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STEROIDAL 1,2,4-OXADIAZOLES BY 1–3 DIPOLAR CYCLOADDITION

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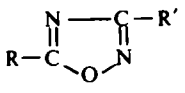
Abstract—Studying the behaviour of 1–3 dipolar additions of nitrile-oxides to dipolarophilic steroid systems, the relative reactivity of the double bond C=C (endo or exocyclic) and of the nitrile-group has been examined, using two unsaturated and a saturated one nitrile as control. The C≡N group has been found more reactive than the C=C bond. The physico-chemical properties of 1,2,4 oxadiazoles obtained and of intermediates are discussed.

VARIOUS STUDIES of 1–3 dipolar interaction between nitrile-oxides and the nitrile dipolarophile have been reported; these addition reactions normally lead to the formation of 1,2,4 oxadiazole derivatives, the yield obtained depending on the nature of the dipolarophile, the dipolar ion and the reaction conditions.[1a–d] Generally aromatic, heterocyclic and aliphatic nitriles if activated by an electron-attracting substituent, give spontaneous addition with nitrile-oxides; non activated aliphatic nitriles however only react if catalised by borontrifluoride.[2a–d]

Oxadiazole derivatives of the 1,2,5 type (furazanes), 3-4 condensed in different positions in the steroid nucleus have also been described, together with their N-oxides and have shown interesting biological activities. Normally these derivatives have been obtained *via* the dioxime of dicarbonil systems.[3a–f]

We report here the synthesis of 1,2,4 oxadiazole derivatives of the type



where R′ = Ph;

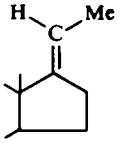
and R = steroid moiety

in which the oxadiazole is bonded to either position 16 or 20 of the steroid. These derivatives were obtained during a course of studies of 1-3 dipolar addition of nitrile oxides to steroidal dipolarophiles.

For the dipolarophilic substrates two unsaturated nitriles, one with an exocyclic, the other with an endocyclic double bond in ring D(**2** and **3** respectively), and also a saturated nitrile **4e** were chosen. This choice of substrates was governed by our desire to study the relative reactivities of the endocyclic and exocyclic C=C double bonds with respect to that of the —C≡N group, the saturated nitrile being chosen as a control. However, contrary to what we expected, the reactivities of the nitrile groups proved greater than those of the double bonds.

This unexpected result is even more strange in view of the description of nitriles as

dipolarophiles which are much less reactive than structurally analogous C=C double bonds,[4a,b] and also in view of the fact that we have shown[5] that addition to a 16–17 enolic system unsubstituted in position 16 gives practically quantitative yields, and that it has been shown that addition to the system proceeds at the double bond



without particular difficulty.[6] We cannot explain the apparent lack of reactivity of the C=C double bond found in this work by steric hinderance at the double bond due to the C_{18} Me group, nor on electronic grounds.

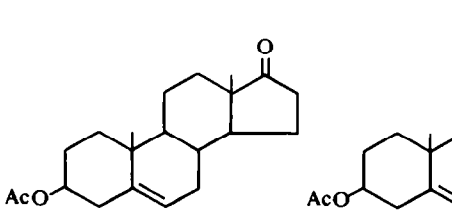
The synthesis of **3** has been described previously.[7]

2 was synthesised by transformation of 17-oxo-5 androsten-3β-yl-acetate **1** according to the method of Kaiser *et al.*,[8] instead of by the more direct route using cyanomethylphosphonate.[9] By this synthetic route we also obtained intermediate **4a** which we required for the synthesis of **4e**.

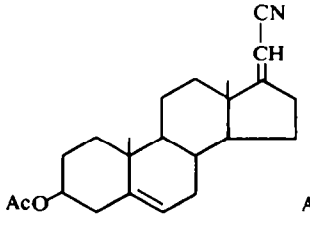
4a was identified by elementary analysis and by its IR spectrum. The NMR spectrum showed a singlet at 2·55 ppm (the methylene group of the cyanomethyl group). All these data are in accord with those reported for an analogous structure of a —CH_2—CN group by Cook *et al.*[10] The configuration at C_{17} of this compound is discussed below.

The crude reaction product was purified from traces of the starting material by chromatography, but, however, the purified product was *not* recrystallized, in order not to lose any possible product epimeric at C_{17}.

