RESEARCH ON IMIDAZO[2,1-a]ISOQUINOLINE DERIVATIVES.

3. ACYLATION OF 2-SUBSTITUTED IMIDAZO[2,1-a]ISOQUINOLINES

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The acylation of 2-alkyl, 2-aryl, and 2-hetaryl derivatives of imidazo[2,1-a]isoquinoline was studied. 3-Acetyl-substituted derivatives of this system were synthesized by the action of acetic anhydride on 2-arylimidazoisoquinolines in the presence of magnesium perchlorate. Under similar conditions 2-hetaryl derivatives are acetylated not only in the 3 position but also in the hetaryl ring. 3-Acetyl-2-methylimidazoisoquinoline, which is not formed as a result of direct acylation, was synthesized by indirect methods, viz., on the basis of 1-aminoisoquinoline and 3-chloroacetylacetone or from 1-acetamidoisoquinoline and bromoacetone. The compounds obtained are extremely resistant to hydrolysis, give the usual reactions at the carbonyl group, condense with aromatic aldehydes, and undergo bromination to give 3-bromo- and 3-dibromoacetyl derivatives.

Continuing our study of the reactivity of imidazo[2,1-a]isoquinoline, in the present paper we report the acylation of 2-alkyl, 2-aryl, and 2-hetaryl derivatives of this condensed system. On the basis of data on the relatively small degree of π-surplus character of imidazoisoquinolines, their ability to undergo electrophilic substitution should be substantially reduced as compared with other bridged heterocycles with similar structures [2]. In fact, 2-arylimidazoisoquinolines (Ia-c) [3, 4] are not acylated when they are heated with acetic anhydride and are inert with respect to the action of acetic acid in polyphosphoric acid or acetyl chloride in pyridine. The recently recommended (for imidazo[1,2-a]-pyridines) method of acylation with acetic anhydride in the presence of potassium carbonate [5] also proved to be ineffective in this case.

3-Acetyl-2-phenylimidazoisoquinoline (IIa) was synthesized in 56% yield only as a result of prolonged (45 h) refluxing a 2-phenyl derivative Ia with acetic anhydride in the presence of magnesium perchlorate. Donor substituents (OCH_3) in the phenyl ring shorten the reaction time and lead to an increase in 15-20% in the yields of the corresponding ketones IIb,c. It is characteristic that even for 3,4-dimethoxy-substituted Ic acylation proceeds extremely selectively, involving exclusively the imidazole ring.

In addition, 2-furyl(thienyl)imidazoisoquinolines IIIa,b, which also do not react with acetic anhydride without a catalyst, are acylated in the presence of magnesium perchlorate in only 1.5 h, not only in the 3 position but also in the hetaryl ring to give a mixture of mono- (IVa,b) (47-50% yield) and diacetyl (Va,b) (18-20% yield) derivatives. When the process is carried out for up to 16 h, the yield of diketones Va,b increases to 70%. However, one cannot select conditions under which monoacylation would proceed sufficiently completely without admixtures of the starting compounds or diacetyl derivatives V.

The location of the acetyl group in the 3 position of the system for ketones II follows from the data from the PMR spectra, in which the signal of the 5-H proton is shifted 1.5 ppm to weak field as compared with the starting compounds and is observed at 9.2-9.5 ppm, which we also link with the deshielding effect of the adjacent carbonyl group. Just as in the case of 2-aryl-substituted II, one observes a weak-field (as compared with the starting compound) shift of the signal of the 5-H proton in the PMR spectrum of monoacetyl derivative IVb, and the triplet signal of the 4-H' proton of the thienyl residue is retained. In the spectrum of diketone Vb this triplet vanishes, and the signals of the 4-H' and 3-H' protons show up in the

*See [1] for Communication 2.

