182. The Synthesis and Transition Temperatures of Ester Derivatives of 2-Fluoro-4-hydroxy- and 3-Fluoro-4-hydroxybenzonitriles also Incorporating Aliphatic Ring Systems

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Summary

The synthesis and liquid-crystal transition temperatures of forty ester derivatives of 2-fluoro-4-hydroxybenzonitrile and 3-fluoro-4-hydroxybenzonitrile are reported. The esters contain the *trans*-1,4-disubstituted cyclohexane or the 1,4-disubstituted bicyclo[2.2.2]octane rings (some contain an additional phenyl ring). Many of the novel F-substituted esters exhibit substantially *higher* nematic-isotropic transition temperatures than the corresponding unsubstituted esters. The order of clearing points of these laterally substituted esters differing only in the presence of a benzene ring and the above-mentioned rings is established.

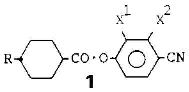
Introduction. – In a parallel publication [1], we have reported the preparation and liquid-crystal transition temperatures of substituted benzoate derivatives of 2-fluoro- and 3-fluoro-4-hydroxybenzonitrile. In this publication, we give the corresponding data for analogous esters containing either a *trans*-1,4-disubstituted cyclohexane ring or the 1,4-disubstituted bicyclo[2.2.2]octane ring in place of a benzene ring in the acid moiety [1].

The synthesis of the required 3-fluoro-4-hydroxybenzonitrile and 2-fluoro-4-hydroxybenzonitrile has already been described [1]. The synthesis of 4-hydroxy-1,3-benzenedicarbonitrile is given in the *Exper. Part*. The 1,4-disubstituted bicyclo-[2.2.2]octane-1-carboxylic acids and various benzoic acids were prepared according to [2] [3]. The preparation of the required *trans*-4-alkylcyclohexanecarboxylic acids [4] was accomplished *via* hydrogenation, using *Nishimura*'s catalyst, of the corresponding methyl 4-alkylbenzoates, equilibration, using *t*-BuOK, to achieve a higher proportion of *trans*-isomer, and subsequent hydrolysis using NaOH and finally treatment with conc. HCl to liberate the acid, which was obtained in the pure *trans*-form by crystallization. The esterification and purification procedures used have been described in [3].

Results and Discussion. – The liquid-crystal transition temperatures and several enthalpies of fusion of the 4-cyano-2-fluorophenyl and 4-cyano-3-fluorophenyl *trans*-4-alkylcyclohexane-1-carboxylates **1** are recorded in *Table 1*. The liquid-crystal temperatures are plotted against the number of C-atoms (n) in the terminal C-chain in *Fig. 1* and *2*, respectively. In addition, the differences between the clearing points (N–I) of the fluoro-substituted-phenyl esters **1** and **2** and those of the corresponding homologues of the analogous non-fluoro-substituted-phenyl esters (with a H-atom instead of the F-atom) are listed in the sixth column.

Most of the homologues of the cyclohexane-carboxylates **1** exhibit enantiotropic nematic phases. The plots of the nematic-isotropic transition temperatures (*T*) against the length of the terminal C-chain (n) of the esters increase from very low values for

Table 1. *Transition Temperature* (°C) *and Enthalpies of Fusion* (kcal · mol^{-1}) *for Compounds* **1**



1

R	X^1	X^2	C–N/I	N–I[a])	ΔT_{N-I} (H→F)	ΔH
CH_3	F	H	102	[28]	–	–
C_3H_7	F	H	84	87.5	+ 18.5	6.3
C_5H_{11}	F	H	75.5	93.5	+ 14.5	7.2
C_7H_{15}	F	H	76	92	+ 9.5	8.4
C_9H_{19}	F	H	79.5	91.5	–	9.8
CH_3	H	F	60	[– 30]	–	–
C_3H_7	H	F	45	(15)	– 54.5	–
C_5H_{11}	H	F	40	42	– 37	–
C_7H_{15}	H	F	45	50	– 32.5	–
C_9H_{19}	H	F	54	54.5	–	–

[a]) ( ) Represents a monotropic transition temperature; [ ] represents a 'virtual' transition temperature.

