STRUCTURE OF REACTION PRODUCT OF 3-AMINOCROTONONITRILE WITH ESTERS OF ALKOXYMETHYLENECYANOACETIC ACID

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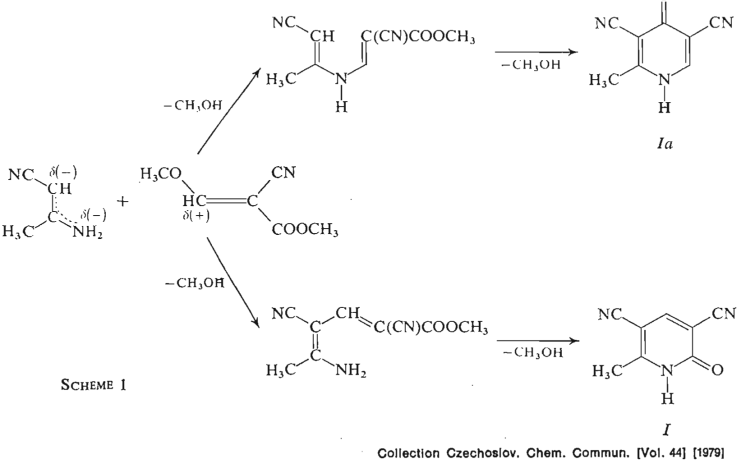
Study of dipole moments of 3,5-dicyanopyridine derivatives *II*—*IV* has shown that cyclocondensation of 3-aminocrotononitrile with esters of alkoxymethylenecyanoacetic acid gives the 2-pyridone derivative *I* which can be transformed in 2-chloro- or 2-bromo derivatives *IV* and *V* by action of the respective halogenation agents. The substance *IV* is conversed into 2-iodo- and 2-dimethylamino derivatives *VI* and *VII* on action of HI and dimethylformamide, respectively. Alkylation of the 2-pyridone *I* with methyl iodide takes place at nitrogen atom to give the compound *IX*. The 1,4-dihydropyridine derivative *X* has been obtained by action of $NaBH_4$ on *IV*.

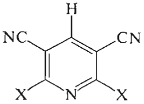
In cyclocondensation of 3-aminocrotononitrile with methyl methoxymethylenecyanoacetate formation of two isomeric 3,5-dicyano-6-methylpyridones *I* and *Ia* (Scheme 1)



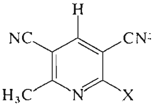
SCHEME 1

can be admitted depending on whether C- or N-attack of the starting enamine-nitrile by electrophilic centre of the alkoxymethylene derivative takes place. In fact, only one pyridone derivative could be isolated[1] (formed by primary C-attack) to which the authors ascribed intuitively the structure *I*. We verified this conclusion above all after the recent finding[2] that in analogous reaction of N-alkyl-3-amino-crotononitriles N-attack of these compounds is important. It is noteworthy that similar course is also encountered if arylamines are used[3-6] instead of the mentioned enamines.

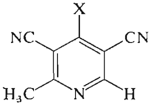
In the present paper it is shown that the presumed formation of the compound *I* (ref.[1]) really takes place. Verification of the presumption consists in transformation of the mentioned cyclocondensation product into 2-chloro-3,5-dicyano-6-methylpyridine (*IV*) in which position of halogen atom can be determined unambiguously by confrontation of electric dipole moment of the compound *IV* with analogous data of the model substances *II* and *III*. Thereby it is also shown that some further products of chemical transformations of the compounds *I* and *IV* belong to the group of 2-substituted compounds *IV*–*VIII* and not to the alternative compound group *IVa*–*VIIIa*.



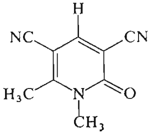
II, X = H
III, X = CH_3



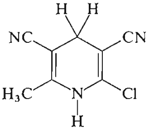
IV, X = Cl
V, X = Br
VI, X = I
VII, X = $(CH_3)_2N$
VIII, X = C_2H_5O



IVa, X = Cl
Va, X = Br
VIa, X = I
VIIa, X = $(CH_3)_2N$
VIIIa, X = C_2H_5O



IX



X

^{1}H-NMR spectra of the starting pyridone derivative showed that splitting of the proton signal of heterocyclic proton by spin interaction with N—H proton was not recorded. This finding suggests its location at 4 position (formula *I*), but it does not exclude the possibility of extremely low $^3J_{NH}$ value in the molecule *Ia* due to rapid prototropic exchange of the type N—H···O=C (refs[7,8]).