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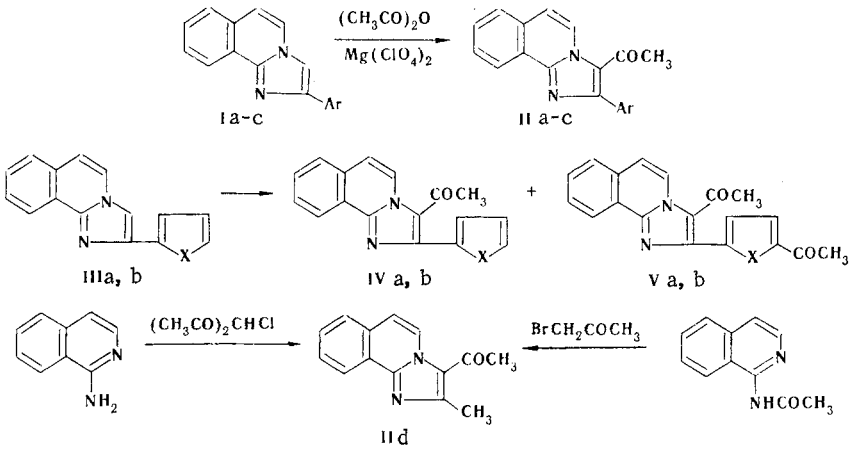
form of doublets, from which one may conclude that secondary acylation takes place in the α position of the thiophene ring.



I, II a Ar=C_6H_5, b Ar=4-$OCH_3C_6H_4$, c Ar=3,4-$(OCH_3)_2C_6H_3$; III, IV, V a X=O; b X=S

Attempts to subject 2-methylimidazo[2,1-a]isoquinoline to direct acylation were unsuccessful. However, the corresponding 3-acetyl derivative IId can be synthesized either by fusing 1-aminoisoquinoline with 3-chloroacetone or by refluxing 1-acetamidoisoquinoline and bromoacetone in alcohol. In both cases the intermediately formed quaternary salts undergo cyclization spontaneously with the simultaneous formation of the hydrohalide of the starting amine. The corresponding 3-benzoyl derivative is formed from acetamidoisoquinoline and phenacyl bromide.

Despite the fact that the band of carbonyl absorption in the IR spectra of acetyl derivatives II, IV, and V show up in the low-frequency region (1630-1635 cm^{-1}), which is characteristic for bridged systems [6-8] that contain a carbonyl group attached to a carbon atom with increased electron density, 3-acetylimidazoisoquinolines nevertheless display properties that are characteristic of aromatic ketones. Thus they are extremely resistant to acidic and alkaline hydrolysis, give reactions at the carbonyl group, and condense with aromatic aldehydes under alkaline-catalysis conditions to give cinnamoyl derivatives VIa,b.

A mixture of 3-bromoacetyl- (VII) and 3-dibromoacetylimidazoisoquinolines (VIII) in 67 and 10-12% yields, respectively, is formed in the bromination of 3-acetyl-2-methyl derivative IId with N bromo succinimide (NBS) in dry carbon tetrachloride. The positions of the halogen atoms were established on the basis of the IR and PMR spectra and by the reaction of dibromo ketone VIII with o-phenylenediamine, as a result of which a bright-yellow quinoxaline derivative was obtained. The IR spectrum of the latter does not contain the absorption band of a C=O group that is observed in the spectrum of the starting compound at 1645 cm^{-1}.

The bromination of ketones IIa, d by the action of bromine in refluxing acetic acid also proceeds unambitiously to give, in addition to bromo ketones, dibromo ketones and hydrobromides of acetyl derivatives IIa,d. An increase in the amount of bromine introduced into the reaction to 3 moles makes it possible to increase the yields of the dibromo ketones to 80-85%.

Attempts to subject ketones IIa,d to the Willgerodt–Kindler reaction were unsuccessful. A complex mixture of substances, from which we isolated a compound with mp 255-256°C, which, judging from the analytical and spectral data, is dithiooxalodimorpholide [9], is formed when these compounds are heated with excess sulfur in morpholine.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a UR-20 spectrometer. The PMR spectra were recorded with a Tesla BS-467 spectrometer with hexamethyldisiloxane as the internal standard.