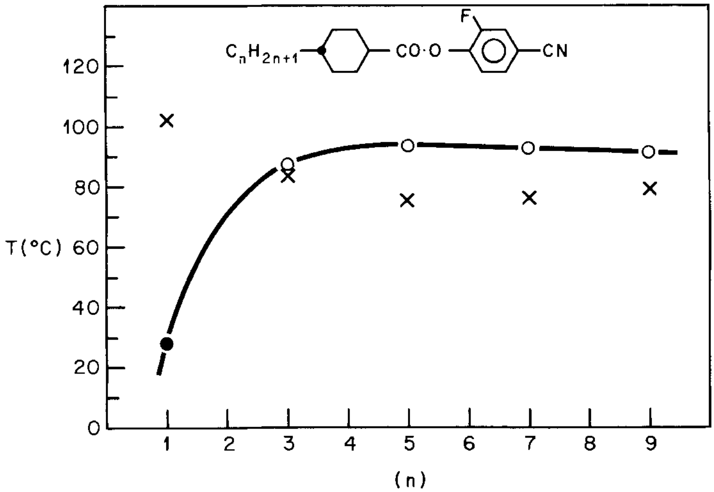


Fig. 1. *Plot of the transition temperatures* vs. *the number of* CH_2*-groups* (n) *in the C-chain* (C_nH_{2n+1}) *of the esters formulated* (X, crystal-nematic/isotropic liquid transition; ○, enantiotropic nematic-isotropic liquid transition; ●, monotropic nematic-isotropic liquid transition)

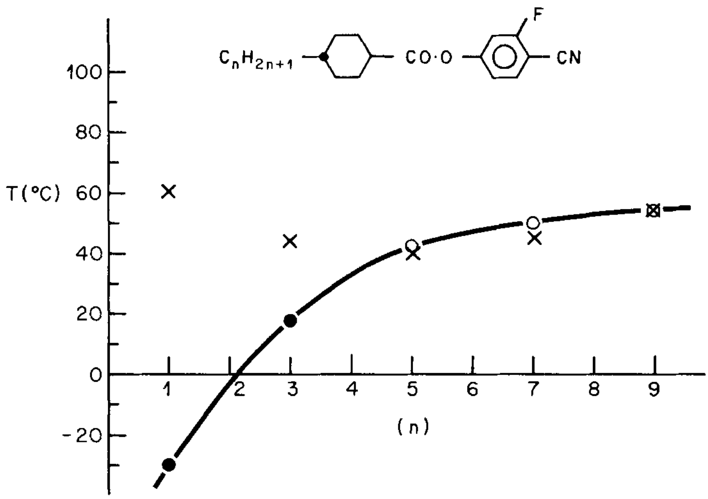


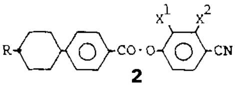
Fig. 2. *Plot of the transition temperatures* vs. *the number of CH$_2$-groups* (n) *in the C-chain* (C$_n$H$_{2n+1}$) *of the esters formulated* (X, crystal-nematic/isotropic liquid transition; ○, enantiotropic nematic-isotropic liquid transition; ●, monotropic nematic-isotropic liquid transition)

the methyl homologues (extrapolated values, see *Exper. Part*). The curve for the 2-fluorophenyl esters (X^1 = F; X^2 = H) reaches a plateau for R = C_5H_{11} and remains almost constant for longer chain-lengths, see *Fig. 1*. The curve for the 3-fluorophenyl esters (X^1 = H; X^2 = F) is still rising slightly at the longest C-chain lengths studied (R = C_9H_{19}), see *Fig. 2*. A similar sharply rising plot is observed for the analogous, non-fluoro-substituted-phenyl esters [5] with a H-atom instead of a F-atom.

The clearing and melting points of the 2-fluorophenyl esters (X^1 = F; X^2 = H) are greater than those of the corresponding homologues of the 3-fluorophenyl esters (X^1 = H; X^2 = F). The clearing points of the 2-fluorophenyl esters (X^1 = F; X^2 = H) are higher (*ca.* +14°, on average, comparing only C-chains of equal length) than those of the corresponding non-F-substituted-phenyl esters (X^1 = X^2 = H). The melting points are also higher (*ca.* +25°, on average). The 3-fluorophenyl esters exhibit lower clearing points (*ca.* −34°, on average) and lower melting points (*ca.* −8°, on average) than those of the non-F-substituted esters.