The theoretical dipole moment was obtained as a vector sum of the individual groups moments. The latter were determined from difference of the dipole moments of the 4-substituted pyridines and that of pyridine (method *A*) and from values of dipole moments of the monosubstituted benzenes (method B)[9]. We also studied dipole moments of the model substances *II* and *III* to eliminate influence of various techniques of measurements, as the necessary values were taken from literature. The values found experimentally agreed with those calculated by vector analysis with the use of the individual groups moments by both the method *A* and *B* (Table I). From the measured values of the models *II* and *III* we also tried to calculate the partial contributions of moments of cyano and methyl groups (method *C*). It must be noted that the calculated value of contribution of *ortho* methyl group is considerably higher than that given by vector differences of the dipole moments obtained for 4-picoline and toluene (methods *A* and *B*). This can probably be explained by the presence

TABLE I

Dipole Moments (10^{-30} Cm) of Individual Groups Used in Methods *A*—*C*

Group	*A*	*B*	*C*
CH_3	1·23[a]	1·23	3·20
CN	—12·84	—13·51	—12·44
Cl	— 4·34	— 5·30	—

[a] 10^{-30} Cm = 0·2998 D.

TABLE II

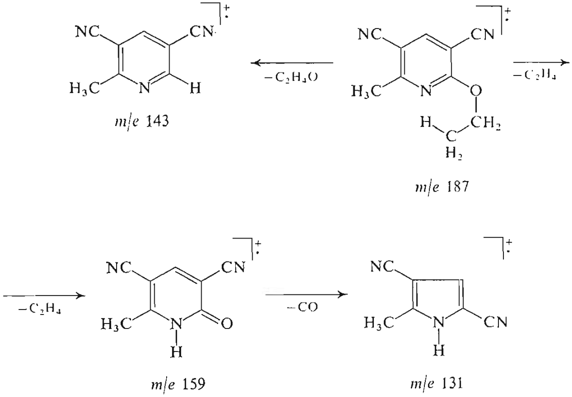
Dipole Moments (10^{-30} Cm) of the Studied Compounds Calculated by the Methods *A*—*C* and Found Experimentally

Compound	*A*	*B*	*C*	Experiment
II	5·50[a]	6·17	—	5·10
III	6·74	7·40	—	8·31
IV	6·34	7·17	8·37	7·47
IVa	10·51	12·14[c]	12·34	—

[a] 10^{-30} Cm = 0·2998 D.

of nitrogen atom in the vicinity of methyl group, which polarizes the bond markedly, or by hyperconjugation interaction of the 3,5-dicyano-skeleton with the donor methyl group. The calculation did not involve any correction factors expressing the conjugation effect. For pyridine the experimental value of dipole moment 7·34 . 10^{-30} Cm (ref.[10]) was used. The dipole moments are summarized in Table II. From comparison if follows unambiguously that the experimental value 7·47 . 10^{-30} Cm agrees with the calculated dipole moment value of 2-chloro-3,5-dicyano-6-methylpyridine (*IV*) which was prepared from the respective 2-pyridone.

In accordance with this conclusion mass spectrum of 2-ethoxy-3,5-dicyano-6-methylpyridine (*VIII*) shows the McLafferty rearrangement in ethoxy group which is due[11,12] to the presence of free electron pair at nitrogen atom of pyridine ring (Scheme 2). Fragmentation of the derivatives *V* and *VI* is characterized by splitting off of halogen atom from molecular ion, whereas that of the derivative *IV* involves elimination of a HCl molecule.



SCHEME 2

In analogy to preparation of the 2-chloro derivative *IV*, reaction of PBr_3 with 2-pyridone *I* gives the very reactive 2-bromo derivative *V* which undergoes substitution of 2-bromine by ethoxyl group even during its crystallization from ethanol. The iodo derivative *VI* was prepared by substitution of chlorine in the compound *IV* on action of HI. Reaction of the compound *IV* with dimethylformamide gave the corresponding 2-dimethylamino derivative, the dimethylformamide acting as a source of dimethylamine[13]. Reaction of potassium salt of the compound *I* with methyl