After alkaline hydrolysis the acid **4b** was obtained, which was then converted by CH_2N_2 to its methyl ester **4c**. The physico-chemical data of this corresponded to those reported in the literature.[11a,b,c]



1



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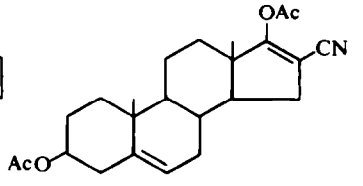

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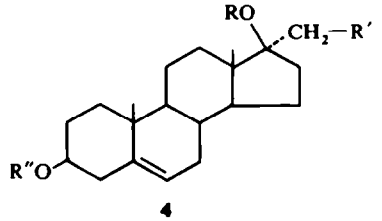


4

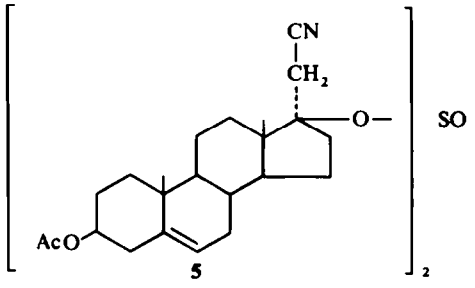
4a	R = H;	R′ = CN;	R″ = H
4b	R = H;	R′ = COOH;	R″ = H
4c	R = H;	R′ = COOMe;	R″ = H
4d	R = H;	R′ = CN;	R″ = Ac
4e	R = Ac;	R′ = CN;	R″ = Ac

Considering now the configuration at C_{17} of **4a**, the ORD data are in agreement with a β-configuration of the hydroxyl. Conversion of the chromatographically purified **4a** to **4d** and to its nitrosyl ester according to Velluz *et al.*[12] gave a product which exhibited a negative Cotton effect in its ORD spectrum, in agreement with a 17-β-ONO.[13]

All of the above data agrees with a nucleophilic attack α to the molecule by the acetonitrile carbanion and the formation of only one isomer, in analogy with the ethynilation in position 17α in 17-ketosteroids.

According to Kaiser *et al.*[8] the following dehydration of a hydroxynitrile to α-β unsaturated nitrile can be produced by phosphoric acid, in high yield. In our case every attempt at this reaction failed, and, in fact, **4a**, after selective acetylation in position 3 (compound **4d**), gave a very complex mixture of products when this reaction was attempted. Also, reaction with Ac_2O and *p*-toluene sulphonic acid under reflux gave only the 3,17 diacetate **4e**.

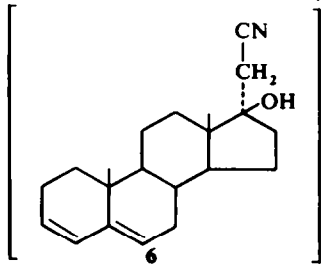
The desired dehydration was however obtained using $SOCl_2$ and pyridine at *ca.* −20°, albeit only indirectly. In fact, it was found that low reaction temperature led to an easily isolable product, which, however, was not the desired product **2**, because its IR spectrum showed no hydroxyl absorption but acetyl absorption, along with that of a saturated C≡N group. The elementary analysis was in accordance with formula **5**, as was its molecular weight obtained by VPO:



5

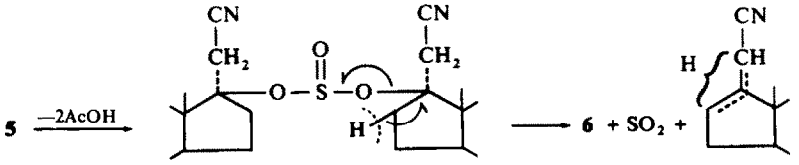
It is well known that alkyl sulphites give bands in the region 1150–1215 cm^{-1} in the IR due to S=O stretching;[14] the product of the reaction, as well as giving an acetate band at 1245 cm^{-1}, also gave a band at 1220 cm^{-1}, with a shoulder at 1210 cm^{-1}. While, due to the inherent complexity of the IR spectra of steroid derivatives, the presence of a band at *ca* 1200 cm^{-1} cannot be a definitive proof, its presence, together with the other data reported above, is consistent with the proposed structure **5**.

