Fused polycyclic nitrogen-containing heterocycles

24.* Three-component condensation of diethyl 2,4,6-trioxoheptanedicarboxylate with salicylaldehydes and ammonium acetate as a new method for the synthesis of 7- and 9-substituted benzo[*e*]pyrano[4,3-*b*]pyridines

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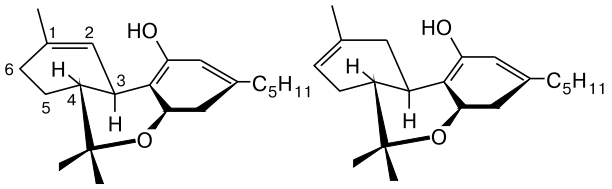
The three-component condensation of diethyl 2,4,6-trioxoheptanedicarboxylate with salicylaldehyde and its 3,5-dichloro-, 3-methoxy-, and 5-methoxy-substituted derivatives in EtOH in the presence of ammonium acetate affords tricyclic products, *viz.*, tetrahydrobenzo[*e*]-pyrano[4,3-*b*]pyridines. In the reaction with 3-nitrosalicylaldehyde, the intramolecular closure of the pyran ring does not occur due to the deactivation of the hydroxy group by the nitro group, and this reaction stops at the formation of the monocyclic product, *viz.*, tetrahydropyridin-4-one.

Key words: diethyl 2,4,6-trioxoheptanedicarboxylate, salicylaldehyde, three-component condensation, benzopyrano[4,3-*b*]pyridine, IR spectroscopy, NMR spectroscopy, X-ray diffraction study.

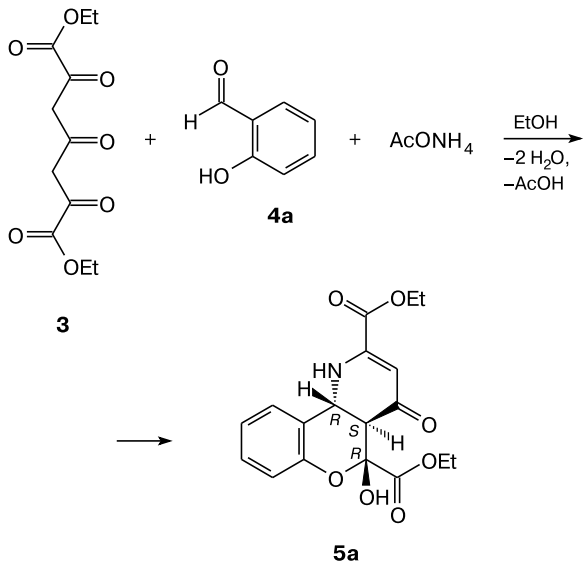
Tetrahydrobenzo[*e*]pyrano[4,3-*b*]pyridines[2—19] (or pyrido[3,2-*c*]coumarines[20]) are aza analogs of Δ^1-*trans*-tetrahydrocannabinol (**1**)[21] and $\Delta^{1(6)}$-*trans*-tetrahydrocannabinol (**2**),[22] which are known physiologically active components of *Cannabis*.[23] In this context, a search for new methods for the synthesis of this interesting tricyclic system has attracted considerable attention.[2—20]



1 **2**

Previously,[24] we have found that the reaction of diethyl 2,4,6-trioxoheptanedicarboxylate (**3**) (hereinafter, diethoxalylacetone) with salicylaldehyde (**4a**) in EtOH in the presence of ammonium acetate produces the aza analog of the heterocyclic cannabinol system, *viz.*, 2,5-diethoxycarbonyl-5-hydroxy-4-oxo-1,4,4a,10b-tetrahydrobenzo[*e*]pyrano[4,3-*b*]pyridine (**5a**) (Scheme 1).

Scheme 1



3 **4a** **5a**

The ^{1}H NMR spectrum of the reaction product, which was isolated in the pure form in 70% yield, shows, along with other signals, two doublets at δ 3.27 and 5.00 (J = 16.2 Hz), which are indicative of the presence of protons of the AX system in the mutual *trans* arrangement. It should be noted that the signals for protons in the spectrum of the crude product are doubled, which is evidence for the formation of two diastereomers. The integrated intensity ratio for the signals of these diastereomers is 1 : 10. We failed to isolate the diastereomer,

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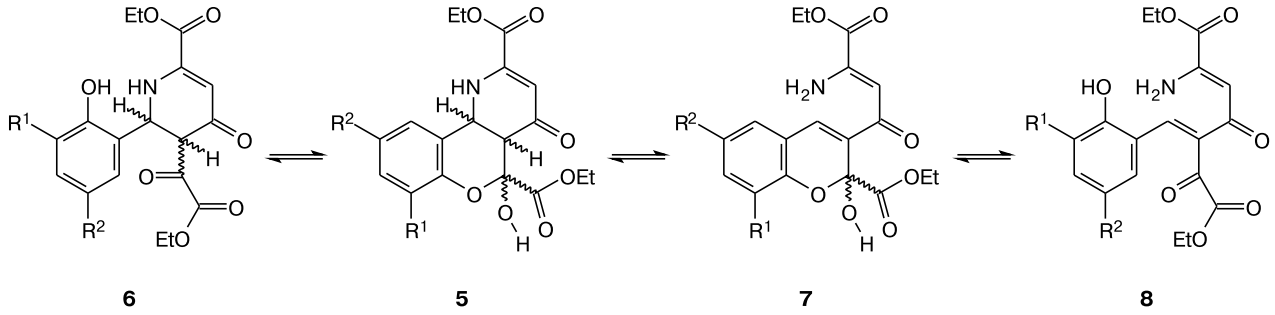
Scheme 2



6 **5** **7** **8**

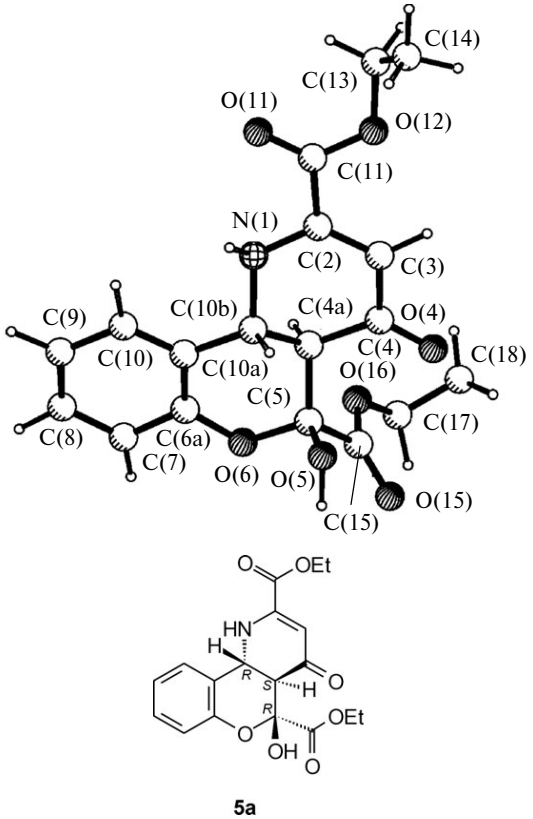
which was present in the mixture in an amount of ~9%, in the pure form.

The X-ray diffraction study showed[24] that the asymmetric carbon atoms in compound **5a** have the relative configuration C(4a)*S*,C(5)*R*,C(10b)*R* (Fig. 1).

Since both steps of the pyrid-4-one and pyran ring closure in the reaction giving tetrahydrobenzo[*e*]pyrano-[4,3-*b*]pyridine **5a** are reversible[25,26] and lead to the formation of three asymmetric centers, compound **5** can exist as eight isomers, which can potentially be isolated as four diastereomeric pairs.

The presence of two systems capable of forming tautomers (2-hydroxypyran and tetrahydropyridin-4-one) in tetrahydrobenzo[*e*]pyrano[4,3-*b*]pyridine **5** suggests that the latter compound can exist in different forms, including open-chain structures, depending on the phase state and the polarity of the medium (Scheme 2).

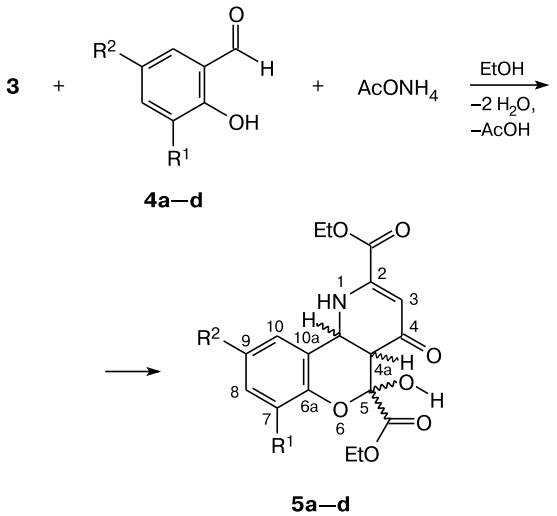
The nature of the substituents in substituted salicylaldehyde can influence the tautomeric equilibrium from the very beginning of the formation of the tricyclic system, thus determining the formation of a particular tautomer and, consequently, of the diastereomer. In this context, in the present study we made efforts to elucidate the influence of the nature of the substituents in salicylaldehydes on the structure of the final products and the pathways of their formation in the three-component condensation under consideration (Scheme 3).



5a

Fig. 1. Molecular structure of **5a** in the crystal.

