PREPARATION AND PHOTOCHEMISTRY OF 3-CYANOSUBSTITUTED CONDENSED ISOXAZOLINES CONTAINING AN OXYGEN ATOM*

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The 1,3-dipolar cycloaddition of cyanonitrile oxide to 2,3- and 2,5-dihydrofurane, 7-oxabicyclo-[2,2,1]-2-heptene and derivatives of 1,3-dioxep-5-ene is described. The condensed isoxazolines *Ia*, *IIIa*, *Va*, *Vc*, *Vd* thus prepared are rearranged on irradiation into cyanosubstituted heterocyclic enaminoaldehydes *IIa*, *IVa*, *VIa*, *VIc*. The quantum yields of the photorearrangement of cyanoderivatives are higher than those of the phenyl derivatives, being within the limits from 0·068 to 0·19. The reaction of *II* with hydrazine gives the derivative *IX* of oxazino[4,5-*d*]pyridazine.

Recently isoxazolines have proved useful intermediates in organic synthesis[1]. We found[2-8] that introduction of an oxygen atom into β position to the isoxazoline oxygen results in a highly selective photo-induced rearrangement which gives cyclic enaminoaldehydes, *e.g.*, $I \rightarrow II$, $III \rightarrow IV$, and $V \rightarrow VI$ (R^1 = aryl). From our studies it is obvious that the new synthetic principle found – the 1,3-dipolar cycloaddition of nitrile oxides to *n*-membered oxygen heterocycles followed by the photorearrangement giving the $(n + 1)$-membered hetrocycles – would find broader applications, if some more reactive functional group were introduced instead of aryl. Therefore, our aim was to test the above-mentioned hypothesis on model isoxazolines containing a cyano group. As far as we know, no paper dealing with photochemistry of isoxazolines containing non-arylated chromophore is available at present[9-12].

The reaction of cyanonitriloxide with suitable dipolarophiles as 2,3- and 2,5-dihydrofurane, 2,3-dihydropyrane, 5,6-bis(methoxycarbonyl)-7-oxabicyclo[2,2,1]-2--heptene, 2*H*,4*H*,7*H*-1,3-dioxepine, and 7-phenyl-2*H*,4*H*,7*H*-1,3-dioxepine was used for preparation of the corresponding isoxazolines *Ia*, *IIIa*, *Va*, *Vc*, *Vd*, *VIIa*, *VIIIa* containing cyano group at position 3 (yields from 25 to 71%). The cyanonitrile oxide was obtained *in situ* from cyanohydroximic acid chloride[13] in dichloromethane by addition of aqueous solution of sodium carbonate in the presence of the above-mentioned dipolarophiles. Structure of the condensed isoxazolines prepared was determined from ^1H and ^{13}C NMR spectral data on the basis of the analogy with

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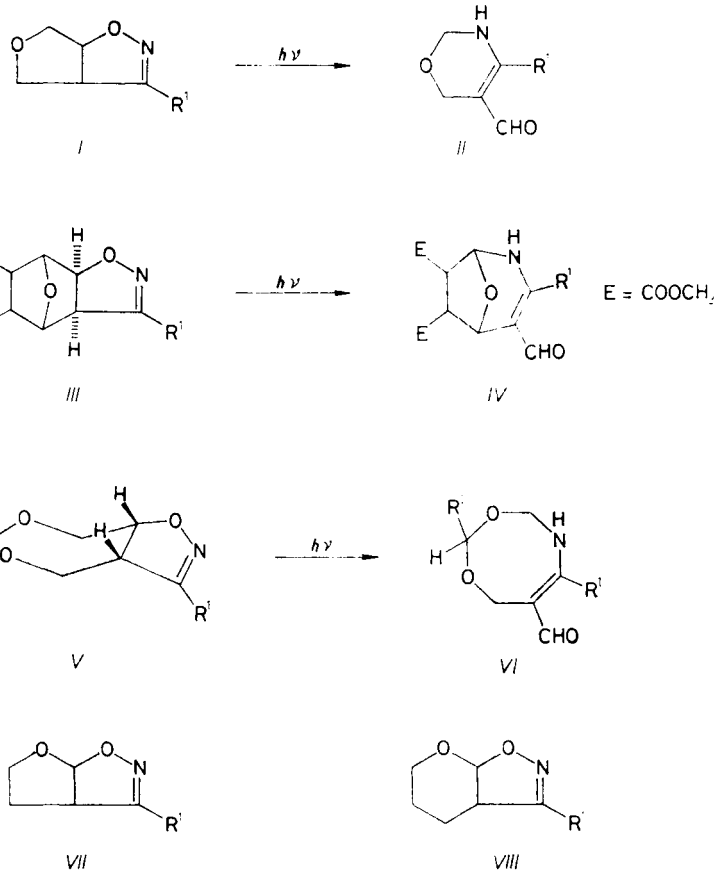
the corresponding phenyl derivatives *Ib*, *IIIb*, *Vb*, *VIIb*, *VIIIb* (refs[2–8]). In the case of 2,3-dihydrofurane and -pyrane, similarly, the head-to-head cycloadducts *VIIb*, *VIIIb* are only formed. The *exo* (*Vd*) and *endo* (*Vc*) derivatives formed in the reaction with 2-phenyl-2*H*,4*H*,7*H*-1,3-dioxepine in the ratio of 1 : 3 in favour of the *exo* derivative *Vd* (like the derivatives *Ve*, *Vf* in the cycloaddition with benzenenitrile oxide[4]) could be obtained in pure state. The structure of the *exo* derivative *Vd* and the *endo* derivative *Vc* was assigned in analogous way as in the case of the derivatives *Ve*, *Vf*.