The mass spectrum also agrees with a sulphite structure: while it does not show a peak corresponding to the molecular ion, it does show a peak at $m/e = 311$ attributable to the ion



6

according to the scheme:

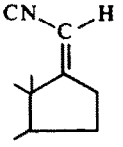


and also peaks at $m/e = 48$ (SO^+) and $m/e = 64$ (SO_2^+).

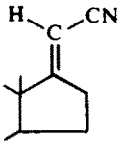
The subsequent transformation of **5** to **2**, (which was in part already formed, as well as the product **5**) was obtained by treatment of **5** with $SOCl_2$ at *ca.* $-10°$.

The product of this reaction was identified, by elementary analysis and IR, as the unsaturated nitrile **2**.

This compound has been synthesised by Bose *et al.*[9] using diethylcyanomethylphosphonate, and the reported physico-chemical data agree with ours. However these authors did not define the stereochemistry at C_{20}. In fact **2** can exist as two possible isomers, *cis* and *trans* with respect to the C_{18} Me group (nomenclature according to Inhoffen *et al.*[15]).

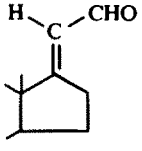


cis



trans

In order to define the stereochemistry, the product was selectively reduced according to Zakharkin *et al.*[16] to give the corresponding aldehyde **7**, in which its NMR spectrum agrees with analogous systems *trans*.[17]



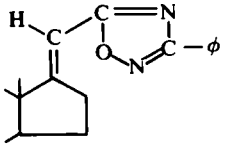
7

The addition reactions were carried out under various conditions according to the substrates used in order to maximise the yield. The nitrile oxides were generated in *situ* from the chloroximes either by alkali or by thermal generation.[1c, 18]

Compounds **2** and **3** were reacted using the former method of generation using benzhydroxamoyl chloride and triethylamine in THF.

After 8 hr at room temperature for **2**, 3 hr for **3** and reflux for 2 hr, **8** and **9** were obtained respectively in 42% and 40% yield. Previous reaction using ether as solvent under otherwise identical conditions gave low yields, and an increase of the amount of benzhydroxamoyl chloride had no effect on the yield. However by recovering the unreacted starting materials and reacting once again, the same yield was obtained as the first time, suggesting the reaction to involve an equilibrium. In no case were any by products isolated or indicated to have been formed.

The derivatives **8** and **9** were identified, after crystallization, by elementary analysis, IR[19a, b, c, d] and UV spectra. Further their mass spectra indicated a 1/1 adduct between the steroid and the nitrile oxide.



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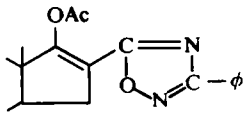
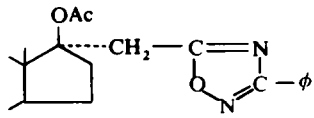


9



10

With compound **4e** thermal generation of the nitrile-oxide from benzhydroxamoyl chloride was used, and this method gave, after refluxing for 36 hr., **10** in 62% yield. The same reaction using alkaline *in situ* generation of the nitrile-oxide gave a much poorer yield.

10 was identified by elementary analysis and by its UV, IR[19a, b, c, d] and mass spectra, the latter indicating a 1/1 steroid-nitrile oxide adduct.

The comparison of the relative reactivities of the substrates **2**, **4e** and **3** was by the addition of benzonitrile oxide, generated *in situ*, with Et_3N and in THF solvent and measuring the yield obtained after 3 hr reaction at room temperature and refluxing for 2 hr.

The amount of oxadiazole formed was obtained by weighing the product after separation by column chromatography. We have found: for **10** < 5%; **8** 10%; **9** 40% yield.