Scheme 3



4a—d

5a—d

4, 5: $R^1 = R^2 = H$ (**a**); $R^1 = R^2 = Cl$ (**b**); $R^1 = OMe$, $R^2 = H$ (**c**); $R^1 = H$, $R^2 = OMe$ (**d**)

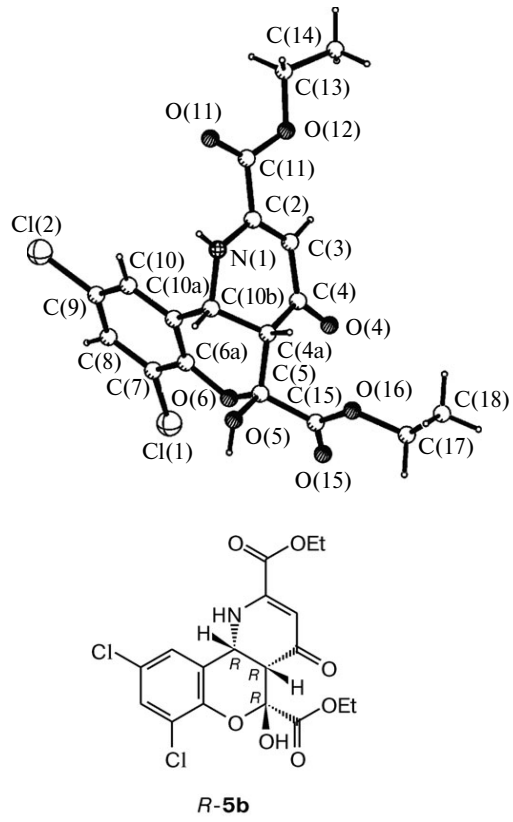
The reactions of diethoxalylacetone **3** (see Ref. 24) with 3,5-dichloro-, 3-methoxy-, and 5-methoxysalicylaldehydes **4b—d**, respectively, in EtOH in the presence of ammonium acetate give products **5b—d** with a tricyclic

structure in good yields. An analysis of the ^{1}H NMR spectra of the crude products showed that all reactions afford mixtures of diastereomers. Thus, the signals for protons in the ^{1}H NMR spectrum of the product prepared with the use of 3,5-dichlorosalicylaldehyde (**4b**) are doubled, which is indicative of the formation of two diastereomers; the integrated intensity ratio is 1 : 5. For the major diastereomer, the bridgehead protons H(4a) and H(10b) resonate at δ 3.58 and 5.02 (J = 7.4 Hz), respectively; for the minor diastereomer, the signals for the bridgehead protons are observed at δ 3.12 and 4.86 (J = 15.8 Hz). These diagnostic signals provide evidence for the formation of the tricyclic systems containing bridgehead protons in different orientations rather than for the formation of only the pyridin-4-one or benzopyran systems. The X-ray diffraction data confirmed the *cis* orientations of the protons H(4a) and H(10b) in the major product of the reaction occurring with the participation of 3,5-dichlorosalicylaldehyde, the asymmetric carbon atoms of this compound having the relative configuration C(4a)*R*,C(5)*R*,C(10b)*R* (Fig. 2). It should also be noted that the nonequivalence of the diastereomeric methylene protons of two ethoxycarbonyl fragments of compound **5b** is manifested in the ^{1}H NMR spectrum in different ways. The signals for the methylene protons of the ethoxycarbonyl group at the C(2) atom coincide, whereas the signals for the methylene protons of the same group at the C(5) atom differ by 0.02 ppm, which is apparently associated with the fact that the former protons are more distant from the asymmetric centers.

The reactions of 3- and 5-methoxy-substituted salicylaldehydes give diastereomeric mixtures of compounds **5c** and **5d** with the *cis* (J = 6.5 Hz and J = 6.6 Hz) and *trans* arrangement (J = 15.8 Hz and J = 16.1 Hz) of the bridgehead hydrogen atoms of the tricyclic systems, respectively. The ratio of the diastereomers of tricyclic compound **5c** in the mixture is ~1 : 2, whereas the corresponding ratio for tricyclic compound **5d** is 2 : 1. The nonequivalence of the methylene protons of the ethoxycarbonyl group at the C(5) atom in tricyclic systems **5c,d** is manifested in the ^{1}H NMR spectra as the 0.18 ppm difference between the chemical shifts. This difference is approximately equal for both systems.

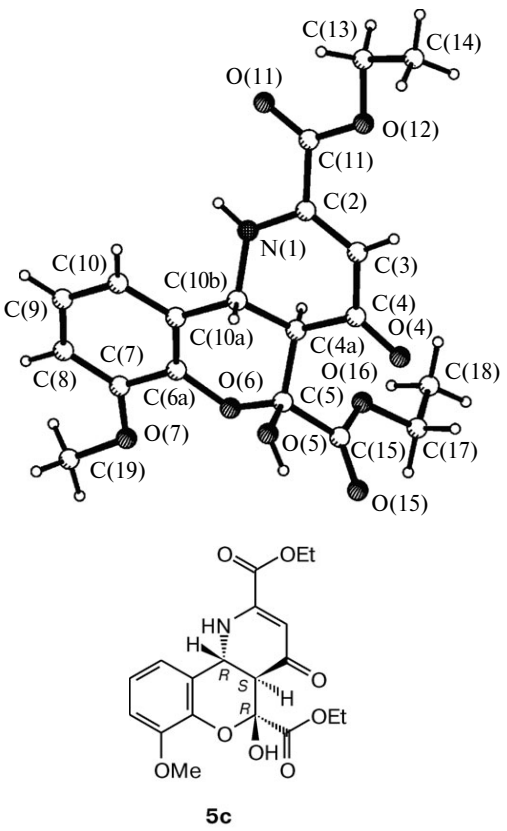
According to the X-ray diffraction data, the asymmetric carbon atoms in the diastereomer isolated from the reaction with 3-methoxysalicylaldehyde (**4c**) have the relative configuration C(4a)*S*,C(5)*R*,C(10b)*R* (Fig. 3), whereas the asymmetric carbon atoms in the diastereomer isolated from the reaction with 5-methoxysalicylaldehyde (**4d**) have the configuration C(4a)*R*,C(5)*R*,C(10b)*R* (Fig. 4).

The crystal and molecular structures of compounds **5a,c,d** (see Figs 1, 3, and 4, respectively) have been described in detail previously.[27] In the present study, we



R-**5b**

Fig. 2. Molecular structure of **5b** in the crystal.



5c

Fig. 3. Molecular structure of **5c** in the crystal.

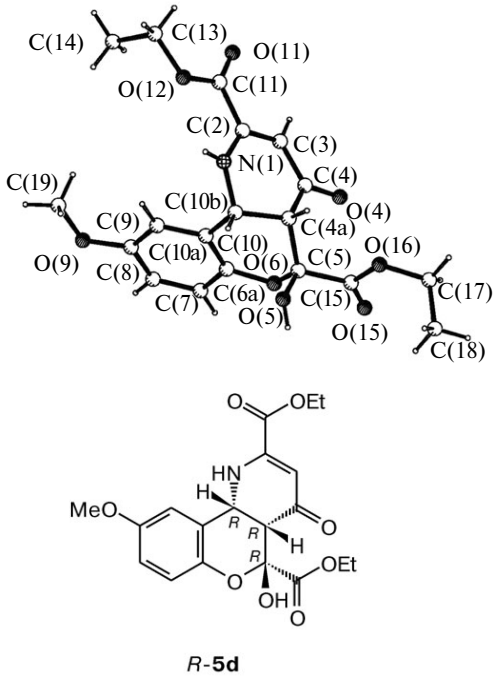


Fig. 4. Molecular structure of **5d** in the crystal.

analyzed the structure of compound **5b**; the structures of compounds **5a,c,d** were used for the comparison.

Compound **5b** (see Fig. 2) crystallizes as a racemate with the chiral centers having the relative configuration C(4a)*R*,C(5)*R*,C(10b)*R* (or C(4a)*S*,C(5)*S*,C(10b)*S* in the molecule related to the reference molecule by a center of symmetry). The bond lengths and bond angles in the tricyclic system of molecule **5b** (Table 1) are similar to the corresponding values for molecules **5a,c,d**.[27] The ethoxycarbonyl substituent at the C(2) atom in molecule **5b**, like those in molecules **5a,c**, is in an eclipsed conformation (the C(3)—C(2)—C(11)—O(12) torsion angle is 8.8(3)°). This conformation of the substituent is stabilized by the intramolecular N(1)—H(1)...O(11) hydrogen bond (the hydrogen bond parameters are given in Table 2).

The pyran ring in molecule **5b**, like these rings in molecules **5a,c,d**, adopts a half-chair conformation. The O(6)C(6a)C(10a)C(10b) fragment is planar within 0.006(2) Å. The C(4a) and C(5) atoms deviate from this plane by 0.585(2) and –0.167(2) Å, respectively. The tetrahydropyridine ring in molecule **5b** adopts a C-envelop conformation, in which the C(10b)N(1)C(2)C(3)C(4) fragment is planar within 0.110(2) Å and the C(4a) atom deviates from this plane by 0.551(2) Å, whereas the tetrahydropyridine ring in molecules **5a,c,d** has a half-chair conformation.

In the crystal structure of compound **5b**, the molecules are linked to each other by classical hydrogen bonds to form a 1D structure, similar to those observed in the crystals of compounds **5a,c,d** (the hydrogen bond parameters are given in Table 2). Thus, the dimers of the molecules formed through the O(5)—H(5)...O(15) hydrogen bond are linked to each other by the N(1)—H(1)...O(4) hydrogen bonds to form chains running along the 0*a* axis of the crystal (Fig. 5). In the crystal structure of compound **5b**, a layered structure is formed through C—H...O and C—H...Cl interactions. The layers are parallel to the *a*0*b* plane of the crystal.

The X-ray diffraction study of compounds **5a—d** showed that all these compounds are tricyclic isomers.