I *II* *III* *IV* *V* *VI* *VII* *VIII*

In formulae *I–IV*, *VII*, *VIII*: *a*, $R^1 = CN$; *b*, $R^1 = C_6H_5$

in formula *V*: *a*, $R^1 = CN$; $R^2 = R^3 = H$; *b*, $R^1 = C_6H_5$; $R^2 = R^3 = H$; *c*, $R^1 = CN$; $R^2 = H$; $R^3 = C_6H_5$; *d*, $R^1 = CN$; $R^2 = C_6H_5$; $R^3 = H$; *e*, $R^1 = R^3 = C_6H_5$; $R^2 = H$; *f*, $R^1 = R^2 = C_6H_5$; $R^3 = H$

in formula *VI*: *a*, $R^1 = CN$; $R^2 = H$; *b*, $R^1 = C_6H_5$; $R^2 = H$; *c*, $R^1 = CN$; $R^2 = C_6H_5$

In contrast to the phenyl derivative, the UV absorption maxima are shifted from about 263 nm to 240–252 nm, *e.g.*, 242 nm for *Ia*. The IR spectra contain characteristical absorption bands of CN group in the region of 2 260–2 230 cm^{-1}. In contrast to the arylisoxazolines prepared so far[2-8], we found a significant shift (about 15–20 ppm) to higher field for the respective C=N singlet in the ^{13}C NMR spectra of the cyano derivatives, *e.g.*, δ 137·22 for *VIIa*. The singlet of nitrile carbon atom is found in the region about 110 ppm.

The photochemical reactions were carried out in ether, methanol or acetonitrile with application of monochromatic radiation (λ_{max} = 254 nm) as in the previous studies[2-8]. The results obtained confirmed the ability of the oxygen atom at β-position (with respect to the isoxazoline oxygen) to stabilize the primary biradical (see Discussion in refs[2-8]), which enabled the preparation of the expected cyano-substituted heterocyclic enaminoaldehydes *IIa*, *VIa*, and *VIc*. In the case of the photorearrangement of derivative *IIIa*, the expected derivative *IVa* is also formed (as it follows from the analysis of ^1H NMR spectrum of the raw reaction mixture) in the form of a viscous oil which is rapidly decomposed. The ^1H NMR spectra of all the enaminoaldehydes contain a singlet for the aldehydic proton in the region of δ 8·0–10·0 whose presence was also confirmed by the doublet at δ 180·0–190·0 in the ^{13}C NMR spectrum. Structures of the enaminoaldehydes prepared: *IIa* (76%), *IVa* (41%), *VIa* (63%), *VIc* (56% from *Vc* and 67% from *Vd*) were proved by comparison[2-8] of the spectral data with those of the corresponding phenyl derivatives. We suppose that the rearrangements of the cyano derivatives and aryl derivatives *I*, *III*, and *V* (whose mechanism was dealt with in detail in our previous papers[2-8]) proceed by the same mechanism. In this case, too, the formation of enaminoaldehydes *IIa*, *IVa*, *VIa*, and *VIc* as the single products must be caused by the intervention of an intermediate biradical in which one of the radical centres can be stabilized by lone electron pair at the α-oxygen.