The liquid-crystal transition temperatures of the three-ring ester derivatives **2** of the *trans*-4-(4-alkylcyclohexyl)benzoic acids and 3-fluoro-4-hydroxybenzonitrile or 2-fluoro-4-hydroxybenzonitrile are recorded in *Table 2*. The literature data for 2,4-dicyanophenyl and 3,4-dicyanophenyl *trans*-4-(4-pentylcyclohexyl)benzoates are also included [6]. The liquid-crystal transitions of the three-ring esters **2** decrease with increasing chain lengths for the few homologues studied. The melting points and clearing points of the 2-fluorophenyl esters (X^1 = F; X^2 = H) are greater for each homologue than those of the 3-fluorophenyl esters (X^1 = H; X^2 = F). The clearing points of the fluorophenyl esters **2** are always lower than those of the corresponding non-F-substituted-phenyl esters (X^1 = X^2 = H) [7]. The clearing points of the dicyanophenyl substituted esters [6] are lower than those of the corresponding esters with a F-atom in either the 2- or 3-position instead of the CN-moiety (see *Table 2*).

Table 2. *Transition Temperature* (°C) *for Compounds* **2**

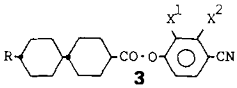


2

R	X^1	X^2	C–N	N–I	ΔT_{N-I} (H→F, CN)	
C_3H_7	F	H	108.5	227.5	– 8.5	
C_5H_{11}	F	H	97	217	– 8	
C_7H_{15}	F	H	89.5	204	– 22	
C_3H_7	H	F	101	201	– 35	
C_5H_{11}	H	F	91.5	194.5	– 30.5	
C_7H_{15}	H	F	85.5	183.5	– 52.5	
C_5H_{11}	CN	H	132	179	– 57	[6]
C_5H_{11}	H	CN	85	144	– 92	[6]

The liquid-crystal transition temperatures of the three-ring 4-cyano-2-fluorophenyl and 4-cyano-3-fluorophenyl all-*trans*-4-(4-alkylcyclohexyl)cyclohexane-1-carboxylates **3** are recorded in *Table 3*. The clearing points of the bicyclohexyl esters **3** are higher for each homologue than the analogous cyclohexylbenzoates **2**, see *Table 2*. The nematic ranges of several homologues of the esters **3** are significantly broader than those of the esters **2**.

Table 3. *Transition Temperatures* (°C) *for Compounds* **3**



3

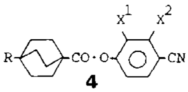
R	X^1	X^2	C–S_A/N	S_A–N	N–I	ΔT_{N-I} (H→F, CN)	
C_3H_7	F	H	104	–	249	–	
C_5H_{11}	F	H	113	–	242	+ 10	
C_7H_{15}	F	H	112	–	222	0	
C_3H_7	H	F	76	–	212	–	
C_5H_{11}	H	F	79	–	209	– 13	
C_7H_{15}	H	F	90	–	194.5	– 27.5	
C_5H_{11}	CN	H	115	165	201	– 31	
C_5H_{11}	H	CN	97	–	165.5	– 56.5	[14]

The effect of introducing F- or CN-substituents in either the 2- or 3-position of 4-cyanophenyl all-*trans*-4-(4-pentylcyclohexyl)cyclohexane-1-carboxylate (C–S_A = 90°; S_A–N = 118°; N–I = 222° [7]) is instructive. The substitution of an H-atom in the 2-position by a F-atom gives rise to an increase in melting point (+23°) and clearing point (+10°), see *Table 3*. This ester (X^1 = F; X^2 = H) may be supercooled to room temperature without observing a smectic phase. This represents a significant depression (more than –100°) of the smectic-nematic transition temperature. Thus the temperature range over which a nematic phase can be observed is considerably greater than that of the non-F-substituted-phenyl ester. A similar substitution by a CN-function leads to an increase in melting point (*ca.* +25°), a decrease in clearing point (*ca.* –20°), and a large increase in the smectic-nematic transition temperature (*ca.* +45°), see *Table 3*. This results in a significant decrease in the temperature range of the observed nematic phase (*ca.* −65°). The introduction of a F-atom in the 3-position leads to a small decrease in both the melting point (*ca.* −10°) and clearing point (−13°) of the corresponding unsubstituted ester. The incorporation of a CN-group in exactly the same position not only leads to an increase in the melting point (+7°) but also a major decrease in the clearing point (−56.5°). Thus, a significant narrowing of the nematic range (*ca.* −65°) is observed. The substantial depression of the smectic-nematic transition temperature by the F-atom is consistent with earlier results for nematic compounds of low positive or negative dielectric anisotropy [8] [9]. The effect of the CN-function on the temperature at which the smectic-nematic transition takes place is dependent upon the position it occupies in the molecule and is not easily rationalized. The effect of the CN-substitution on the melting points is irregular. This is quite consistent with the usual difficulties associated with attempts to predict the melting points of liquid crystals [8].