Therefore, the three-component condensation of salicylaldehydes containing electron-donating substituents affords a tricyclic system. It should be noted that the formation of the pyran ring occurs strictly diastereoselective. Thus, the diastereomers (10b*R*,4a*S*,5*S*)-**5a** and

Table 1. Selected geometric parameters (bond lengths (*d*), bond angles (ω), and torsion angles (τ)) in molecule **5b**

Parameter	Value	Parameter	Value	Parameter	Value
Bond	*d*/Å	Angle	ω/deg	Angle	ω/deg
N(1)—C(2)	1.338(3)	C(3)—C(4)—C(4a)	116.0(2)	C(6a)—C(7)—Cl(1)	119.1(2)
C(2)—C(3)	1.361(3)	C(5)—O(6)—C(6a)	117.4(2)	C(8)—C(7)—Cl(1)	119.8(2)
C(3)—C(4)	1.431(3)	O(6)—C(5)—C(4a)	111.1(2)	C(8)—C(9)—Cl(2)	119.3(2)
C(4)—C(4a)	1.520(3)	C(2)—N(1)—C(10b)	119.7(2)	C(10)—C(9)—Cl(2)	119.5(2)
C(4a)—C(10b)	1.527(2)	O(6)—C(6a)—C(7)	116.3(2)	Angle	τ/deg
C(10b)—N(1)	1.452(2)	N(1)—C(2)—C(3)	123.6(2)		
C(4a)—C(5)	1.522(2)	O(6)—C(6a)—C(10a)	124.2(2)	C(2)—C(11)—O(12)—C(13)	179.5(2)
C(5)—O(6)	1.422(2)	C(2)—C(3)—C(4)	119.9(2)	C(11)—O(12)—C(13)—C(14)	173.9(2)
O(6)—C(6a)	1.369(3)	C(4)—C(4a)—C(10b)	110.9(2)	O(11)—C(11)—O(12)—C(13)	–1.7(3)
C(6a)—C(10a)	1.392(3)	C(5)—C(4a)—C(10b)	109.2(2)	C(3)—C(2)—C(11)—O(12)	–8.8(3)
C(10a)—C(10b)	1.519(3)	O(4)—C(4)—C(3)	124.2(2)	N(1)—C(2)—C(11)—O(11)	–6.9(3)
C(4)—O(4)	1.230(2)	O(4)—C(4)—C(4a)	119.7(2)	C(5)—C(15)—O(16)—C(17)	179.9(2)
C(5)—O(5)	1.388(3)	C(6a)—C(10a)—C(10b)	119.6(2)	C(15)—O(16)—C(17)—C(18)	176.7(2)
C(7)—Cl(1)	1.727(2)	N(1)—C(10b)—C(4a)	109.1(2)	O(15)—C(15)—O(16)—C(17)	4.3(3)
C(9)—Cl(2)	1.743(3)	C(4a)—C(10b)—C(10a)	108.2(2)	O(5)—C(5)—C(15)—O(15)	101.8(2)

Table 2. D—H...A hydrogen bond parameters (D is a donor and A is an acceptor) in the crystals of compounds **5b** and **9b**

Bond	D—H	H...A	D...A	DHA /deg	Symmetry code
		Å			
			5b		
N(1)—H(1)...O(4)	0.86	2.00	2.772(2)	149	$1+x, y, z$
O(5)—H(5)...O(15)	0.82	2.08	2.850(2)	158	$1-x, 1-y, -z$
C(4a)—H(4a)...Cl(1)	0.98	2.80	3.742(2)	161	$x, 1+y, z$
C(10b)—H(10b)...O(15)	0.98	2.49	3.446(3)	165	$1+x, y, z$
N(1)—H(1)...O(11)	0.86	2.39	2.700(3)	102	—
			9b		
N(1A)—H(1A)...O(7B)	0.86	2.25	2.98(1)	144	$x, y, -1+z$
N(1B)—H(1B)...O(7A)	0.86	2.37	3.13(1)	147	$x, y, 1+z$
O(15A)—H(15A)...O(10A)′	0.82	2.39	2.79(1)	111	$1+x, y, z$
O(15B)—H(15B)...O(11B)′	0.82	2.39	3.05(1)	138	$-1+x, y, z$
O(15A)—H(15A)...N(16A)	0.82	2.53	2.95(2)	113	—
O(15A)—H(15A)...O(17A)	0.82	1.94	2.61(1)	140	—
N(1A)—H(1A)...O(7A)	0.86	2.31	2.66(2)	104	—
N(1A)—H(1A)...O(15A)	0.86	2.48	2.81(1)	104	—
N(1B)—H(1B)...O(7B)	0.86	2.31	2.65(1)	104	—
N(1B)—H(1B)...O(15B)	0.86	2.50	2.81(1)	103	—
O(10A)—H(10A)...O(4A)	0.82	1.70	2.44(2)	150	—
O(10B)—H(10B)...O(4B)	0.82	1.69	2.44(1)	151	—
O(15B)—H(15B)...O(16B)	0.82	1.96	2.64(1)	140	—
O(15B)—H(15B)...N(16B)	0.82	2.52	2.95(1)	113	—
C(6A)—H(6A)...O(11A)	0.98	2.25	2.75(2)	110	—
C(6B)—H(6B)...O(12B)	0.98	2.22	2.85(2)	121	—

(10b*S*,4a*R*,5*R*)-**5a**, (10b*R*,4a*R*,5*S*)-**5b** and (10b*S*,4a*S*,5*R*)-**5b**, (10b*R*,4a*S*,5*S*)-**5c** and (10b*S*,4a*R*,5*R*)-**5c**, (10b*S*,4a*R*,5*R*)-**5d** and (10b*R*,4a*R*,5*S*)-**5d** were not detected in the crude reaction mixtures. In addition, (10b*R*,4a*S*,5*R*)-**5a** and (10b*S*,4a*R*,5*S*)-**5a**, (10b*R*,4a*S*,5*R*)-**5c** and (10b*S*,4a*R*,5*S*)-**5c** are formed predominantly as the *trans* isomers, whereas (10b*R*,4a*R*,5*R*)-**5b** and (10b*S*,4a*S*,5*S*)-**5b**, (10b*R*,4a*R*,5*R*)-**5d** and (10b*S*,4a*S*,5*S*)-**5d** are formed mainly as the *cis* isomers. This is evidently associated with the presence of the substituent (MeO or Cl) at position 5 of the starting aromatic aldehyde or at position 9 of the resulting tricyclic system.

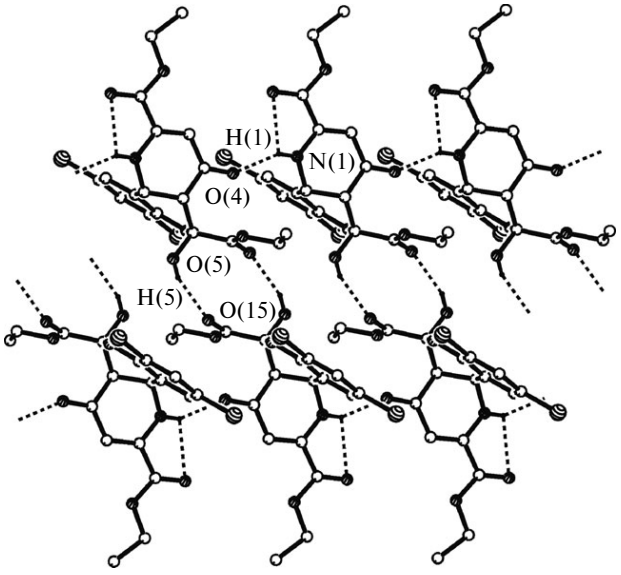
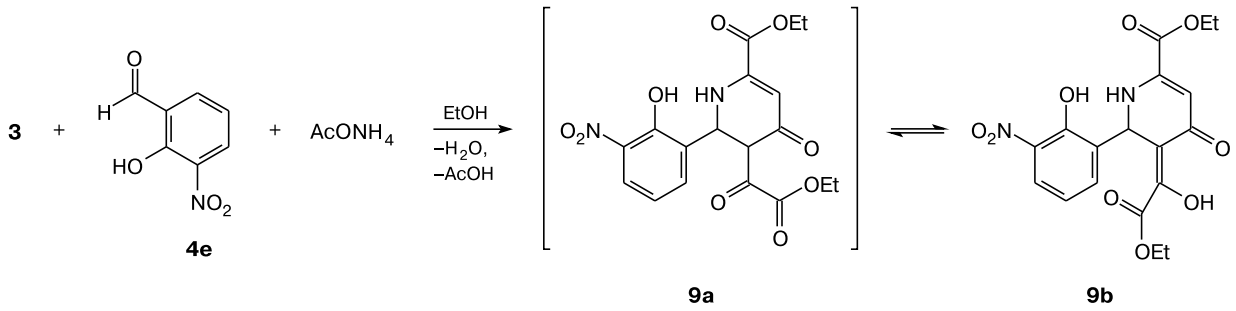


Fig. 5. Ribbons formed by the molecules *via* classical hydrogen bonds in the crystal structure of compound **5b**.