The UV spectral investigation of the photolysis of isoxazoline *Ia* at low concentration (0·1 mmol l^{-1}) with application of monochromatic radiation (254 nm; Fig. 1) revealed isosbestic points at 222 and 263 nm, which indicates a photochemical reaction of the A→B type. The quantum yield of all the photorearrangements does not depend on the presence or absence of oxygen, which indicates the singlet mechanism. Table I contains the results of measurements of the photorearrangement quantum

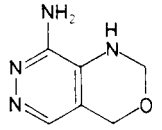
TABLE I

Photorearrangement quantum yields Φ (methanol)

Compound	*Ia*	*Ib*	*IIIa*	*IIIb*	*Va*	*Vb*	*Vc*	*Vd*	*Ve*	*Vf*
Φ	0·10	0·04	0·19	0·13	0·086	0·16	0·096	0·068	0·026	0·008

yields. In all the cases, the cyano derivatives show considerably higher values of quantum yields than the corresponding phenyl derivatives. In the case of the cyano derivatives, too, the surprising dependence of Φ on stereochemical arrangement was found: the *endo* derivative *Vc* ($\Phi = 0{\cdot}096$) shows a higher value than the *exo* derivative *Vd* ($\Phi = 0{\cdot}068$), which is similar to the values of the phenyl substituted derivatives *Ve* and *Vf*. Irradiation of isoxazolines *VIIa* and *VIIIa* (containing an oxygen atom at α-position to the isoxazoline oxygen) also gave only polymeric products like those from the phenyl derivatives *VIIb* and *VIIIb* (ref.[14]).

The rearrangement product *IIa*, which contains two functional groups, was used for synthesis of the pyridazine derivative. The reaction of *IIa* with hydrazine in methanol gave 64% yield of the expected 3-amino-4,5-dihydro-(7*H*)-4,6-oxazino-[4,5-*d*]pyridazine (*IX*) which represents a new heterocyclic condensed system.



IX

EXPERIMENTAL

The melting points are not corrected. The ^{1}H NMR spectra were measured with a Tesla 487C apparatus, the ^{13}C NMR spectra were measured with a JEOL JX-60 apparatus in deuterio-

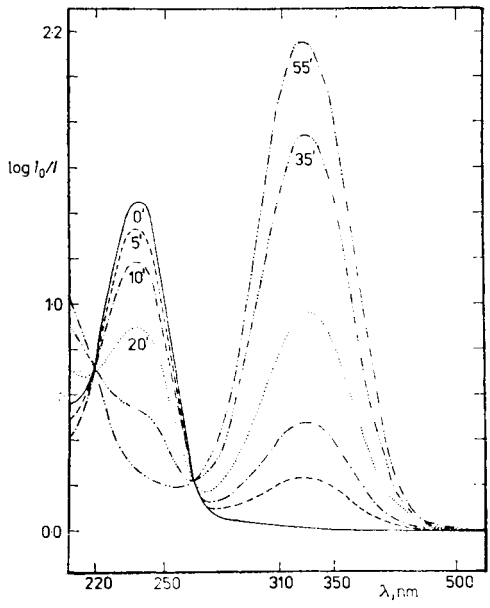


FIG. 1
UV spectrum of photolyzed *Ia* at low concentration and 254 nm

chloroform (if not otherwise stated) with tetramethylsilane as the internal standard. The UV spectra were measured with a Perkin–Elmer 323 apparatus in thermostated cells in methanol. The ε values are presented in $m^2\ mol^{-1}$. The mass spectra were measured with an MS 902 S apparatus with direct inlet system, the ionization energy 70 eV, the trap current 100 μA. The IR spectra were measured in chloroform with a Specord IR-60 apparatus calibrated with the use of the polystyrene film. The cyanoformhydroximic acid chloride was prepared according to ref.[13].