The liquid-crystal transition temperatures and some enthalpies of fusion of one 3-substituted and various 2-substituted 4-cyanophenyl 4-alkylbicyclo[2.2.2]octane-1-carboxylates **4** are listed in *Table 4*. Each homologue of the 4-cyano-2-fluorophenyl bicyclooctanecarboxylates ($X^1 = F$; $X^2 = H$) exhibits an enantiotropic nematic phase. The clearing points of the 2-fluorophenyl esters are in each case significantly higher (*ca.* +24.5°, on average) than those of the corresponding non-F-substituted-phenyl esters ($X^1 = X^2 = H$) [10] with an H-atom in place of the F-atom. The melting points of the esters are sometimes greater and sometimes lower than those of the corresponding non-substituted esters. The one 3-substituted-phenyl ester prepared melts at approximately the same temperature as the corresponding 2-substituted-phenyl ester, but possesses a much lower clearing point (−68°).

The so-called 'shielding effect' of the 1,4-disubstituted bicyclo[2.2.2]octane rings [9] is demonstrated by the 2-substituted-4-cyanophenyl esters **4**. The 2,4-dicyanophenyl bicyclooctanecarboxylate ($X^1 = CN$; $X^2 = H$) exhibits a clearing point only marginally lower (−7.5°) than that of the corresponding ester ($X^1 = X^2 = H$) with an H-atom instead of the CN-function in the 2-position. This is in contrast to the large decreases (more than *ca.* −45°, on average) observed for the few examples of similar ester derivatives of benzoic and cyclohexane carboxylic acids where a smaller or no shielding effect is presumed to act [9], see *Tables 2* and *3*. There appears to be no 'shielding effect' with respect to the 3-fluorophenyl ester ($X^1 = H$; $X^2 = F$) where a large decrease in clearing

Table 4. *Transition Temperatures* (°C) *and Enthalpies of Fusion* (kcal · mol^{-1}) *for Compounds* **4**



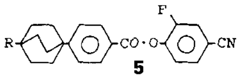
4

R	X^1	X^2	C–N/I	N–I[a])	ΔT_{N-I} (H→F, CN)	ΔH (kcal · mol^{-1})
C_3H_7	F	H	112	129	+ 29	6.95
C_4H_9	F	H	91.5	125	+ 31	7.1
C_5H_{11}	F	H	84	133	+ 24	7.7
C_6H_{13}	F	H	82	123.5	+ 21.5	–
C_7H_{15}	F	H	81	125.5	+ 19.4	9.1
C_8H_{17}	F	H	81.5	120	+ 22	–
C_5H_{11}	H	F	80.5	(65)	− 44	–
C_5H_{11}	CN	H	128.5	(101.5)	− 7.5	–

[a]) () Represents a monotropic transition temperature.

point is observed (*ca.* –44°). The liquid-crystal transition temperatures of five homologues of the 4-cyano-2-fluorophenyl 4-(4-alkylbicyclo[2.2.2]oct-1-yl)benzoates **5** are recorded in *Table 5*. The nematic-isotropic transition temperatures of the esters **5** containing an additional benzene ring are much higher (*ca.* +125°) than those of the analogous esters **4** as is always the case. The melting points are also greater (*ca.* +35°) but not to the same degree, which is consistent with the observed behaviour of many comparable nematic liquid crystals [8] [10].