To elucidate the influence of the electron-withdrawing substituents in salicylaldehyde on the pathway of the reaction under study, we performed the reaction of diethoxalylacetone **3** with 3-nitrosalicylaldehyde (**4e**). In this case, the formation of the tricyclic benzo[*e*]pyrano[4,3-*b*]-pyridine structure is not observed. According to the TLC data, the reaction affords two products, which strongly differ in the R_f values. These products were separated by column chromatography and were finally purified by recrystallization. The IR spectrum of one product (orange-red crystals, R_f 0.62) has absorption bands of the NH group at 3290 cm^{-1} and of the OH group at 3360 cm^{-1}, as well as a broadened intense band at 1727 cm^{-1}, which is indicative of the presence of the ester group in this product. The ^1H NMR spectrum of the latter product, unlike the spectra of compounds **5a**—**d**, does not show diagnostic signals

Scheme 4



for the protons of the AB system at δ 3.20 and 5.00 corresponding to the benzo[*e*]pyrano[4,3-*b*]pyridine structure. The ^{1}H NMR spectrum has three doublets of doublets of the aromatic ring and doublets of triplets and quartets of two ethoxycarbonyl groups along with broadened singlets of the OH and NH groups and signals for the protons at the C(sp^2) and C(sp^3) atoms. The spectrum has doublets at δ 5.65 and 6.62 (J = 2.0 Hz and J = 3.6 Hz, respectively). The doublet at δ 5.65 belongs to the proton at the C(sp^3) atom. The small spin-spin coupling constant of the doublet compared to that observed for the doublet of the AB system in the same region is indicative of the absence of the proton H(4a), which is apparently associated with the enolization of the carbonyl group of the ethoxalyl substituent. The spectroscopic data are not contradictory to the structure 2-ethoxycarbonyl-5-(2-ethoxy-1-hydroxy-2-oxoethylidene)-6-(2′-hydroxy-3′-nitrophenyl)-1,4,5,6-tetrahydropyrid-4-one (**9b**) (Scheme 4).

Actually, according to the X-ray diffraction data, the reaction of diethoxalylacetone **3** with 3-nitrosalicylaldehyde (**4e**) produces pyridin-4-one derivative **9b**.

Compound **9b** (Fig. 6), unlike the above-described compounds, crystallizes as a monocyclic isomer (in the presence of the electron-withdrawing nitro group as the substituent in the phenyl group, the central pyran ring of the molecule is cleaved). The crystals of compound **9b** are noncentrosymmetric, and there are two independent molecules (A and B) per asymmetric unit. The chiral centers in the independent molecules adopt opposite configurations, *i.e.*, the crystal is a racemic mixture. The bond lengths and bond angles in the tetrahydropyridine heterocycle of molecules **9b**(A) and **9b**(B) are equal within experimental error (Table 3); however, the

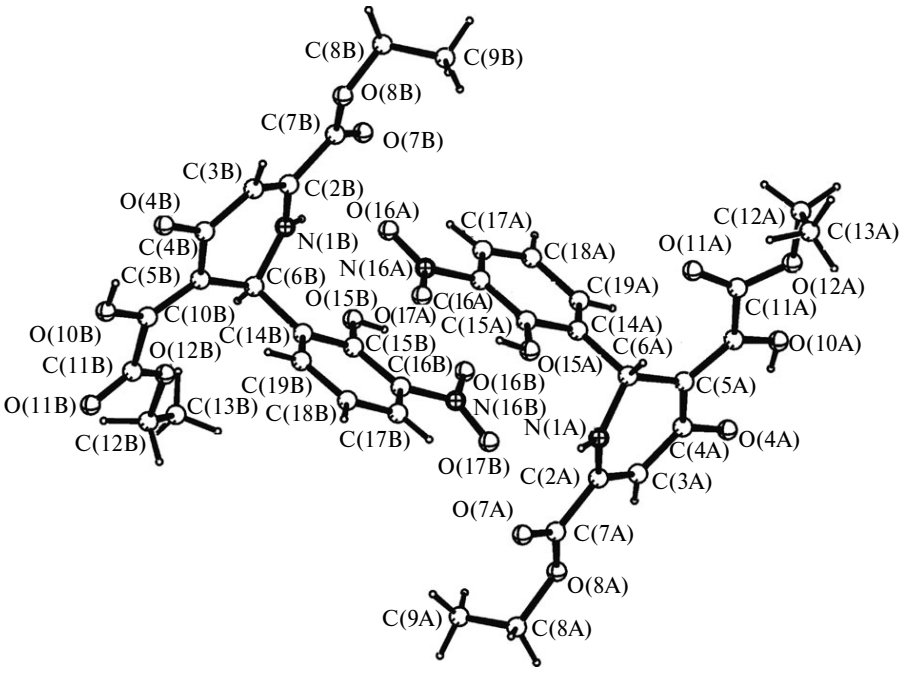


Fig. 6. Molecular structures of two independent molecules of compound **9b** in the crystal.

Table 3. Selected geometric parameters (bond lengths (*d*), bond angles (ω), and torsion angles (τ)) in the independent molecules of compound **9b**

Parameter	**9b**(A)	**9b**(B)	Parameter	**9b**(A)	**9b**(B)
Bond	*d*/Å		Bond	*d*/Å	
O(4)—C(4)	1.31(1)	1.30(1)	C(2)—C(7)	1.49(2)	1.50(2)
N(16)—C(16)	1.49(1)	1.45(2)	O(15)—C(15)	1.35(1)	1.36(1)
O(7)—C(7)	1.22(2)	1.20(2)	C(3)—C(4)	1.39(2)	1.40(2)
O(8)—C(7)	1.30(2)	1.30(2)	O(16)—N(16)	1.19(2)	1.21(2)
N(1)—C(6)	1.48(2)	1.46(2)	C(4)—C(5)	1.41(2)	1.43(2)
O(8)—C(8)	1.48(2)	1.42(2)	O(17)—N(16)	1.20(2)	1.18(2)
N(1)—C(2)	1.31(2)	1.32(2)	C(5)—C(6)	1.52(2)	1.51(1)
O(10)—C(10)	1.31(1)	1.28(1)	C(5)—C(10)	1.40(2)	1.39(1)
O(11)—C(11)	1.20(2)	1.19(2)	C(6)—C(14)	1.53(2)	1.54(1)
O(12)—C(11)	1.30(2)	1.26(2)	C(8)—C(9)	1.39(3)	1.40(3)
C(2)—C(3)	1.38(2)	1.39(2)	C(10)—C(11)	1.50(2)	1.51(2)
O(12)—C(12)	1.48(3)	1.43(3)	C(12)—C(13)	1.35(3)	1.31(3)
Angle	ω/deg		Angle	ω/deg	
C(7)—O(8)—C(8)	116(1)	117(1)	C(6)—C(5)—C(10)	122(1)	126(1)
C(11)—O(12)—C(12)	116(1)	116(1)	C(4)—C(5)—C(6)	120(1)	118(1)
N(1)—C(6)—C(14)	106.8(8)	108.2(8)	C(5)—C(6)—C(14)	114.2(8)	113.2(8)
N(1)—C(6)—C(5)	107.6(9)	110(1)	O(7)—C(7)—C(2)	121(1)	121(1)
O(8)—C(7)—C(2)	113(1)	113(1)	O(7)—C(7)—O(8)	126(1)	126(1)
C(2)—N(1)—C(6)	122.8(8)	122.0(9)	O(8)—C(8)—C(9)	109(2)	112(2)
O(16)—N(16)—C(16)	118(1)	118(1)	C(5)—C(10)—C(11)	122(1)	127(1)
O(16)—N(16)—O(17)	123(1)	120(1)	O(10)—C(10)—C(5)	121(1)	123(1)
O(17)—N(16)—C(16)	119(1)	121(1)	O(10)—C(10)—C(11)	117(1)	111(1)
O(11)—C(11)—O(12)	126(2)	124(2)	O(12)—C(11)—C(10)	111(1)	115(1)
O(11)—C(11)—C(10)	123(2)	120(1)	O(15)—C(15)—C(14)	116.0(9)	115.7(9)
O(12)—C(12)—C(13)	112(2)	113(2)	N(1)—C(2)—C(3)	123(1)	122(1)
C(3)—C(2)—C(7)	123(1)	125(1)	N(1)—C(2)—C(7)	114(1)	113.4(9)
O(15)—C(15)—C(16)	126.2(9)	124.3(9)	C(3)—C(4)—C(5)	121.2(9)	121(1)
C(2)—C(3)—C(4)	118(1)	118(1)	O(4)—C(4)—C(5)	121(1)	123(1)
O(4)—C(4)—C(3)	118(1)	117(1)	C(4)—C(5)—C(10)	119(1)	116.7(9)
Angle	τ/deg		Angle	τ/deg	
C(8)—O(8)—C(7)—O(7)	5(2)	−7(2)	C(12)—O(12)—C(11)—O(11)	−5(3)	0(3)
C(8)—O(8)—C(7)—C(2)	−178(1)	175(1)	C(12)—O(12)—C(11)—C(10)	−180(1)	175(2)
C(7)—O(8)—C(8)—C(9)	−94(2)	89(2)	C(11)—O(12)—C(12)—C(13)	−79(2)	−168(3)
C(6)—N(1)—C(2)—C(3)	−17(2)	13(1)	C(2)—N(1)—C(6)—C(5)	32(1)	−33(1)
N(1)—C(2)—C(3)—C(4)	−5(2)	13(2)	C(2)—C(3)—C(4)—C(5)	8(1)	−15(2)
C(3)—C(4)—C(5)—C(6)	11(1)	−8(1)	C(4)—C(5)—C(6)—N(1)	−28(1)	29(1)
O(10)—C(10)—C(11)—O(11)	−159(2)	7(2)	C(5)—C(10)—C(11)—O(11)	17(2)	−170(2)
C(5)—C(10)—C(11)—O(12)	−169(1)	14(2)	O(10)—C(10)—C(11)—O(12)	16(2)	−169(1)
O(17)—N(16)—C(16)—C(15)	1(2)	167(2)	O(17)—N(16)—C(16)—C(17)	−178(2)	−14(2)

ethoxycarbonyl fragments at the C(10) atom in these molecules are twisted differently. In molecule **9b**(A), the hydroxy and oxyethyl groups are in the eclipsed conformation, whereas the hydroxy and carbonyl groups are in the eclipsed conformation in molecule **9b**(B) (see Fig. 6 and Table 3).