EXPERIMENTAL

All m.ps are uncorrected. UV data were recorded for solutions in 95% EtOH using a Beckman DU 2; IR spectra using a Perkin-Elmer 237, (nujol). The NMR spectra were obtained using a Perkin-Elmer R 12 (60 MHz) with TMS as internal reference, and the mass spectra using a Perkin-Elmer 270 Mass Spectrometer with an electron potential of 80 eV. The elementary analysis were performed using a C, H, N Mod. 185 F & M apparatus and the specific rotations using a Perkin-Elmer 141 Polarimeter. The ORD curves were obtained using a Perkin-Elmer P 22 Spectropolarimeter. The molecular weight of **5** was obtained with Hitachi Perkin-Elmer MW Apparatus 115. The purity of the products were checked by TLC by a method previously described.[20]

17-α-*Cyanomethyl-5-androsten*-3β,17β *diol* (**4a**). Anhyd. THF, (3·5 ml), was added rapidly to 2.5 ml of a 20% solution of n-BuLi stirred at − 70° and then immediately afterwards a solution of 0·25 ml MeCN in 5 ml anhyd THF added. After standing 1 hr at − 70° a solution of 1·78 g of **1** in 10 ml anhyd. THF was slowly added dropwise. The temperature was allowed to rise to 0° and 200 ml of ice cold 5% HCl solution added. A white precipitate was obtained. After filtration and drying it was chromatographed on a column of silica gel/celite 1/1, eluant n-hexane/benzene/EtOAc 5/5/1. 1·07 g (60%) of **4a** was obtained; m.p. 214–216°; $[\alpha]_D^{25}$ −80° (*c* 0·23, $CHCl_3$); IR 3480, 3440, 2270 cm^{-1}. (Calc. for $C_{21}H_{31}NO_2$: C, 76·55; H, 9·48; N, 4·25. Found: C, 76·71; H, 9·41; N, 4·34%.) A sample of the crude reaction product (1 g) after recrystallization from acetone gave 0·45 g of a compound with identical physico-chemical characteristics as those of the chromatographically purified material.

17α-*Cyanomethyl-5-androsten*-3β, 17β *diol diacetate* (**4e**). 0·5 g of **4a** were refluxed for 4 hr in 50 ml Ac_2O containing 0·25 g *p*-TsOH then poured into crushed ice and the mixture extracted with EtOAc. After evaporating to dryness and recrystallization from MeOH 0·46 g (73% yield) of **4e** was obtained; m.p. 140–142° (MeOH); $[\alpha]_D^{25}$ −67° (*c* 0·56, $CHCl_3$); IR 2250, 1735 with shoulders at 1745 and 1725, 1265 and 1240 cm^{-1}. (Calc. for $C_{25}H_{35}NO_4$: C, 72·60; H, 8·53; N, 3·39 Found: C, 72·74; H, 8·49; N, 3·46%.)

17α-[1,2,4 *Oxadiazol-3-phenyl-5-yl*]-*5-androsten*-3β, 17β *diol*-3, 17-*diacetate* (**10**). 0·175 g of **4e** and 0·2 g of benzhydroxamoyl chloride were dissolved in 50 ml anhyd. toluene and the solution refluxed for 36 hr.,

poured into water, the organic phase separated and the acqueous phase extracted with diethylether. The combined organic phases were then evaporated to dryness and the residue recrystallized from MeOH to give 0·14 g (62%) of **10**; m.p. 160–162° (MeOH); $[\alpha]_D^{25} - 57°$ (*c* 0·56, $CHCl_3$); UV max 238 mμ (ε 13750); IR 1735 and 1240 (acetate), 1600 weak and 1585 weak (aromatic ring), 1575 and 1535 weak (oxadiazole ring) cm^{-1}; mass spectrum M^+ 532. (Calc. for $C_{32}H_{40}N_2O_5$: C, 72·15; H, 7·57; N, 5·26. Found: C, 72·30; H, 7·48; N, 5·34%.)

17α-*Cyanomethyl-5-androsten*-3β,17β-*diol*-3 *monoacetate* (**4d**). 300 mg of **4a** were dissolved in a mixture of 3 ml Ac_2O and 3 ml anhyd. pyridine and the solution allowed to stand at room temp for 24 hr., poured into crushed ice and the suspension obtained, on filtering gave 310 mg (92%) of **4d**, chromatographically pure; m.p. 190–191°; $[\alpha]_D^{25} - 79°$ (*c* 0·50, $CHCl_3$); IR 3430, 2270, 1730, 1250 cm^{-1}; NMR ($CDCl_3$) δ 0·92 (s, 3, Me-18), 1·04 (s, 3, Me-19), 2·03 (s, 3, OAc-3), 2·55 (s, 2, CH_2-20), 2·72 (s, 1, OH-17), 5·3 (m, 1, CH-6). (Calc. for $C_{23}H_{33}NO_3$: C, 74·36; H, 8·95; N, 3·77. Found: C, 74·27; H, 8·86; N, 3·84%.)