The photochemical reactions were carried out with application of a Toshiba GL-15 (15 W) low-pressure discharge lamp in a temperated 300 ml quartz reactor with forced circulation of the irradiated solution at 15°C (ref.[15]). The course of the photoreactions was followed by TLC on Silufol plates and by UV spectroscopy. The reactions were conducted until complete consumption of the starting isoxazolines. The measurement of quantum yields is described in ref.[8].

Preparation of 3-Cyanosubstituted Isoxazolines, General Procedure

A solution of 1·05 g (0·01 mol) cyanohydroximic acid chloride and 0·01 to 0·05 mol of the respective dipolarophile in 20 ml dichloromethane was stirred, and 0·01 mol of sodium carbonate (as a 10% solution) was added thereto drop by drop within 4 h. After 12 h stirring at room temperature and separation of layers, the aqueous layer was extracted with 2 × 15 ml dichloromethane. The combined extracts were concentrated in vacuum and the respective isoxazolines *Ia*, *IIIa*, *Va*, *Vc*, *Vd*, *VII*, and *VIII* were obtained by column chromatography (silica gel, chloroform) of the evaporation residue.

3-*Cyano*-3a,4,6,6a-*tetrahydrofuro*[3,4-*d*]*isoxazole* (Ia) was prepared from 2,5-dihydrofurane, yield 65%, m.p. 40—42°C. For $C_6H_6N_2O_2$ (138·1) calculated: 52·17% C, 4·38% H, 20·28% N; found: 52·31% C, 4·49% H, 20·16% N. ^{1}H NMR spectrum: 5·51 (d, d, J(3a, 6a) = 4·5 Hz, J(6, 6a) = 3·0 Hz, 1 H, H-6a), 4·42—4·00 (m, 3 H, 2× H-6, H_A-4), 3·85—3·57 (m, 2 H, H_B-4, H-3a). ^{13}C NMR spectrum: 135·75 (s, C=N), 110·65 (s, C≡N), 89·01 (d, 6a-C), 75·63 (t, 6-C), 70·89 (t, 4-C), 54·25 (d, 3a-C). UV spectrum, λ_{max} (log ε): 236 nm (2·47). IR spectrum: 2 235 cm^{-1} ν(C≡N).

7-*Cyno*-3,4-*bis*(*methoxycarbonyl*)-9,10-*dioxa*-8-*azatricyclo*[4,3,0,$1^{2,5}$]-7-*decene* (IIIa) was prepared from 5,6-bis(methoxycarbonyl)-7-oxabicyclo[2,2,1]-2-heptene, yield 71%, m.p. 239—241°C. For $C_{12}H_{12}N_2O_6$ (280·2) calculated: 51·43% C, 4·32% H, 9·99% N; found: 51·37% C, 4·46% H, 9·71% N. ^{1}H NMR (hexadeuteriodimethyl sulphoxide): 5·20 (d, J(1, 6) = 8·0 Hz, 1 H, H-1), 4·90 and 4·87 (s, s, 2 H, H-2, H-5), 4·05 (d, 1 H, H-6), 3·52 (s, 6 H, 2× CH_3), 3·33—3·21 (d, d, 2 H, H-3, H-4). ^{13}C NMR (hexadeuteriodimethyl sulphoxide): 170·10 (s, 2× C=O), 134·89 (s, C=N), 110·84 (s, C≡N), 88·49 (d, C-1), 83·30 (d, C-2), 79·27 (d, C-5), 57·31 (d, C-6), 51·72 (q, 2× CH_3), 48·73 (d, C-3), 45·61 (d, C-4). UV spectrum: λ_{max} (log ε): 244 nm (2·74). IR spectrum: 2 235 cm^{-1} ν(C≡N).

8-*Cyano*-3,5,10-*trioxa*-9-*azabicyclo*[5,3,0]-8-*decene* (Va) was prepared from 2*H*,4*H*,7*H*-1,3-dioxepine, yield 43%, m.p. 54—56°C. For $C_7H_8N_2O_3$ (168·2) calculated: 50·00% C, 4·80% H, 16·66% N; found: 50·29% C, 4·77% H, 16·93% N. ^{1}H NMR spectrum: 5·17—4·95 (m, 3 H, H-1, 2× H-4), 4·55—3·69 (m, 5 H, 2× H-2, 2× H-6, H-7). ^{13}C NMR spectrum: 136·18 (s, C=N), 110·20 (s, C≡N), 99·15 (t, C-4), 85·37 (d, C-1), 70·56 (t, C-2), 66·40 (t, C-6), 52·24 (d, C-7). UV spectrum: λ_{max} (log ε): 247 nm (2·43). IR spectrum: 2 259 cm^{-1} ν(C≡N).