In both molecules, the tetrahydropyridine ring adopts the C-envelop conformation (in molecule **9b**(A), the N(1)C(2)C(3)C(4)C(5) fragment is planar within 0.03(1) Å, and the C(6) atom deviates from the plane by 0.41(1) Å; in molecule **9b**(B), the N(1)C(2)C(3)C(4)C(5) fragment is planar within 0.07(1) Å, and the C(6) atom deviates from the plane by −0.43(1) Å).

It should be noted that the conformations of molecules **9b**(A) and **9b**(B) in the crystal are stabilized by intramolecular hydrogen bonds (see Table 2). In addition, the intermolecular hydrogen bonds stabilize the crystal structure. Thus, molecules **9b** form ribbons running along the 0*a* axis of the crystal (the hydrogen bond parameters are given in Table 2; the hydrogen bond network is shown in Fig. 7).

The mass-spectrometric study of the second product (**10**) (colorless crystals, R_f 0.45, *m*/*z* 306 $M]^+$) provide

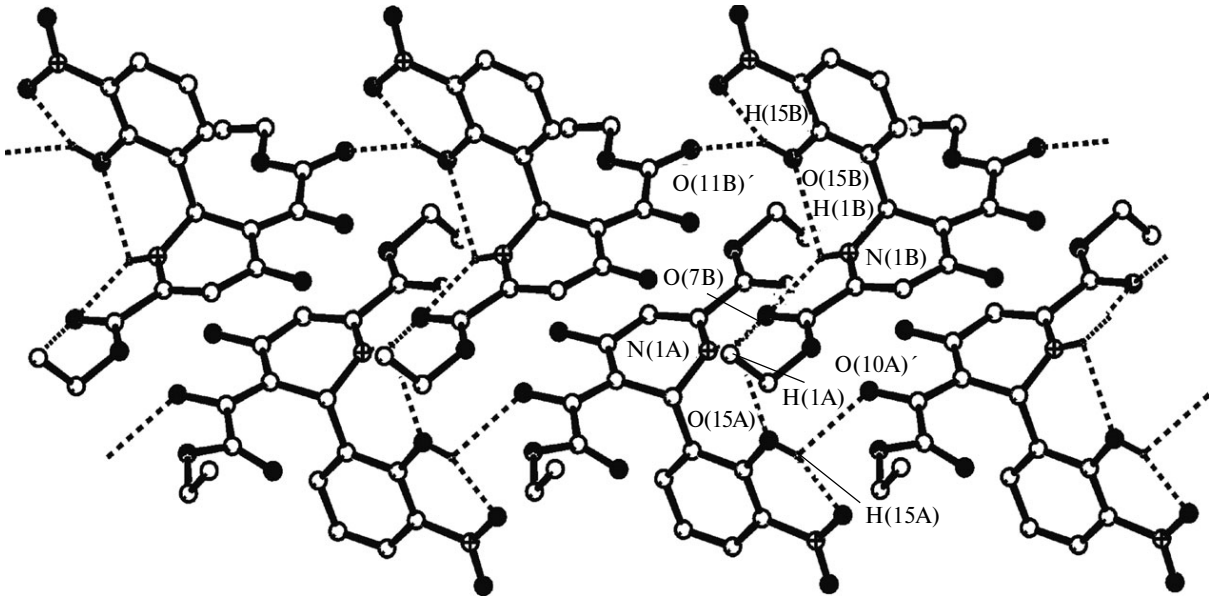
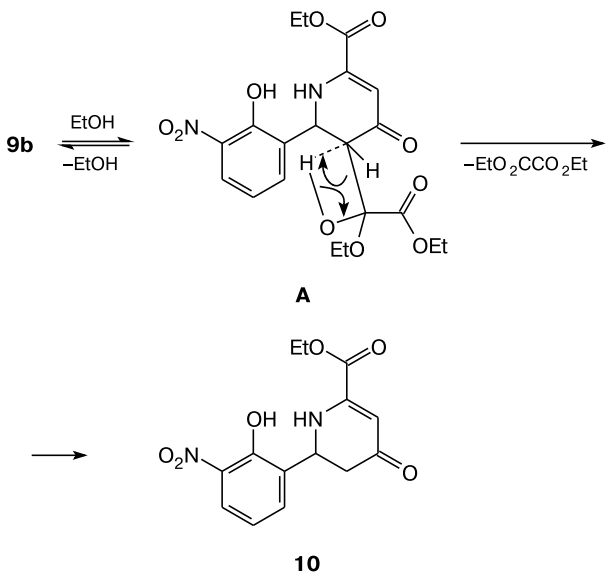


Fig. 7. Hydrogen bond network (indicated by dashed lines) in the crystal of **9b**.

evidence that this product is generated as a result of the elimination of the ethoxalyl group (—C(O)CO_2Et) from the initially formed product **9b** under the conditions of the reaction of diethoxalylacetone **3** with 3-nitrosalicylaldehyde (**4e**) in EtOH.

The ^{1}H NMR spectrum of this product has resonances of the pronounced ABX system, which is apparently indicative of the hydrodiethoxalylation that occurs according to the scheme of the retro-aldol condensation in the intermediate hemiketal **A** (Scheme 5) to form 2-ethoxycarbonyl-6-(2´-hydroxy-3´-nitrophenyl)-1,4,5,6-tetrahydropyrid-4-one **10**.

Scheme 5



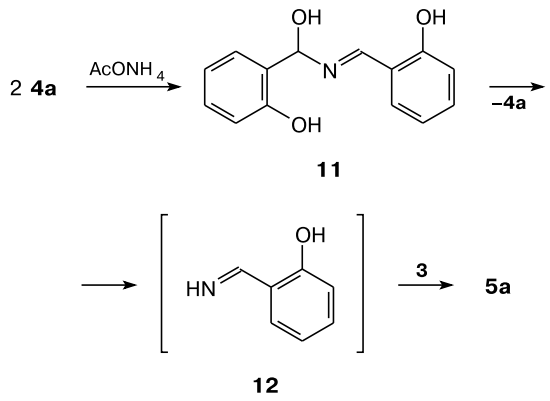
As can be seen from the above-given examples, salicylaldehyde and its substituted derivatives containing electron-donating substituents in the *ortho* or *para* positions with respect to the hydroxy group facilitate the pyran ring closure in the intermediate pyridin-4-one derivatives containing the *o*-hydroxyphenyl and ethoxalyl groups at positions 2 and 3, respectively, to form the tricyclic 1,4,4a,10b-tetrahydrobenzo[*e*]pyrano[4,3-*b*]pyridine system. By contrast, the reaction with 3-nitrosalicylaldehyde (**4e**) stops at the formation of the pyridin-4-one derivative. The intramolecular closure of the pyran ring does not occur due to the deactivation of the hydroxy group by the nitro group.

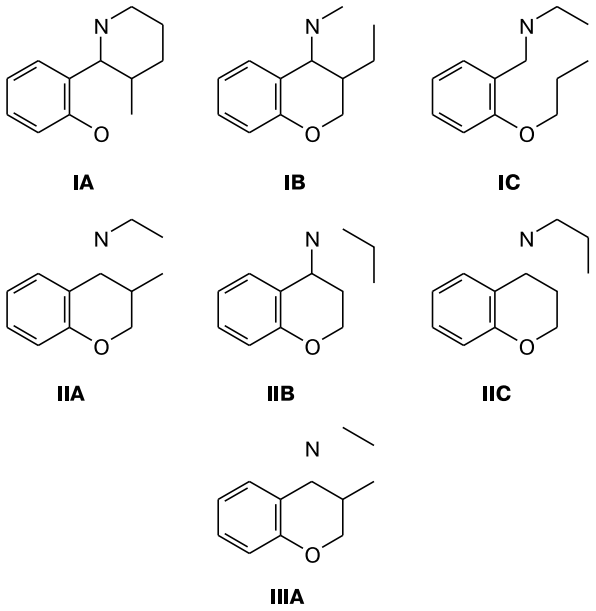
Since compound **5a** can be synthesized in two steps, involving the synthesis of benzylimine **11** (in the first step) and its reaction with diethoxalylacetone **3** (in the second step), the reaction in the three-component system occurs, apparently, through the intermediate formation of salicylaldimine **12** (Scheme 6).

Based on the results of the present study, which showed that the tricyclic benzo[*e*]pyrano[4,3-*b*]pyridine structure is formed in the reactions with salicylaldehyde and its 3,5-dichloro-, 3-methoxy-, and 5-methoxy derivatives, whereas pyridin-4-one derivatives are produced in the reaction with 3-nitrosalicylaldehyde, we suggest Scheme 7 for the reaction pathway.