50 mg of **4d** were dissolved in 1 ml of anhyd pyridine; the temperature lowered to −10° and 3 drops of liquid NOCl added to the mixture. The solution was kept at −10° for 4 hr. Afterwards 30 ml of ice chilled water were added and the precipitate centrifuged and washed with cold water. The product was dried under vacuum at room temperature. The compound was analyzed by ORD. (*c*, 0·00125 g/ml dioxane containing 0·2% pyridine) $[\phi]_{500} - 2565°$, $[\phi]_{450} - 2950°$, $[\phi]_{400} - 4325°$, $[\phi]_{350} - 6250°$, $[\phi]_{325} - 8810°$, $[\phi]_{302} - 12240°$, $[\phi]_{275} - 8010°$.

17-*Cyanomethylene-5-androsten*-3β-*yl-acetate* (**2**). 0·8 g of **4d** was dissolved in 10 ml anhyd. pyridine, the solution cooled to −20°, and 2 ml of $SOCl_2$ added. The mixture was kept at −20° for 16 hr then poured into ice. After filtration and recrystallization from MeOH 0·35 g (46%) of **2** was obtained: m.p. 229–231° (MeOH); $[\alpha]_D^{25} - 82°$ (*c*, 0·10, EtOH); IR 3065, 2220, 1735, 1645, 1250 cm^{-1}; NMR ($CDCl_3$) δ 0·87 (s, 3, Me-18), 1·03 (s, 3, Me-19), 2·02 (s, 3, OAc-3), 2·67 (m, 2, CH_2-16), 4·62 (m, 1, CH-3), 5·05 (t, 1, J_{20-16} = 2·6 Hz, CH-20), 5·40 (m, 1, CH-6), J_{20-16} verified by decoupling; ORD (*c* 0·005 g/ml dioxane) $[\phi]_{450} - 530°$, $[\phi]_{400} - 650°$, $[\phi]_{350} - 1075°$, $[\phi]_{300} - 1980°$, $[\phi]_{275} - 3040°$, $[\phi]_{250} - 5800°$. (Calc. for $C_{23}H_{31}NO_2$: C, 78·14; H, 8·84; N, 3·96. Found: C, 78·02; H, 8·90; N, 3·94%.)

Di[17α-*cyanomethyl-5-androsten*-3β-*yl-acetate*)-17β-*yl*]*sylphite* (**5**). The mother liquor from the recrystallization of **2** on evaporation gave a raw which after chromatography on silica gel/celite 1/1 using acetone/n-hexane 1/10 as eluant yielded 0·3 g of **5**; m.p. 210–212° (acetone); $[\alpha]_D^{25} - 64°$ (*c*, 0·41, $CHCl_3$); IR 2250, 1740, 1245, 1220 with a shoulder at 1210 cm^{-1}; mass spectrum: *m/e* (rel. intensity): 312 (20), 311 (80), 294 (22), 293 (100), 278 (30), 145 (40), 143 (20), 131 (20), 121 (78), 120 (20), 119 (20), 108 (20), 107 (75), 106 (75), 106 (20), 105 (48), 93 (30), 91 (50), 81 (30), 79 (50), 77 (35), 67 (20), 64 (70), 56 (20), 48 (20), 43 (80), 41 (40). Mw (VPO) = 786 (benzene, 40°C). (Calc. for $C_{46}H_{64}N_2O_7S$: C, 70·01; H, 8·17; N, 3·54; S, 4·06. Found: C, 69·98; H, 8·20; N, 3·61; S, 4·10%). Compound **5** was completely transformed into **2** by standing for 24 hr at −10°, when dissolved in $SOCl_2$.