2-(3,4-Dimethoxyphenyl)imidazo[2,1-a]isoquinoline (Ic). A solution of 2.88 g (20 mmole) of 1-aminosoquinoline and 5.18 g (20 mmole) of 3,4-dimethoxyphenacyl bromide in 25 ml of alcohol was refluxed in the presence of 1.66 g (12 mmole) of potassium carbonate for 2 h, after which the solvent was removed by distillation, and the residue was chromatographed with

TABLE 1. Acetyl Derivatives of Imidazo[1,1-a]isoquinoline

Compound	mp,[a] °C	νC=O, cm⁻¹	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
IIa	149—150	1635	79,5	5,1	9,6	$C_{19}H_{14}N_2O$	79,7	4,9	9,8	55,9
IIb	178—179	1630	76,2	5,1	8,7	$C_{20}H_{16}N_2O_2$	76,4	5,1	8,9	77
IIc	161—162	1630	72,8	5,3	8,3	$C_{21}H_{18}N_2O_3$	72,8	5,2	8,1	73
IId	172—173	1635	74,8	5,1	12,7	$C_{14}H_{12}N_2O$	75,0	5,4	12,5	71
IVa	134—135	1632	73,7	4,6	10,3	$C_{17}H_{12}N_2O_2$	73,9	4,3	10,1	43
IVb	158—159	1630	70,2	4,3	9,6	$C_{17}H_{12}N_2OS$ [b]	69,9	4,1	9,6	46,5
Va	193—194	1630, 1635	71,5	4,5	8,6	$C_{19}H_{14}N_2O_3$	71,7	4,4	8,8	67
Vb	195—196	1630, 1635	68,5	4,5	8,2	$C_{19}H_{12}N_2O_2S$ [c]	68,2	4,2	8,4	72

[a]The compounds were recrystallized: IIb,c and IV and Va,b from alcohol, IIa from heptane, and IId from octane. [b]Found: S 11.2%. Calculated: S 11.0%. [c]Found: S 9.3%. Calculated: S 9.6%.

a column filled with Al_2O_3 by elution with benzene to give 4.2 g (70%) of colorless crystals with mp 135-136°C (from alcohol). Found: C 75.3; H 5.3; N 9.6%. $C_{19}H_{16}N_2O_2$. Calculated: C 75.0; H 5.3; N 9.2%.

3-Acetyl-2-phenylimidazo[2,1-a]isoquinoline (IIa). A solution of 2.44 g (10 mmole) of 2-phenylimidazoisoquinoline (Ia) [3] in 20 ml of acetic anhydride was refluxed in the presence of 0.67 g (3 mmole) of magnesium perchlorate for 45 h, after which it was cooled, and the dark-green solution was poured into 30 ml of water. The aqueous mixture was made alkaline with 22% ammonium hydroxide and extracted with chloroform. The extract was chromatographed with a column filled with Al_2O_3 by elution with chloroform with selection of the first fraction (1.6 g). The 2,4-dinitrophenylhydrazone of IIa was obtained by heating saturated alcohol solutions of ketone IIa and 2,4-dinitrophenylhydrazine. Workup gave dark-claret-colored needles with mp 263-264°C (from DMF). Found: C 64.1; H 4.2; N 17.7%. $C_{25}H_{18}N_6O_4$. Calculated: C 64.4; H 3.9; N 18.0%.

Ketones IIb,c were similarly obtained, but heating for 25 h was sufficient for their formation. PMR spectrum of IIb (CF_3COOH): 2.05 (3H, s. $COCH_3$), 3.6 (3H, s, OCH_3), 6.88 (2H, d, J = 7.5 Hz, 3',3'-H), 7.33 (2H, d, J = 7.5 Hz, 2',2'-H), 7.55 (1H, d, J = 7.5 Hz, 6-H), 7.70 (3H, m, 7–9-H), 8.25 (1H, m, 10-H), and 9.25 ppm (1H, d, J = 7.5 Hz, 5-H). PMR spectrum of IIc (CF_3COOH) 2.05 (3H, s, $COCH_3$), 3.57 (3H, s, 3'-OCH_3), 3.65 (3H, s, 4'-OCH_3), 6-9 (3H, m, 2',5',6'-H), 7.3-7.7 (4H, m, 6-9 H), 8.17 (1H, m, 10-H), and 9.47 ppm (1H, d, J = 7.5 Hz, 5-H). Other characteristics of IIa-c are presented in Table 1.