Apparently, the reaction starts with the pyridinone ring closure involving the imine bond between the salicylaldimine moiety and one of the carbonyl groups followed by the closure of the tricyclic system with the participation of the OH group of salicylaldehyde and the electrophilic car-

Scheme 6



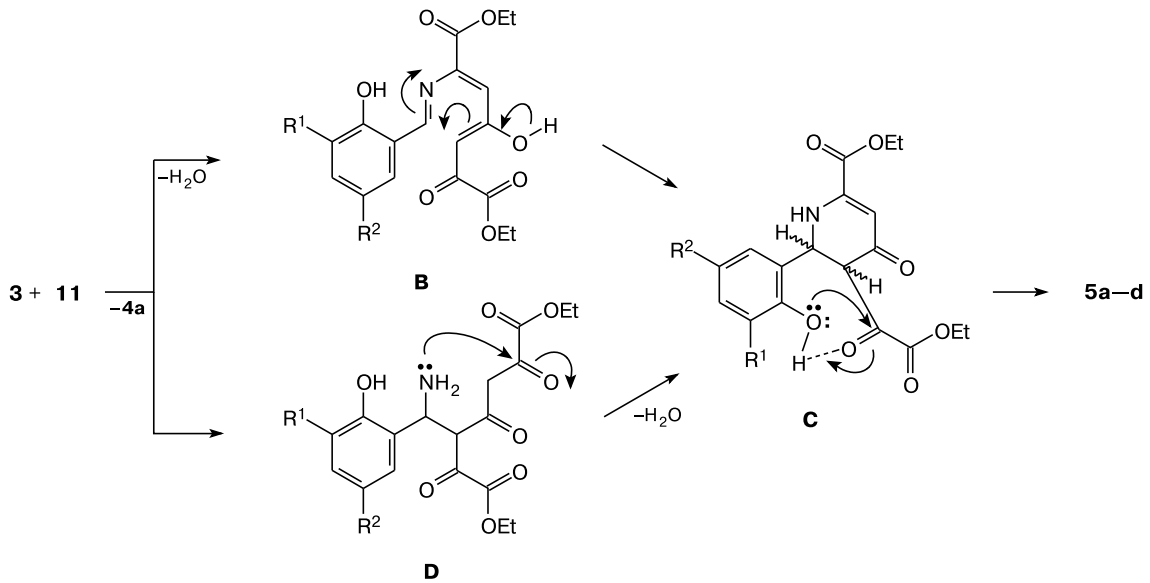


bon atom of the ethoxalyl moiety. It should be noted that the pyridinone ring can be closed not only through the initial formation of the N(1)—C(2) bond (intermediate **B**) but also through the formation of the C(4a)—C(10b) bond (intermediate **D**).

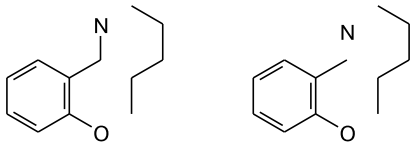
An analysis of the published data showed that there are different approaches to the synthesis of the benzo[*e*]pyrano[4,3-*b*]pyridine system depending on which bond in the compound is involved in the ring closure or which method for supplying necessary units is more accessible. These approaches were exemplified with the fragments of the structures **IA**,[23,28] **IB**,[15] **IC**,[8–14,16–18] **IIA**,[3–5,8–14,16–18,29] **IIB**,[7] **IIC**,[6,30,31] and **IIIA**.[20]

Hence, we showed for the first time that diethyl 2,4,6-trioxoheptanedicarboxylate can be used as the synthetic equivalent of the five-atom synthon for the synthesis of fused polycyclic systems. It was found that the reaction pathway and the structures of the reaction products that are formed in the three-component diethoxalylacetone—salicylaldehyde—ammonium acetate system are determined by the nature of the substituents in salicylaldehyde. The reactions with unsubstituted salicylaldehyde and 3,5-dichloro-, 3-methoxy-, and 5-methoxysalicylaldehydes produce diastereomeric mixtures of benzopyranopyridines in different ratios. In the case of 3-nitrosalicylaldehyde, various functionalized pyridines are formed depending on the reaction conditions. New methods were developed for the synthesis of the benzo[*e*]pyrano[4,3-*b*]-

Scheme 7



pyridine system, which can be classified as **IID** and **IIIB** according to the retrosynthetic analysis.



IID **IIIB**

Experimental

The ^{1}H NMR spectra were recorded on a Bruker Avance-600 spectrometer operating at 600.13 MHz in $CDCl_3$ for compounds **3**, **5a**, and **9b**, in DMSO-d_6 for compound **5b**, and in acetone-d_6 for compounds **5c,d**, **10**, and **11**. The ^{13}C NMR spectra were measured on a Bruker WM-400 spectrometer (100.6 MHz) at 35 °C. The chemical shifts are given on the δ scale with respect to the residual signals of the corresponding solvents as the internal standard (δ_H 7.26 for $CDCl_3$, δ_H 2.54 for DMSO, and δ_H 2.09 for $(CD_3)_2CO$). The IR spectra were measured on a Bruker Vector-22 spectrometer in KBr pellets in the frequency range of 400—3600 cm^{-1}. The course of the reactions was monitored and the purity of the reaction products was checked by TLC (Silufol UV-254; diethyl ether—petroleum ether—methanol, 2 : 1 : 0.1, as the eluent). The column chromatography was carried out on silica gel L100/160. The melting points were determined on a Boetius hot-stage apparatus.

Diethyl 2,4,6-trioxoheptanedicarboxylate (3) was synthesized according to a known procedure.[32] M.p. 98—101 °C. After the recrystallization from 80% ethanol, m.p. 100—101 °C (*cf.* lit. data[32]: m.p. 102—103 °C). The IR spectrum of the crystalline sample, ν/cm^{-1}: 1730, 1650, 1640 (C=O), 3440 (OH). According to the ^{1}H NMR spectra in acetone-d_6 and $CDCl_3$, compound **3** exists predominantly as dienol. ^{1}H NMR ($CDCl_3$), δ: 1.39 (t, 6 H, CH_3, J = 7.1 Hz); 4.37 (q, 4 H, CH_2, J = 7.1 Hz); 6.32 (s, 2 H, CH); 13.25 (s, 2 H, OH).

2,5-Diethoxycarbonyl-5-hydroxy-4-oxo-1,4,4a,10b-tetrahydrobenzo[*e*]pyrano[4,3-*b*]pyridine (5a) was synthesized according to a procedure described previously.[4]

2-(Hydroxy-{[2-(hydroxyphenyl)methylene]amino}methyl)-phenol (11). A solution of salicylaldehyde (0.49 g, 4 mmol) in EtOH (5 mL) was added to a solution of ammonium acetate (0.184 g, 2.4 mmol) in EtOH (20 mL). The reaction mixture was stirred for 6 h and then concentrated under reduced pressure to 1/5 of the initial volume. The pale-yellow precipitate was separated and washed with EtOH (2×10 mL). The yield was 0.36 g (73%), m.p. 257—259 °C. Found (%): C, 69.02; H, 5.41; N, 5.63. $C_{14}H_{13}NO_3$. Calculated (%): C, 69.15; H, 5.35; N, 5.76. IR, ν/cm^{-1}: 754, 797, 903, 992, 1019, 1043, 1150, 1239, 1275, 1392, 1492, 1592, 1628, 3048, 3253 (br). ^{1}H NMR (acetone-d_6), δ: 6.49 (s, 1 H, C<u>H</u>OH); 6.76—7.50 (m, 10 H, 2 C_6H_4 + 2 OH); 8.84 (s, 1 H, C<u>H</u>=N); 13.19 (br.s, 1 H, OH).

Synthesis of tetrahydrobenzo[*e*]pyrano[4,3-*b*]pyridine 5a with the use of compound 11. A solution of diethoxalylacetone (0.26 g, 1 mmol) in EtOH (10 mL) was added to a solution of imine **11** (0.24 g, 1 mmol) in EtOH (20 mL). The reaction mixture was refluxed for 3 h. Then the most part of the solvent was distilled off *in vacuo*, and white crystals were filtered off, washed with cold ethanol (2×15 mL), dried in air, and recrystallized from Pr^{i}OH. The yield of compound **5a** was 0.15 g (42%), m.p. 178—179 °C. The melting point, the R_f value, and the spectroscopic characteristics of compound **5a** are identical to those of the compound described above.

7,9-Dichloro-2,5-diethoxycarbonyl-5-hydroxy-4-oxo-1,4,4a,10b-tetrahydrobenzo[*e*]pyrano[4,3-*b*]pyridine (5b). A solution of 3,5-dichlorosalicylaldehyde (**4b**) (0.38 g, 2 mmol) in EtOH (10 mL) was added with stirring to a solution of ammonium acetate (0.2 g, 3.3 mmol) in EtOH (5 mL). The reaction mixture was stirred for 10 min, and then a solution of diethoxalylacetone **3** (0.53 g, 2 mmol) in EtOH (10 mL) was added dropwise. The reaction mixture was stirred at 45—50 °C for 12 h. The solvent was removed *in vacuo*. The pale-yellow crystals that formed were filtered off, washed with cold EtOH (2×15 mL), dried in air, and recrystallized from EtOH. The yield of compound **5b** was 0.28 g (34%), m.p. 162—164 °C. Found (%): C, 59.20; H, 3.91; Cl, 16.57; N, 3.28. $C_{18}H_{17}Cl_2NO_7$. Calculated (%): C, 50.23; H, 3.95; Cl, 16.51; N, 3.25. IR, ν/cm^{-1}: 745, 776, 792, 823, 837, 865, 888, 909, 977, 1016, 1035, 1055, 1090, 1113, 1135, 1189, 1213, 1252, 1280, 1325, 1341, 1524, 1584, 1636, 1731, 1743, 3236, 3423. The ratio of the major to the minor products was 5 : 1. The ^{1}H NMR spectrum of the major isomer in the crude product (DMSO-d_6), δ: 1.26 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.1 Hz); 1.28 (t, 3 H, $OCH_2C\underline{H}_3$, J = 6.7 Hz); 3.58 (d, 1 H, H(4a), J = 7.4 Hz); 4.22 (q, 2 H, $OC\underline{H}_2CH_3$, J = 7.1 Hz); 4.26—4.33 (m, 2 H, $OC\underline{H}_2CH_3$); 5.02 (d, 1 H, H(10b), J = 7.4 Hz); 5.23 (s, 1 H, H(3)); 7.41 (d, 1 H, H(10) or H(8), J = 2.8 Hz); 7.50 (d, 1 H, H(8) or H(10), J = 2.8 Hz); 8.37 (br.s, 1 H, NH or OH); 8.83 (br.s, 1 H, NH or OH). ^{1}H NMR spectrum of the minor isomer in the crude product (DMSO-d_6), δ: 1.22 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.0 Hz); 1.27 (t, 3 H, $OCH_2C\underline{H}_3$, J = 6.7 Hz); 3.12 (d, 1 H, H(4a), J = 15.8 Hz); 4.17 (q, 2 H, $OC\underline{H}_2CH_3$, J = 7.0 Hz); 4.26—4.33 (m, 2 H, $OC\underline{H}_2CH_3$); 4.86 (d, 1 H, H(10b), J = 15.8 Hz); 5.56 (s, 1 H, H(3)); 7.40 (d, 1 H, H(10) or H(8), J = 2.8 Hz); 7.41 (d, 1 H, H(8) or H(10), J = 2.8 Hz); 7.58 (br.s, 1 H, NH or OH); 8.00 (br.s, 1 H, NH or OH).

