products. **10** (Z = H, R = n-Bu), 98%, m.p. 163–4° (EtOH). Found C, 67·54; H, 8·71; N, 24·03. Calc. for $C_{13}H_{20}N_4$: C, 67·20; H, 8·68; N, 24·12%. **10** (Z = Cl, R = n-Bu), 93%, m.p. 158° (toluene). Found: C, 58·28; H, 7·30; N, 20·85. Calc. for $C_{13}H_{19}ClN_4$: C, 58·53; H, 7·18; N, 21·00%.

(b) The dihydrobromide, m.p. 281–2° (from EtOH-Et_2O), of the latter compound was obtained by evaporating to dryness *in vacuo* its 48% aq HBr soln.

(c) **6** (Z = H) (3·0 g; 15 mmole) was kept in a sealed tube with an ethanolic (30 ml) NH_3 (2·4 g) soln for 16 hr at 120°. The NH_4Cl was filtered off, and 48% aq HBr was added. The dry residue of the mixture was triturated with acetone and recrystallized from MeOH-Et_2O to yield 2·5 g (49%) of **10** · 2 HBr (Z = R = H), identical, according to m.ps and IR spectra with a sample obtained as described under (d).

(d) **9** · HBr (8·7 g; 30 mmole) was refluxed for 1 hr with a mixture of 48% aq HBr and water (25 ml each). The mixture was evaporated to dryness, and the residue was triturated with acetone and recrystallized from MeOH-Et_2O to yield 8·35 g (64%) of **10** · 2 HBr (Z = R = H), m.p. 281–2°. Found: Br, 47·35; N, 16·18. Calc. for $C_9H_{14}Br_2N_4$: Br, 47·38; N, 16·56%. UV spectra (EtOH): **10** · 2 HBr (Z = R = H): 204 (4·69); 250 (3·34); 276 (3·90); 282 (3·88); **10** (Z = H, R = n-Bu): 212 (4·71); 250 (3·93); 285 (3·94); 334 (2·31) {same in EtOH + conc. HCl: 204 (4·72); 222 (4·18), sh; 276 (3·98); 282 (3·94); 328 (2·40); 338 (2·40)}. **10** (Z = Cl, R = n-Bu): 218 (4·66); 253 (3·80); 295 (3·99) {same in EtOH + conc. HCl: 210 (4·69); 229 (4·00), sh; 286 (3·92)}. **10** · 2 HBr (Z = Cl, R = n-Bu): 213 (4·62); 254 (3·55); 292 (3·88).

4,5-Dihydro-1H-[1,3,5]triazepino[1,2-a]benzimidazol-2(3H)-ones **11a**

(a) **10** (Z = R = H) (1·76 g; 10 mmoles), dissolved in anhydrous dioxane (100 ml), and 1,1'-carbonyldi-imidazole[8] (2·0 g; 13 mmole), dissolved in dry $CHCl_3$ (40 ml), were mixed and refluxed for 2 hr to yield 0·7 g (35%) of **11a** (Z = R = H), m.p. 298–300° (from DMF). Found: C, 59·17; H, 5·15; N, 27·80. Calc. for $C_{10}H_{10}N_4O$: C, 59·40; H, 4·98; N, 27·71%. UV (EtOH): 250; 282: 300, sh. Owing to the extremely poor solubility of the product, the log ε values were not determined.

(b) **10** (Z = Cl, R = n-Bu) (2·1 g; 7·6 mmole) was refluxed for 1·5 hr with a soln of 1,1'-carbonyldi-imidazole (1·3 g; 8 mmole) in a mixture of anhydrous dioxane (30 ml) and dry $CHCl_3$ (10 ml) to yield 1·18 g (53%) of **11a** (Z = Cl, R = n-Bu), colourless crystals, m.p. 291–4° (from AcOH). Found: Cl, 12·18; N, 18·85. Calc. for $C_{14}H_{17}ClN_4O$: Cl, 12·03; N, 19·01%. ν C=O (KBr) 1695 cm^{-1}.

Reaction of compounds **10** *with carbon disulphide and 1,1'-thiocarbonyldi-imidazole*

(a) **10** · 2 HBr (Z = R = H) (1·0 g; 3 mmole) was treated with a soln of Na (0·15 g; 6 mmole) in MeOH (10 ml). CS_2 (10 ml) was added, and the mixture was refluxed for 1 hr to yield 0·65 g (86%) of the inner salt **12** (R = H), m.p. 203° (dec.). Found: N, 22·72; S, 25·13. Calc. for $C_{10}H_{12}N_4S_2$: N, 22·20; S, 25·41%.

(b) A mixture of **10** (Z = H, R = n-Bu) (0·5 g; 2·1 mmole), MeOH and CS_2 (10 ml, each) and pyridine (0·1 ml) was refluxed for 30 min to yield 0·55 g (85%) of **12** (R = n-Bu), m.p. 162–3° (dec.). Found: N, 18·00; S, 20·43. Calc. for $C_{14}H_{20}N_4S_2$: N, 18·16; S, 20·78%.

Owing to their poor solubility and low thermal stability, compounds **11** could not be recrystallized. However, when prepared from pure starting compounds **10**, they were pure without recrystallization.

(c) A mixture of **10** (Z = Cl, R = n-Bu) (1·7 g; 6·3 mmole), 1,1'-thiocarbonyldi-imidazole (1·6 g; 9·0 mmole) and $CHCl_3$ (20 ml) was refluxed for 10 hr to yield, after cooling, 0·7 g of crystalline **11b** (Z = Cl, R = n-Bu), m.p. 264–6°. A second crop of the product (0·2 g, m.p. 263–6°; total yield 46%) was obtained by triturating the gummy dry residue of the filtrate of the first crop with MeOH. The pure product had a m.p. of 264–6° (from BuOH or $MeNO_2$). Found: C, 54·39; H, 5·54; Cl, 11·61. Calc. for $C_{14}H_{17}ClN_4S$: C, 54·45; H, 5·55; Cl, 11·48%. UV (EtOH): 211 (4·52); 222 (4·37), sh; 266 (4·26); 298 (4·30).