2-(2'-Furyl)imidazo[2,1-a]isoquinoline (IIIa). A solution of 4.32 g (0.03 mole) of 1-aminoisoquinoline and 5.67 g (0.003 mole) of 2-bromoacetylfuran in 30 ml of alcohol was refluxed for 3 h in the presence of 2.76 g (0.02 mole) of potassium carbonate, after which the solvent was removed by distillation, and the residue was purified by chromatography with a column filled with AL_2O_3 by elution with chloroform to give 4.7 g (67%) of colorless crystals with mp 106-107°C (from isooctane). Found: C 76.7; H 4.6; N 12.3%. $C_{15}H_{10}N_2O$. Calculated: C 76.9; H 4.3; N 12.0%.

2-(2'-Thienyl)imidazo[2,1-]isoquinoline (IIIb). This compound was obtained in 72% yield by the procedure used to prepare IIIa. The slightly greenish crystals had mp 123-125°C (from isooctane). PMR spectrum CF_3COOH): 6.75 (1H, t, 4'-H), 7.0-7.35 (3H, m, 3',5',6-H), 7.55 (3H, m, 7-9-H), 7.82 (1H, d, J = 7.5 Hz, 5-H), and 8.1 ppm (1H, m, 10-H). Found: C 72.0; H 4.3; S 12.6%. $C_{15}H_{10}N_2S$. Calculated: C 72.0; H 4.0; S 12.8%.

3-Acetyl-2-(2'-thienyl)imidazo[2,1-a]isoquinoline (IVb) and 3-Acetyl-2-(5'-acetyl-2'-thienyl)imidazo[2,1-a]isoquinoline (Vb). A solution of 0.5 g (2 mmole) of 2-thienylimidazoisoquinoline IIIb in 5 ml of acetic anhydride was refluxed in the presence of 0.1 g of magnesium perchlorate for 1.5 h, after which it was cooled and poured into water, and the aqueous mixture was made alkaline with 22% ammonium hydroxide. The precipitate was removed by filtration, washed with water, dried, and dissolved in chloroform. The mixture of compounds formed in the reaction was separated by chromatography with a column filled with Al_2O_3 by elution with benzene. The first substance separated was monoacetyl derivative IVb [0.27 g (46.5%)]. PMR spectrum (CF_3COOH) 2.10 (3H, s, $COCH_3$), 6.95 (1H, t, 4'-H), 7.23

(1H, d, J = 3.8 Hz, 3'-H), 7.45-7.65 (5H, m, 5',6-9-H), 8.18 (1H, m, 10-H), and 9.18 ppm (1H, d, j = 7.5 Hz, 5-H). Diketone Vb [0.13 g (19.7%)] was then eluted with chloroform. PMR spectrum (CF_3COOH): 2.10 (3H, s, 3-$COCH_3$), 2.38 (3H, s, 5'-$COCH_3$), 7.4 (2H, m, 3',4'-H), 7.68 (4H, m, 6-9-H), 8.18 (1H, m, 10-H), and 9.18 ppm (1H, d, J = 7.5 Hz, 5-H). Diketone Vb was formed in 72% yield when the reaction mixture was refluxed for 16 h.

Acetyl derivatives of 2-furylimidazoisoquinoline IVa and Va were similarly synthesized.