Reaction of Cyanonitrile Oxide with 2-Phenyl-2*H*,4*H*,7*H*-1,3-dioxepine

The column chromatography (silica gel, chloroform) of the reaction mixture gave *endo Vc* and *exo Vd*.

endo-4-*Phenyl*-8-*cyano*-3,5,10-*trioxa*-9-*azabicyclo*[5,3,0]-8-*decene* (Vc), yield 17%, m.p. 92 to 97°C. For $C_{13}H_{14}N_2O_3$ (246·3) calculated: 63·40% C, 5·73% H, 11·38% N; found: 63·12% C, 5·87% H, 11·17% N. ^{1}H NMR spectrum: 7·47—7·30 (m, 5 H, aromatic H), 5·70 (s, 1 H, H-4), 5·16—4·85 (m, 1 H, H-1), 4·30—3·58 (m, 5 H, 2× H-2, 2× H-6, H-7). UV spectrum: λ_{max} (log ε): 250 nm (2·73).

exo-4-*Phenyl*-8-*cyano*-3,5,10-*trioxa*-9-*azabicyclo*[5,3,0]-8-*decene* (Vd), yield 45%, m.p. 79 to 81°C. For $C_{13}H_{14}N_2O_3$ (246·3) calculated: 63·40% C, 5·37% H, 11·38% N; found: 63·47% C, 5·55% H, 11·44% N. ^{1}H NMR spectrum: 7·42—7·33 (m, 5 H, aromatic H), 5·31 (s, 1 H, H-4), 5·10—4·88 (m, 1 H, H-1), 4·58—3·57 (m, 5 H, 2× H-2, 2× H-6, H-7). ^{13}C NMR spectrum: 137·60 (s, C=N), 136·43, 129·00, 128·71, 127·24, 126·02 (aromatic C), 110·45 (s, C≡N), 107·59 (d, C-4), 85·41 (d, C-1), 69·50 (t, C-2), 65·17 (t, C-6), 52·36 (d, C-7). UV spectrum: λ_{max} (log ε): 248 nm (2·67).

3-*Cyano*-3a,4,5,6a-*tetrahydrofuro*[2,3-*d*]*isoxazole* (VIIa) was prepared from 2,3-dihydrofurane, yield 25%, m.p. 45—47°C. For $C_6H_6N_2O_2$ (138·1) calculated: 52·17% C, 4·38% H, 20·28% N; found: 51·94% C, 4·28% H, 20·37% N. ^{1}H NMR spectrum: 6·40 (d, J(3a, 6a) = = 6·0 Hz, 1 H, H-6a), 4·45—3·90 (m, 2 H, 2× H-3), 3·75—3·42 (m, 1 H, H-3a), 2·37—2·20, (m, 2 H, 2× H-4). ^{13}C NMR spectrum: 137·22 (s, C=N), 110·97 (s, C≡N), 110·97 (d, C-6a). 66·92 (t, C-5), 52·11 (d, C-3a), 29·50 (t, C-4). UV spectrum: λ_{max} (log ε): 243 nm (2·53). IR spectrum: 2 230 cm^{-1} (C≡N).

7-*Cyano*-2,9-*dioxa*-8-*azabicyclo*[4,3,0]-7-*nonene* (VIIIa) was prepared from 2,3-dihydropyrane, yield 35% of viscous oil. For $C_7H_8N_2O_2$ (152·1) calculated: 55·27% C, 5·30% H, 18·40% N; found: 55·41% C, 5·22% H, 18·69% N. ^{1}H NMR spectrum: 6·06 (d, J(1, 6) = 8·0 Hz, 1 H, H-1), 3·96—3·25 (m, 3 H, 2× H-3, H-6), 2·10—1·19 (m, 4 H, 2× H-4, 2× H-5).

Photochemical Rearrangement of Isoxazolines, General Procedure

Solution of the respective isoxazoline (0·003 mol) in 300 ml acetonitrile was irradiated until complete consumption of the starting derivative (TLC). After concentrating the solution in vacuum, we obtained the rearrangement product by column chromatography (silica gel, chloroform).