3β-*Hydroxy*-5,17 *pregnadien*-21-*al*. (**7**). 1 g of **2** was dissolved in 10 ml anhyd. THF, and then, under a N_2 atmosphere, a solution of 2 ml di-isobutyl aluminium hydride in 5 ml heptane added. After stirring at room temp for 1 hr the solution was poured into water and the mixture extracted with EtOAc. After removal of solvent the dry residue was chromatographed on silica gel/celite 1/1 and eluted with $CHCl_3$/acetone 100/3. 0·7 g of **7** was obtained; m.p. 176–178°; $[\alpha]_D^{25} - 51°$ (*c*, 0·54, $CHCl_3$); UV max 243 mμ (ε 18100); IR (nujol) 3480, 1660 with shoulders at 1670 and 1640 cm^{-1}; IR ($CHCl_3$) 3610, 1665 with shoulder at 1640, 1610 cm^{-1}; NMR ($CDCl_3$) δ 0·88 (s, 3, Me-18), 1·04 (s, 3, Me-19), 2·90 (m, 2, CH_2-16), 3·55 (m, 1, CH-3), 5·46 (m, 1, CH-6), 5·76 (sext, 1, J_{20-21} = 7·5 Hz, J_{20-16} = 2·2 Hz, CH-20), 9·87 (d, 1, J_{20-21} = 7·5 Hz, CH-21), J_{20-16} verified by decoupling; ORD (*c*, 0·005 g/ml dioxane) $[\phi]_{500} - 314°$, $[\phi]_{450} - 356°$, $[\phi]_{415} - 385°$, $[\phi]_{380} \pm 0°$, $[\phi]_{370} + 196°$, $[\phi]_{363} + 36°$, $[\phi]_{358} + 71°$, $[\phi]_{355} \pm 0°$, $[\phi]_{350} - 588°$. (Calc. for $C_{21}H_{30}O_2$: C, 80·21; H, 9·62. Found: C, 80·30; H, 9·56%).

17-[1,2,4-*Oxadiazol*-3-*phenyl*-5-*yl*]-*methylene*-5-*androsten*-3β-*yl acetate* (**8**). To a solution of 0·175 g of **2** and 0·2 g of benzhydroxamoyl chloride in 20 ml anhyd. THF was added, with shaking, 0·2 ml Et_3N dissolved in 6 ml anhyd. THF over a period of 1·5 hr. After 8 hr at room temperature the solution was refluxed for 2 hr, poured into ice and the mixture extracted with ether. The ether solution was evaporated to dryness then chromatographed on silica gel/celite 1/1, the eluant being acetone/n-hexane 5/100; 0·1 g (42%) of **8** was obtained; m.p. 200–202° (MeOH); $[\alpha]_D^{25}$-75° (*c*, 0·48, $CHCl_3$); UV max 243 mμ (ε 36500); IR 1745 and 1240 (acetate), 1650 (C=C), 1595 weak and 1580 weak (aromatic ring), 1560 and 1530 weak (oxadiazole ring) cm^{-1}; mass spectrum M^+ 472. (Calc. for $C_{30}H_{36}N_2O_3$: C, 76·24; H, 7·68; N, 5·93. Found: C, 76·18; H, 7·74; N, 6·00%).

16-[1,2,4-*Oxadiazol*-3-*phenyl*-5-*yl*]5,16-*androstadien*-3β,17 *diol diacetate* (**9**). To a solution of 0·5 g 3

and 0·6 g benzohydroxamoyl acid chloride in 50 ml anhyd. THF was added, with shaking, 0·6 ml Et_3N in 15 ml anhyd. THF over a period of 1·5 hr. After 3 hr at room temp the solution was refluxed for 2 hr poured into ice and extracted with ether. The solution was evaporated to dryness and the product chromatographed on silica gel/celite 1/1 and eluted with acetone/n-hexane 1/20. This separated the reaction product from the phenyl furoxan also formed. After recrystallization from MeOH 0·26 g (40%) of **9** was obtained; m.p. 171–173° (MeOH); $[\alpha]_D^{25}$-56° (*c*, 0·51, $CHCl_3$): UV max 244 mμ (ε 23900); IR 1785 (enol-acetate), 1740 and 1255 (acetate), 1640 (C=C), 1600 weak and 1590 weak (aromatic ring), 1570 and 1530 weak (oxadiazole ring) cm^{-1}; mass spectrum M^+ 516. (Calc. for $C_{31}H_{36}N_2O_5$: C, 72·07; H, 7·02; N, 5·42. Found: C, 72·14; H, 7·08; N, 5·52%).

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