Ring closure of **12** *(R = H)*

The title compound (0·88 g; 3·6 mmole) was refluxed for 5 min with DMF (5 ml). The starting compound gradually went into soln, and H_2S was evolved. The initially yellow soln finally turned green. On cooling, 0·55 g (73%) of **11b** (Z = R = H) was obtained, m.p. 258–60° (DMF). Found: C, 55·06; H, 4·45; S, 14·50. Calc. for $C_{10}H_{10}N_4S$: C, 55·04; H, 4·62; S, 14·70%. UV (EtOH): 205 (4·49); 266 (4·12); 298 (4·37).

S-Methylation of **11b** *(R = Z = H)*

A suspension of **11b** (R = Z = H) (2·2 g; 10 mmole) in MeOH (20 ml) was refluxed for 30 min with MeI (4 ml). The resulting clear soln was allowed to cool. Ether (60 ml) was added to precipitate 3·4 g (92%) of crystalline **13** · HI (Z = R = H) m.p. 275° (dec.). The salt was dissolved in a mixture of MeOH (20 ml) and water (10 ml). 10% aq NaOH was added to precipitate 2·14 g (90%) of crystalline **13** (Z = R = H), m.p. 308–9° (from DMF). Found: N, 24·22; S, 13·87. Calc. for $C_{11}H_{12}N_4S$: N, 24·12; S, 13·74%. UV (EtOH): 214 (4·36); 242 (4·0), sh; 280 (3·95), sh; 313 (4·42). HI salt: 217 (4·56); 242 (4·0), sh; 312 (4·44).

Hydrolysis of **13** *(Z = R = H)*

13 (Z = R = H) (0·6 g; 2·6 mmole) was refluxed for 1 hr with a mixture of 48% aq HBr and water (4 ml each). The dry residue of the resulting soln was recrystallized from MeOH-Et_2O to yield 0·75 g (88%) of **10** · 2 HBr (Z = R = H), m.p. 280–2°, identical according to its IR spectrum with a sample obtained by synthesis as described above.

2-Amino-3-(n-butyl)-9-chloro-4,5-dihydro-3H-[1,3,5]triazepino[1,2-a]benzimidazole (**14**, *Z = Cl, R = n-Bu*)

(a) **10** (Z = Cl, R = n-Bu) (2·7 g; 10 mmole) was refluxed for 1 hr with BrCN (1·2 g; 11 mole) in EtOH (40 ml). The solvent was distilled off, and the dry residue was dissolved in hot water (50 ml). 40% aq NaOH was added (pH ≈ 9) to precipitate 1·5 g (51·5%) of the title compound, m.p. 267–8° (from water or EtOH). Found: C, 57·48; H, 5·88; Cl, 12·68. Calc. for $C_{14}H_{18}ClN_5$: C, 57·62; H, 6·22; Cl, 12·26%.

(b) A mixture of **10** (Z = Cl, R = n-Bu) (2·7 g; 10 mmole), $(MeS)_2C{=}NH{\cdot}HI$[9] (2·6 g; 10 mmole) and anhydrous dioxane (20 ml) was refluxed for 6 hr. An oily product was deposited which (after the solvent has been decanted) was triturated with three portions (20 ml, each) of ether and subsequently with 10% aq NaOH. As a result, the oily product turned crystalline. It was filtered off, thoroughly washed with water until neutral and triturated with MeOH (40 ml) to yield 0·6 g (21%) of the title compound, m.p. 267°, identical according to the IR spectra with the product obtained as described under (a). UV (EtOH): 218 (4·46); 245 (~4·15), sh; 277 (3·98); 314 (4·44).

2-(Tosylimino)-2,3,4,5-tetrahydro-1H-[1,3,5]triazepino[1,2-a]benzimidazole (**11c**, *Z = H = R*)

10 · 2 HBr (Z = R = H) (10·2 g; 30 mmole) was refluxed for 15 min with a methanolic soln (50 ml) of Na (1·5 g; 65 mmole). The NaBr was filtered off, and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in DMF (60 ml). $(MeS)_2C{=}N{-}Tos$[10] (9·0 g; 32·5 mmole) was added, and the mixture was refluxed for 2·5 hr to yield 6·0 g (51%) of the title compound, a highly insoluble substance which was thoroughly washed with MeOH and water, m.p. 334–5° (from DMSO). Found: C, 57·45; H, 5·17; N, 19·63; S, 9·28. Calc. for $C_{17}H_{18}N_5O_2S$: C, 57·29; H, 5·09; N, 19·65; S, 8·79%. UV (EtOH): 252; 309. Owing to the poor solubility of **15**, the log ε values were not determined.

3-(n-Butyl)-9-chloro-4,5-dihydro-3H-[1,3,5]triazepino[1,2-a]benzimidazole (**15**, *Z = Cl, R = n-Bu*)

10 (Z = Cl, R = n-Bu) (1·5 g; 6 mmole) was refluxed for 3 hr with triethyl orthoformate (15 ml). Deposition of the crystals of the title compound started within 15 min, giving 1·1 g (67%) of the title compound, m.p. 260–1° (from $CHCl_3$-light petroleum). Found: C,

60·40; H, 6·15; N, 19·92. Calc. for $C_{14}H_{17}ClN_4$: C, 60·77; H, 6·20; N, 20·25%. UV (EtOH): 208 (4·43); 220 (4·27), sh; 274 (3·92); 319 (4·36).

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