4-*Cyano*-5-*formyl*-2,3-*dihydro*(6*H*)-1,3-*oxazine* (IIa) was prepared from *Ia*, the irradiation time 65 min, yield 76%, m.p. 138—140°C. For $C_6H_6N_2O_2$ (138·1) calculated: 52·17% C, 4·38% H, 20·28% N; found: 52·26% C, 4·51% H, 20·21% N. ^{1}H NMR spectrum: (hexadeuterioacetone): 9·51 (s, 1 H, CHO), 7·72 (br, 1 H, NH), 4·87—4·75 (m, 2 H, 2× H-2), 4·45 (s, 2 H, 2× H-6). ^{13}C NMR spectrum (hexadeuterioacetone): 183·61 (d, CHO), 129·62 (s, C-4), 118·31 (s, C-5), 111·36 (s, C≡N), 73·29 (t, C-2), 62·74 (t, C-6). UV spectrum: λ_{max} (log ε): 314 nm (2·73).

6-*Cyano*-7-*formyl*-2,4,5,8-*tetrahydro*-1,3-*diox*-5-*azocine* (VIa) was prepared from *Va*, the irradiation time 220 min, yield 63%, m.p. 148—150°C. For $C_7H_8N_2O_3$ (168·2) calculated: 50·00% C, 4·80% H, 16·66% N; found: 49·73% C, 4·99% H, 16·41% N. ^{1}H NMR spectrum (hexadeuterioacetone): 9·87 (s, 1 H, CHO), 8·10 (br, 1 H, NH), 5·00—4·88 (m, 2 H, 2× H-4), 4·75 (m, 4 H, 2× H-4, 2× H-8). ^{13}C NMR spectrum (hexadeuterioacetone): 187·31 (d, CHO), 134·04 (s, C-8), 118·64 (s, C-7), 113·51 (s, C≡N), 94·66 (t, C-4), 74·26 (t, C-2), 61·72 (t, C-8). UV spectrum: λ_{max} (log ε): 302 nm (2·72).

2-*Phenyl*-6-*cyano*-7-*formyl*-2,4,5,8-*tetrahydro*-1,3-*diox*-5-*azocine* (VIc) was prepared from *Vc* (yield 56%) or *Vd* (yield 67%), irradiation time 120 min, m.p. 167—169°C. For $C_{13}H_{14}N_2O_3$ (246·3) calculated: 63·40% C, 5·73% H, 11·38% N; found: 63·28% C, 5·71% H, 11·64% N. ^{1}H NMR spectrum (hexadeuterioacetone): 9·77 (s, 1 H, CHO), 7·55—7·22 (m, 5 H, aromatic H),

5·60 (s, 1 H, H-2), 5·17 (s, 2 H, 2× H-4), 5·27 (d, J = 15·0 Hz, 1 H, H_A-8), 4·44 (d, 1 H, H_B-8). ^{13}C NMR spectrum (hexadeuteriodimethyl sulphoxide): 187·45 (d, CHO), 138·39, 128·55, 127·93, 126·24 (aromatic C), 134·30 (s, C-8), 118·96 (s, C-7), 113·57 (s, C≡N), 103·05 (d, C-4), 73·55 (t, C-2), 61·33 (t, C-6).

Reaction of *IIa* with Hydrazine

A mixture of 0·69 g (5 mmol) *IIa*, 0·7 g (11 mmol) 80% hydrazine hydrate, and 10 ml methanol was stirred at room temperature 20 h. The column chromatography (silica gel, chloroform–methanol 19 : 1) gave 0·48 g (64%) 3-amino-4,5-dihydro(7*H*)-4,6-oxazino[4,5-*d*]pyridazine (*IX*), m.p. 138—140°C. For $C_6H_8N_4O$ (152·2) calculated: 47·36% C, 5·30% H, 36·82% N; found: 47·41% C, 5·22% H, 36·99% N. ^{1}H NMR spectrum (hexadeuteriodimethyl sulphoxide): 7·90 (s, 1 H, H-8), 5·76 (br, 2 H, NH_2), 4·69 (s, 2 H, 2× H-5), 4·57 (s, 2 H, 2× H-7).

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