Table 5. *Transition Temperatures* (°C) *for Compounds* **5**

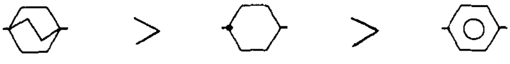


5

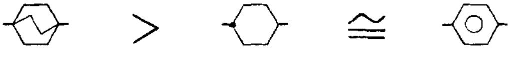
R	C–N/I	N–I[a])
CH_3	177	(173)
C_2H_5	–	–
C_3H_7	166	263
C_4H_9	117.5	257
C_5H_{11}	–	–
C_6H_{13}	116.5	245
C_7H_{15}	112	244

[a]) ( ) Represents a monotropic transition temperature.

The values of the nematic-isotropic transition temperatures listed in *Tables 1–5* and those reported in [1] allow the determination of the order of decreasing clearing point of the esters differing only in the presence of various rings. A comparison of the nematic-isotropic transition temperatures of identical homologues of the 2-fluorophenyl esters [1], **1** and **4** ($X^1 = F$; $X^2 = H$) and the 3-fluorophenyl esters [1], **1** and **4** ($X^1 = H$; $X^2 = F$) which differ only in the presence of the 1,4-disubstituted benzene [1], *trans*-cyclohexane, or bicyclo[2.2.2]octane rings, yields the following order of decreasing clearing point for both ester types:



A similar comparison between the clearing points of the (substituted benzoate) esters containing an additional benzene ring in the acid moiety [1], **2**, and **5** yields the following order:



On the basis of the few examples of the pentyl homologues of the 2,4-dicyanophenyl and 3,4-dicyanophenyl esters available, a similar order of decreasing nematic-isotropic transition temperatures would seem to exist.

The fact that many of the 2-fluorophenyl esters reported in *Tables 1–5* exhibit significantly higher clearing points than the corresponding non-F-substituted-phenyl esters is most unusual. The shielding effect (mentioned above) cannot be invoked alone to explain this substantial rise in the clearing temperature.

The effect which is most likely to be the cause of the observed increases in the clearing temperatures is the degree and form of association of the molecules as dimers. Associating liquids are well described by the *Kirkwood-Froehlich* equation [12] where a factor g was introduced to represent the degree of the correlation of the molecular dipoles. The factor g can be regarded (using the simple model of unassociated molecules (monomers) and associated molecular pairs (dimers)) as the proportion of the free molecules in the hypothetical binary mixture. Values for g can be calculated from the *Kirkwood-Froehlich* equation when all other parameters are known. The particle number density, the refractive index, and the dielectric constants can be determined experimentally. The molecular dipole moments of the free molecule can be calculated from tabulated group and bond moments. For the non-F-substituted-phenyl esters the dimer concentration is about 30% [12] which leads to a 45° higher clearing point than would be found if only monomers were present. (The clearing point of a nematic phase consisting only of dimers, in which the benzonitrile rings of nearest neighbour molecules overlap, would be *ca.* 150° higher. This value can be extrapolated from the clearing point of the corresponding monomer compound of equal length to the dimers.) For the 2-fluorophenyl esters, since the F-atom prevents the overlap of the benzonitrile rings of nearest neighbour molecules, the CN-groups lie next to each other (as is the case for the all-*trans*-4-(4-alkylcyclohexyl)cyclohexanecarbonitriles [13]). This gives rise to an even greater length/breadth ratio, which results in a clearing point for a nematic phase with all the molecules associated as dimers of *ca.* 300–400°. Thus the presence of *ca.* 20% (found from dielectric data [12]) of these dimers in the nematic phase would raise the clearing point by about 60–80°. This explains the higher clearing points of the 2-fluorophenyl esters in *Tables 1–5* compared to those of the corresponding non-F-substituted-phenyl esters. In the case of the 2-fluorophenyl benzoates [1], an increase in clearing point is not observed due to the lower degree of association [12] and the lower clearing point expected for the dimer (*ca.* 200°).

The degree of association of the 3-fluorophenyl esters [1], **1** and **4** ($X^1 = H$; $X^2 = F$) is substantially lower than that observed for the non-F-substituted-phenyl esters ($X^1 = X^2 = H$). It is clear that a much higher proportion of monomers would lead to substantially lower clearing points and a much greater dielectric anisotropy, as, indeed, is observed to be the case [11].

Experimental Part

(Mr. *F. Rime* is thanked for excellent technical assistance)

General. The esters **1**–**5** were synthesized, purified and their structure identified as described in [1]. The liquid-crystal transition temperatures and enthalpies of fusion of the esters were also measured as described in [1]. The 'virtual' nematic-isotropic liquid transition temperatures listed in *Table 1* were determined in the usual manner [14] using the pentyl homologue (substituted in the same position) in binary mixtures.