TABLE III

Properties of the Compounds *IV*—*X*

Compound	Calculated/Found				Melting point °C	IR, cm^{-1}		^{1}H-NMR ppm^d		λ_{max}, nm (log ε)
	% C	% H	% N	% X^a		ν(CH)/ν(CN)	ν_{ring}	δ(CH$_3$)	4 H/6 CH$_3$	
VI $C_8H_4ClN_3$ (177·5)	54·10 54·31	2·25 2·28	23·67 23·50	19·98 19·87	140·5—141	3 020 2 235	1 590 1 560 1 425	1 380	7·94 2·70	284 (3·52)
V $C_8H_4BrN_3$ (222·5)	43·24 43·27	1·80 1·83	18·92 19·02	36·08 36·38	156—158	3 010 2 238	1 525 1 415	1 360	8·11 2·85	286 (3·51)
VI $C_8H_4IN_3$ (268·7)	35·96 35·74	1·49 1·56	15·61 15·49	47·21 47·51	135—136	3 010 2 240	1 580 1 520 1 410	1 380	7·90 2·83	277 (3·86)
VII $C_{10}H_{10}N_4$ (186·3)	64·51 64·32	5·32 5·29	30·10 30·28	—	129—130	3 010 2 220	1 600 1 552 1 420	1 408	7·94 2·68	343 (3·67)
VIII $C_{10}H_9N_3O$ (187·3)	64·17 64·28	4·81 4·76	22·46 22·30	— —	108—109	3 010 2 230	1 600 1 550 1 480 1 445	1 320	8·01 2·74	298 (3·83)
IX $C_9H_7N_3O$ (173·3)	62·43 62·28	4·04 4·00	24·28 24·31	—	176—178	3 010 2 230	1 680^c 1 535 1 430	1 370	7·85 2·73	340 (4·02)
X $C_8H_6ClN_3$ (179·5)	53·48 53·41	3·34 3·29	23·40 23·45	19·78 19·65	209—210	3 020^b 2 210	1 670 1 630 1 480	1 380	— 2·02	341 (3·59)

[a] The corresponding halogen; [b] ν(NH) vibration of dihydropyridine ring 3420 cm^{-1}; [c] ν(C=O) vibration; [d] the other proton signals for the compound *VII* 3·48δ (dimethylamino group), for the compound *VIII* 1·47δ triplet and 4·58δ quadruplet of ethyl group, for *IX* 3·64δ singlet of methyl group at nitrogen, for *X* 2·8δ singlet of methylene group.

iodide gave 1-methyl-2-pyridone *IX*. Reaction with sodium borohydride is an addition at 4 position giving the respective 1,4-dihydro derivative *X* the structure of which agrees with the spectral characteristics and its relative stability. Physical and spectral characteristics of the compounds *IV–X* are summarized in Table III.

EXPERIMENTAL

The given melting points were not corrected. The chromatography was carried out with Al_2O_3 Reanal (activity II according to Brockmann), the compounds were detected by iodine vapours and UV light. The compounds *I* and *IV* were synthetized by the procedure given in ref.[1]. The compounds *II* and *III* were obtained by the analogous procedure given in ref.[14]. The IR spectra were measured with a Perkin-Elmer 625 apparatus in chloroform (concentration $1 . 10^{-4}$M; 0·107 cm cell) and in KBr disc (for the compound *I*). The spectra were measured with an Optica Milano CF 4NI and a UV Specord Zeiss spectrophotometers, the ^{1}H-NMR spectra were measured with a Varian XL-100 apparatus using tetramethylsilane as standard. The mass spectra were measured with a LKB 9000 apparatus at 70 eV. The dipole moments of the studied compounds were measured by the method by Kumler–Halverstadt[15] in benzene at 25°C.

Mass Spectra (masses of the ions and their relative %)

IV: 179 (33), 178 (11), 177 (M^+, 100), 142 (18), 141 (85), 115 (15), 114 (7), 101 (6), 100 (5), 89 (7), 88 (11), 87 (7), 85 (9), 75 (6), 64 (10), 63 (9), 52 (5), 51 (7), 41 (6), m* = 112·3, 92·3.

V: 224 (6), 223 (58), 222 (10), 221 (M^+, 55), 220 (5), 143 (10), 142 (100), 141 (21), 115 (32), 101 (5), 100 (5), 89 (7), 88 (13), 87 (5), 75 (5), 69 (7), 64 (13), 63 (10), 62 (7), 52 (6), 51 (18), 43 (8), 41 (11) m* = 93·3, 67·4.