The pure major diastereomer was isolated from the diastereomeric mixture, which was obtained with the use of 3,5-dichlorosalicylaldehyde, by the recrystallization from EtOH carried out three times. The ^{1}H NMR spectrum of the major product (DMSO-d_6), δ: 1.27 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.1 Hz); 1.29 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.1 Hz); 3.60 (d, 1 H, H(4a), J = 7.3 Hz); 4.23 (q, 2 H, $OC\underline{H}_2CH_3$, J = 7.1 Hz); 4.30 and 4.32 (m, 2 H, AB part of the ABX_3 system, $OC\underline{H}_A\underline{H}_BCH_{3,X}$, $^2J_{AB}$ = 10.9 Hz, $^3J_{AX}$ = $= {}^3J_{BX}$ = 7.1 Hz); 5.02 (dd, 1 H, H(10b), J = 7.3 Hz, J = 4.9 Hz); 5.24 (d, 1 H, H(3), J = 1.6 Hz); 7.44 (d, 1 H, H(10) or H(8), J = 2.4 Hz); 7.55 (d, 1 H, H(8) or H(10), J = 2.4 Hz); 8.48 (br.s, 1 H, OH); 8.93 (dd, 1 H, NH, J = 4.9 Hz, J = 1.6 Hz). The ^{13}C{^{1}H} NMR spectrum of the major product (DMSO-d_6), δ: 13.47 (qt, $\underline{C}H_3CH_2O$, J = 127.4 Hz, J = 2.4 Hz); 13.49 (qt, $\underline{C}H_3CH_2O$, J = 127.4 Hz, J = 2.4 Hz); 45.79 (dd, C(4a) or C(10b), J = 134.0 Hz, J = 3.6 Hz); 45.97 (d, C(10b) or C(4a), J = 150.79 Hz); 60.66 (tq, $CH_3\underline{C}H_2O$, J = 147.2 Hz, J = 4.2 Hz); 62.15 (tq, $CH_3\underline{C}H_2O$, J = 149.6 Hz, J = 4.2 Hz); 94.12 (d, C(5), J = 4.8 Hz); 98.33 (dd, C(3), J = 170.6 Hz, J = 4.2 Hz); 121.72 (d, C(7), J = 3.6 Hz); 124.02 (dd, C(9), J = 8.1 Hz, J = 5.1 Hz); 124.45 (dd, C(10), J = 167.0 Hz, J = 5.4 Hz); 124.77 (dd, C(10a), J = 4.2 Hz, J = 3.6 Hz); 128.92 (dd, C(8), J = 171.8 Hz, J = 6.0 Hz); 146.93 (d, C(2), J = 6.6 Hz); 147.45 (d, C(6a), J = 7.2 Hz); 162.00 (t, C(O)O, J = 3.0 Hz); 166.60 (t, C(O)O, J = 3.0 Hz);

187.39 (dd, C=O, J = 5.4 Hz, J = 6.6 Hz). The $^{13}C\{^1H\}$ NMR spectrum of the minor product (DMSO-d_6), δ: 13.40 ($\underline{C}H_3CH_2O$); 13.41 ($\underline{C}H_3CH_2O$); 47.47 (C(4a) or C(10b)); 48.70 (d, C(10b) or C(4a)); 61.42 ($CH_3\underline{C}H_2O$); 62.15 ($CH_3\underline{C}H_2O$); 95.00 (C(5)); 102.0 (C(3)); 122.31 (C(7)); 123.06 (dd, C(9)); 125.64 (C(10)); 128.02 (C(10a)); 133.58 (C(8)); 147.42 (C(2)); 148.40 (C(6a)); 162.08 (C(O)O); 166.99 (C(O)O); 190.07 (C=O).

2,5-Diethoxycarbonyl-5-hydroxy-7-methoxy-4-oxo-1,4,4a,10b-tetrahydrobenzo[*e*]pyrano[4,3-*b*]pyridine (5c). A solution of 3-methoxysalicylaldehyde (**4c**) (0.3 g, 2 mmol) in EtOH (5 mL) was added with stirring to a solution of ammonium acetate (0.092 g, 1.2 mmol) in EtOH (10 mL). The reaction mixture was stirred for 10 min. Then a solution of diethoxalylacetone **3** (0.26 g, 1 mmol) in EtOH (10 mL) was added dropwise, and the reaction mixture was stirred at 50—55 °C for 70 h. The solvent was removed *in vacuo* using a water jet-pump. The resulting viscous brown residue was separated on a chromatographic column (diethyl ether—propan-2-ol, 20 : 1 → 5 : 1, as the eluent). Pale-yellow crystals were recrystallized from toluene. Compound **5c** was obtained in a yield of 0.09 g (23%), m.p. 128—129 °C. Found (%): C, 68.81; H, 6.38; N, 4.21. $C_{19}H_{21}NO_8$. Calculated (%): C, 68.88; H, 6.34; N, 4.23. IR, ν/cm^{-1}: 748, 781, 829, 847, 899, 927, 973, 1037, 1083, 1129, 1215, 1266, 1325, 1369, 1394, 1422, 1452, 1466, 1495, 1518, 1586, 1633, 1741, 2836, 2872, 2936, 2980, 3320, 3434. The ratio of the diastereomers was ~1 : 2, with the *trans* isomer predominating. The ^1H NMR spectrum of the minor product (acetone-d_6), δ: 1.29 (t, 3 H, $OCH_2C\underline{H}_3$, J = 6.7 Hz); 1.31 (t, 3 H, $OCH_2C\underline{H}_3$, J = 6.7 Hz); 3.67 (d, 1 H, H(4a), J = 6.5 Hz); 3.85 (s, 3 H, OCH_3); 4.30—4.40 (m, 4 H, 2 $OC\underline{H}_2CH_3$); 5.25 (d, 1 H, H(10b), J = 6.5 Hz); 5.36 (s, 1 H, H(3)); 6.66 (d, 1 H, H(8) or H(10), J = 8.0 Hz); 6,78 (dd, 1 H, H(9), J = 8.0 Hz, J = 8.0 Hz); 7.24 (d, 1 H, H(10) or H(8), J = 8.0 Hz). ^1H NMR of the major product (acetone-d_6), δ: 1.22 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.0 Hz); 1.27 (t, 3 H, $OCH_2C\underline{H}_3$, J = 6.7 Hz); 3.12 (d, 1 H, H(4a), J = 15.8 Hz); 3.77 (s, 3 H, OCH_3); 4.17 (q, 2 H, $OC\underline{H}_2CH_3$, J = 7.0 Hz); 4.30—4.40 (m, 2 H, $OC\underline{H}_2CH_3$); 4.86 (d, 1 H, H(10b), J = 15.8 Hz); 5.56 (s, 1 H, H(3)); 6.86 (d, 1 H, H(8) or H(10), J = 7.0 Hz); 6.92 (d, 1 H, H(10) or H(8), J = 7.3 Hz); 6.93 (dd, 1 H, H(9), J = 7.3 Hz, J = 7.0 Hz); 7.58, 8.00, 8.37, 8.83 (br.s, NH + OH of the major and minor products; it is impossible to unambiguously assign the signals in this region).

2,5-Diethoxycarbonyl-5-hydroxy-9-methoxy-4-oxo-1,4,4a,10b-tetrahydrobenzo[*e*]pyrano[4,3-*b*]pyridine (5d). A solution of 5-methoxysalicylaldehyde (**4d**) (0.3 g, 2 mmol) in EtOH (5 mL) was added with stirring to a solution of ammonium acetate (0.092 g, 1.2 mmol) in EtOH (10 mL). The reaction mixture was stirred for 10 min. Then a solution of diethoxalylacetone **3** (0.26 g, 1 mmol) in EtOH (10 mL) was added dropwise, and the mixture was stirred at 50—55 °C for 20 h. The solvent was removed *in vacuo*, and the viscous red residue was separated on a chromatographic column (diethyl ether—propan-2-ol, 20 : 1 → 5 : 1, as the eluent). Pale-yellow crystals were recrystallized from toluene. Compound **5d** was obtained in a yield of 0.14 g (36%), m.p. 137—140 °C. Found (%): C, 68.81; H, 6.38; N, 4.21. $C_{19}H_{21}NO_8$. Calculated (%): C, 68.88; H, 6.34; N, 4.23. IR, ν/cm^{-1} (KBr pellet): 748, 781, 829, 847, 899, 927, 973, 1037, 1083, 1129, 1215, 1266, 1325, 1369, 1394, 1422, 1452, 1466, 1495, 1518, 1586, 1633, 1741, 2836, 2872, 2936, 2980, 3320, 3434. The ratio of the diastereomers was ~2 : 1, with the *cis* isomer predominating. The ^1H NMR spectrum of the mixture of the reaction products (acetone-d_6), δ: 1.27 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.1 Hz); 1.28 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.1 Hz); 1.32 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.2 Hz); 1.35 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.3 Hz); 3.18 (d, 1 H, H(4a), J = 16.1 Hz); 3.66 (d, 1 H, H(4a), J = 6.6 Hz); 3.71 (s, 3 H, CH_3O); 3.81 (s, 3 H, CH_3O); 4.22—4.33 (m, 8 H, 4 $OC\underline{H}_2CH_3$); 4.95 (d, 1 H, H(10b), J = 16.1 Hz); 5.22 (d, 1 H, H(10b), J = 6.6 Hz); 5.60 (s, 1 H, H(3)); 5.40 (s, 1 H, H(3)); 6.81 (d, 1 H, H(7), J = 8.9 Hz); 6.88 (dd, 1 H, H(8), J = 8.9 Hz, J = 2.8 Hz); 7.29 (d, 1 H, H(10), J = 2.8 Hz); 6.83 (d, 1 H, H(7), J = 6.6 Hz); 7.01 (dd, 1 H, H(8), J = 6.6 Hz, J = 2.6 Hz); 7.27 (d, 1 H, H(10), J = 2.6 Hz); 6.12, 6.44, 6.69, 8.37 (br.s, NH + OH of the *cis* and *trans* products; it is impossible to unambiguously assign the signals in this region).