2,4-Dibromophenyl Acetate. Ac_2O (30 ml) was added to a solution of 2,4-dibromophenol (50.0 g, 0.20 mol) and 3M NaOH (100 ml) with ice (*ca.* 150 g). An oily precipitate was formed immediately. The mixture was stirred for a few min and then shaken with $CHCl_3$ (2 × 50 ml). The combined org. layers were washed with H_2O (2 × 1,000 ml) and dried ($MgSO_4$). The filtered solution was evaporated under vacuum and the raw product was crystallized for MeOH at 0°, to yield pure (99.8%) acetate 45 g (77%), m.p. 37–38°. IR: 1750 (C=O), 1240 (AcO), 900 (phenyl). MS: 294 (M^+).

2,4-Dicyanophenyl Acetate. A solution of 2,4-dibromophenyl acetate (40 g, 0.14 mol), anh. CuCN (36.5 g, 0.41 mol) and dry DMF (200 ml) was heated at 185° for 3 h under anh. conditions. The cooled mixture was added to a solution of anh. $FeCl_3$ (36 g) and conc. HCl (2 ml) in H_2O (350 ml) and stirred at 50–60° for 30 min. The resultant mixture was shaken with Et_2O (4 × 300 ml) and the combined org. layers were washed with 1M NaOH (2 × 100 ml) and with brine (2 × 1,000 ml) and dried ($MgSO_4$). The filtered solution was evaporated under slightly reduced pressure to yield raw product, which was crystallized from MeOH at 0° to give pure (99.5%) acetate 20 g (55%), m.p. 156.5–157.5°. IR (KBr): 1730 (C=O), 1245 (AcO), 2215, 2225 (CN). MS: 186 (M^+).

4-Hydroxy-1,3-benzenedicarbonitrile. A solution of 2,4-dicyanophenyl acetate (20 g, 0.11 mol) in $CHCl_3$ (100 ml) was stirred with conc. HCl (100 ml) for *ca.* 30 min. The org. layer was separated and washed with brine (2 × 1,000 ml). The org. layer was shaken with 3M NaOH (2 × 50 ml) and the combined aq. layers were filtered to remove small amounts of org. material (acetate). The NaOH-solution was then acidified with conc. HCl (Congo red) and the cooled mixture was shaken with $CHCl_3$ (3 × 50 ml). The combined org. layers were washed with H_2O (2 × 1,000 ml) and dried ($MgSO_4$). The filtered solution was evaporated under reduced pressure and the raw product was taken up in a minimum of solvent and eluted from a silica-gel column with toluene/AcOEt 1:1. The crude product thus obtained was crystallized from MeOH to yield pure (99.9%) dicarbonitrile, 14.2 g (92%). m.p. 230° (dec.) ([6]: 230° (dec.)). IR (KBr): 3200 (OH), 2215, 2225 (CN), 1300 (C–O), 910 (phenyl). MS: 144 (M^+).

2,4-Dicyanophenyl 4-Pentylbicyclo[2.2.2]octane-1-carboxylate **4** ($R = C_5H_{11}$). A solution of 4-hydroxy-1,3-benzenedicarbonitrile (0.65 g, 0.0045 mol) in 5 ml sieve-dried pyridine was added to a solution of 4-pentylbicyclo[2.2.2]octane-1-carbonyl chloride (1.1 g, 0.0045 mol), prepared in the usual way by treatment with $SOCl_2$, in 10 ml of Na-dried toluene maintained under anh. conditions. The resultant solution was heated at 80° for *ca.* 2 h. The cooled mixture was added to cold dil. HCl and extracted with $CHCl_3$. The combined org. layers were washed with H_2O and dried ($MgSO_4$). The filtered solution was evaporated under reduced pressure and the residue taken up in a minimum of solvent and eluted from a silica-gel column with toluene. Single-spot fractions containing the ester were combined and evaporated together to yield required product, which was crystallized from MeOH until constant temperatures were obtained (see *Tables 1–5* for the liquid-crystal transition temperatures of this ester and the esters **1–5** prepared by this method. The yields of pure product were practically quantitative). IR (KBr): 2215, 2220 (CN), 1700 (C=O).

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