VI: 270 (9), 269 (M^+, 84), 179 (21), 178 (7), 177 (68), 143 (11), 142 (100), 141 (55), 127 (11), 116 (6), 115 (39), 114 (5), 101 (5), 100 (5), 89 (8), 88 (18), 87 (7), 85 (6), 75 (7), 65 (5), 64 (16), 63 (11), 62 (9), 52 (7), 51 (8), 45 (5), 41 (6), m* = 112·5, 93·3, 67·5.

VII: 186 (M^+, 64), 172 (19), 171 (74), 158 (32), 157 (100), 144 (27), 117 (27), 115 (24), 89 (5), 88 (14), 87 (6), 75 (7), 64 (13), 63 (10), 62 (8), 52 (6), 41 (5), m* = 132·6.

VIII: 187 (M^+, 38), 172 (20), 161 (10), 160 (13), 159 (100), 145 (16), 143 (31), 132 (10), 131 (56), 130 (35), 118 (6), 116 (6), 115 (6), 104 (8), 89 (16), 88 (8), 77 (6), 67 (6), 64 (9), 63 (9), 62 (9), 52 (9), 42 (19), m* = 107·9.

IX: 174 (12), 173 (M^+, 100), 146 (29), 145 (51), 130 (8), 118 (13), 103 (5), 89 (12), 64 (5), 63 (5), 62 (6), 56 (27), 52 (6), 42 (6), m* = 121·5.

X: 179 (31), 178 (12), 177 (M^+, 95), 142 (21), 141 (100), 116 (6), 115 (19), 114 (9), 101 (8), 100 (6), 89 (7), 88 (16), 87 (10), 85 (12), 75 (8), 64 (16), 63 (14), 62 (14), 51 (9), m* = 112·5.

2-Bromo-3,5-dicyano-6-methylpyridine (*V*)

5 g compound *I* and 51 g PBr_5 (excess 3·8 mol) were heated from 40 to 110°C within 1 h and then at 110°C for another 1 h. The heating was accompanied by liberation of HBr vapour. The mixture was cooled and extracted with benzene (300 ml), and, after evaporation of the solvent, the residue was poured onto 50 g crushed ice. The precipitated yellow solid was collected by suction, dried and crystallized from mixture benzene–light petroleum. Yield 3·6 g (52%).

2-Iodo-3,6-dicyano-6-methylpyridine (*IV*)

1 g compound *IV* and 6 ml 56% hydriodic acid were heated at 80—100°C 30 min. After cooling the precipitated solid was separated, dried, and crystallized from mixture benzene–CCl_4. Yield 760 mg (51%).

2-Dimethylamino-3,5-dicyano-6-methylpyridine (*VII*)

Mixture of the compound *IV* (1 g) and 0·76 g CuCN in 30 ml dimethylformamide was refluxed 3·5 h, the temperature being kept below 140°C. After removing dimethylformamide by vacuum distillation the residue was extracted with benzene, and the extract was concentrated. The yellow crystals precipitated on cooling were purified by crystallization from petroleum ether and by sublimation. Yield 520 mg (56%).

2-Ethoxy-3,5-dicyano-6-methylpyridine (*VIII*)

Mixture of 2 g compound *IV*, 20 ml ethanol and 3 g sodium ethoxide was refluxed 3 h, dried, and the residue was dissolved in water and extracted in chloroform. The chloroform layer was dried with magnesium sulphate, evaporated, and the residue was purified by sublimation. Yield 1·7 g (80%).

1,6-Dimethyl-3,5-dicyano-2-pyridone (*IX*)

3 g potassium salt of pyridone *I* was treated with 10·8 g methyl iodide and 20 ml hexamethylphosphorustriamide. After 4 days standing at room temperature the solution was poured onto 200 ml water. The separated solid was collected by suction, dried, and crystallized from methanol until constant melting point. Yield 1·78 g (59%).

2-Chloro-3,5-dicyano-6-methyl-1,4-dihydropyridine (*X*)

200 mg compound *IV* was mixed with 100 mg sodium borohydride (excess 2·2 mol) in 5 ml ethanol. The compound *IV* dissolvend with liberation of gas and slight spontaneous heating of the mixture. The mixture was stirred 2 h, left to stand overnight at room temperature, and poured in 50 ml water. The precipitated solid was collected by suction, dried (170 mg) and purified by column chromatography to give 124 mg (62%) yellow crystals of the compound *X* well soluble in ethanol.

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