Three-component condensation of diethyl 2,4,6-trioxoheptanedicarboxylate (3) with 3-nitrosalicylaldehyde (4e) in the presence of ammonium acetate. A solution of 3-nitrosalicylaldehyde (**4e**) (0.7 g, 4 mmol) in EtOH (5 mL) was added with stirring to a solution of ammonium acetate (0.185 g, 2.4 mmol) in EtOH (10 mL). The reaction mixture was stirred for 10 min. Then a solution of diethoxalylacetone **3** (0.52 g, 2 mmol) in EtOH (10 mL) was added dropwise, and the mixture was stirred at 50—55 °C for 10 h. The solvent was removed *in vacuo*, and the viscous brown residue, which consisted mainly of two compounds (TLC data; Silufol UV-254, diethyl ether—petroleum ether—methanol, 2 : 1 : 0.1, as the eluent) with R_f 0.62 and R_f 0.45, was separated by column chromatography on silica gel (diethyl ether—propan-2-ol, 15 : 1, as the eluent). 2-Ethoxycarbonyl-5-(2-ethoxy-1-hydroxy-2-oxoethylidene)-6-(2′-hydroxy-3′-nitrophenyl)-1,4,5,6-tetrahydropyrid-4-one (**9b**) was obtained as orange-red crystals in a yield of 0.09 g (22%), and 2-ethoxycarbonyl-6-(2′-hydroxy-3′-nitrophenyl)-1,4,5,6-tetrahydropyrid-4-one (**10**) was obtained as colorless crystals in a yield of 0.19 g (63%) .

Compound 9b. M.p. 117—119 °C. Found (%): C, 53.05; H, 4.32; N, 6.75. $C_{18}H_{18}N_2O_9$. Calculated (%): C, 53.21; H, 4.46; N, 6.89. IR, ν/cm^{-1}: 523, 597, 663, 743, 755, 815, 854, 862, 912, 1015, 1050, 1092, 1119, 1207, 1259, 1298, 1337, 1535, 1588, 1611, 1727, 2726, 3290, 3364. ^1H NMR ($CDCl_3$), δ: 1.25 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.4 Hz); 1.32 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.4 Hz); 4.15—4.24 (m, 2 H, $OC\underline{H}_2CH_3$); 4.25—4.32 (m, 2 H, $OC\underline{H}_2CH_3$); 5.77 (s, 1 H, H(3)); 6.69 (br.s, 1 H, H(6)); 6.85 (br.s, 1 H, NH); 6.96 (dd, 1 H, H(5′), J = 8.4 Hz, J = 7.3 Hz); 7.26 (br.s, 1 H, HOC(2′)); 7.41 (d, 1 H, H(4′) or H(6′), J = 7.3 Hz); 8.06 (d, 1 H, H(6′) or H(4′), J = 8.4 Hz); 11.28 (br.s, 1 H, HOC(5′)). ^1H NMR (acetone-d_6), δ: 1.25 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.0 Hz); 1.29 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.0 Hz); 4.18 (q, 2 H, $OC\underline{H}_2CH_3$, J = 7.0 Hz); 4.29 (q, 2 H, $OC\underline{H}_2CH_3$, J = 7.0 Hz); 5.65 (d, 1 H, H(6), J = 2.0 Hz); 6.62 (d, 1 H, H(3), J = 3.6 Hz); 7.10 (dd, 1 H, H(5′), J = 8.6 Hz, J = 7.6 Hz); 7.50 (br.s, 1 H, NH); 7.54 (dd, 1 H, H(4′), J = 7.6 Hz, J = 1.3 Hz); 8.10 (dd, 1 H, H(6′), J = 8.6 Hz, J = 1.3 Hz); 11.11 (br.s, 1 H, OH).

Compound 10. M.p. 173—175 °C. Found (%): C, 54.77; H, 4.50; N, 9.22. $C_{14}H_{14}N_2O_6$. Calculated (%): C, 54.90; H, 4.61; N, 9.15. IR, ν/cm^{-1}: 420, 551, 742, 781, 859, 968, 1012, 1068, 1097, 1145, 1196, 1246, 1297, 1357, 1376, 1515, 1535, 1586, 1625, 1733, 3110, 3285. ^1H NMR (acetone-d_6), δ: 1.33 (t, 3 H, $OCH_2C\underline{H}_3$, J = 6.9 Hz); 4.35 (q, 2 H, $OC\underline{H}_2CH_3$, J = 6.9 Hz); protons of $C(5)H_2$ resonate as an AB part of an ABX system; 2.73 ($H(5)_A$, J_{AB} = 16.1 Hz, J_{AX} = 5.6 Hz); 2.90 ($H(5)_B$, J_{AB} = 16.1 Hz, J_{BX} = 9.9 Hz); 5.31 ($H(6)_X$, J_{AX} = 5.6 Hz, J_{BX} = = 9.9 Hz); 5.61 (s, 1 H, H(3)); 7.05 (dd, 1 H,

H(5′), J = 7.7 Hz, J = 7.0 Hz); 7.47 (br.s, 1 H, NH); 7.69 (d, 1 H, H(6′), J = 7.0 Hz); 8.13 (d, 1 H, H(4′), J = 7.7 Hz); 11.28 (br.s, 1 H, OH).

X-ray diffraction study. The results of the X-ray diffraction study of compounds **5a,c,d** have been reported previously.[27] The crystallographic characteristics and the X-ray data collection and refinement statistics for compounds **5b** and **9b** are given in Table 4. The X-ray diffraction data sets for compounds **5b** and **9b** were collected on an automated four-circle Enraf-Nonius CAD-4 diffractometer (graphite monochromator, Cu-Kα radiation, λ = 1.54184 Å, 293 K, ω-scanning technique). The intensities of three check reflections showed no decrease in the course of X-ray data collection. The unit cell parameters were determined, the intensities of reflections were measured, and the X-ray diffraction data were processed with the use of the MolEN program[33] on a DEC AlphaStation 200. All structures were solved by direct methods with the use of the SIR program[34] and refined first isotropically and then anisotropically using the SHELXL-97[35] and WinGX[36] program packages. The hydrogen atoms of molecules **5b** and **9b** were positioned geometrically and refined using a riding model. All figures were drawn and the intermolecular interactions were analyzed with the use of the PLATON program.[37] The atomic coordinates and structural parameters for compounds **5b** and **9d** were deposited with the Cambridge Structural Database (CCDC 626991 (**5b**) and CCDC 640757 (**9b**)).

Table 4. Crystallographic characteristics and the X-ray data collection and refinement statistics

Parameter	**5b**	**9b**
Color, crystal shape	Yellowish, prismatic	Colorless, prismatic
Molecular formula	$C_{18}H_{17}Cl_2NO_7$	$C_{18}H_{18}N_2O_9$
Crystal system	Triclinic	Monoclinic
Space group	$P\bar{1}$	$P2_1$
a/Å	6.701(2)	8.710(6)
b/Å	8.785(3)	20.24(2)
c/Å	17.499(2)	10.756(8)
α/deg	81.56(7)	90
β/deg	78.90(6)	92.98(6)
γ/deg	76.65(6)	90
V/Å^3	977.9(6)	1894(3)
Z	2	4*
Molecular weight	430.23	406.34
d_{calc}/g cm^{-3}	1.46	1.43
μ/cm^{-1}	33.6	10.0
Absorption correction	Empirical	—**
θ_{min}/deg	2.6	4.1
θ_{max}/deg	69.9	68.0
Number of measured reflections (R_{int})	3607 (0.1104)	2547 (0.1879)
Number of reflections with $I > 2\sigma(I)$	2979	1844
Number of refined parameters	254	527
Final R factors	$R_1 = 0.0516$, $wR_2 = 0.1585$	$R_1 = 0.1033$, $wR_2 = 0.3032$

* Two independent molecules A and B.

** The corrections was not applied.

The single crystals of compounds **5b** and **9b** were studied at the Department of X-ray Diffraction Studies of the Center of Collaborative Research on the basis of the Laboratory of X-ray Diffraction Methods of the A. E. Arbuzov Institute of Organic and Physical Chemistry, the Kazan Research Center of the Russian Academy of Sciences. Selected geometric parameters of molecules **5b** and **9b** are given in Tables 1 and 3, respectively.

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