3-Acetyl-2-methylimidazo[2,1-a]isoquinoline (IId). A) A mixture of 2.88 g (0.02 mole) of 1-aminoisoquinoline and 2 g (0.015 mole) of 3-chloroacetylacetone was heated at 90°C for 5-7 min, after which the melt was cooled and triturated with chloroform, and the precipitated hydrochloride of the starting amine was removed by filtration and washed with chloroform. The mother liquor was evaporated, and the residue was chromatographed with a column filled with Al_2O_3 by elution with benzene to give 1.6 g (71%) of product. PMR spectrum ($CDCl_3$): 2.55 (3H, s, 2-CH_3), 2.78 (3H, s, $COCH_3$), 7.0 (1H, d, J = 7.5 Hz, 6-H), 7.6 (3H, m, 7-9-H), 8.53 (1H, m, 10-H), and 9.23 ppm (1H, d, J = 7.5 Hz, 5-H). The 2,4-dinitrophenylhydrazone was obtained as dark-red crystals with mp 275-276°C (from DMF). Found: N 20.4%. $C_{20}H_{16}N_6O_4$. Calculated: N 20.8%.

B) A solution of 1.86 g (10 mmole) of 1-acetamidoisoquinoline and 0.7 g (5 mmole) of bromoacetone in 10 ml of alcohol was refluxed for 5 h, after which the solvent was evaporated to dryness, and the residue was treated with chloroform. The hydrobromide of the starting compound was removed by filtration, and the mother liquor was chromatographed with a column filled with Al_2O_3 by elution with benzene to give 0.62 g (50%) of product. The compound obtained was identical to that described in experiment A.

3-Benzoyl-2-methylimidazo[2,1-a]isoquinoline. This compound was obtained in 63% yield by by the method presented above (B). The colorless needles, after drying in a vacuum desiccator over P_2O_5, had mp 147-148°C (from alcohol). Found: C 79.5; H 4.6; N 9.4%. $C_{19}H_{14}N_2O$. Calculated: C 79.7; H 4.9; N 9.8%.

3-(4-Nitrophenylacrylyl)-2-phenylimidazo[2,1-a]isoquinoline (VIa). An alcohol solution of 0.29 g (1 mmole) of ketone IIa and 0.15 g (1 mmole) of p-nitrobenzaldehyde containing one to two drops of 40% alkali was reflued for 3-5 min, after which the mixture was cooled, and the resulting precipitate was removed by filtration to give 0.38 g (90.6%) of yellow needles with mp 247-250°C (from DMF). IR spectrum: 1580 (C=C), 1595 (C=N), and 1635 cm^{-1} (C=O). Found: C 74.2; H 4.3; N 10.3%. $C_{26}H_{17}N_3O_3$. Calculated: C 74.5; H 4.1; N 10.0%.

3-(4-Nitrophenylacrylyl)-2-methylimidazo[2,1-a]isoquinoline (VIb). This compound was obtained in 94% yield by the method used to prepare VIa. The yellow crystals had mp 260-261°C (from DMF). IR spectrum: 1570 (C=C), 1590 (C=N), and 1635 cm^{-1} (C=O). Found: N 11.5%. $C_{21}H_{15}N_3O_3$. Calculated: N 11.8%.

Bromination of 3-Acetyl-2-methylimidazo[2,1-a]isoquinoline. A) With N-bromosuccinimide (NBS) in Carbon Tetrachloride. A 0.36-g (2 mmole) sample of NBS and catalytic amounts of benzoyl peroxide were added to a solution of 0.45 g (2 mmole) of ketone IId in 20 ml of dry carbon tetrachloride, and the mixture was refluxed for 2 h. The precipitate that formed when the solution was cooled was removed by filtration and washed repeatedly with water. The mass of monobromo ketone VII was 0.28 g. The mother liquor was evaporated to dryness and chromatographed with a column filled with Al_2O_3 by elution with benzene. Workup of the first fraction gave 0.07 g (11%) of 3-dibromoacetyl-2-methylimidazo[2,1-a]isoquinoline (VIII) in the form of colorless crystals with mp 194-195°C (from alcohol). IR spectrum: 1650 cm^{-1} (C=O). Found C 43.7; H 2.6; Br 41.6%. $C_{14}H_{10}Br_2N_2O$. Calculated: C 44.0; H 2.6; Br 41.9%.

Evaporation of the second fraction gave an additional 0.13 g of VII. The yield of 3-bromoacetyl-2-methylimidazo[2,1-a]isoquinoline (VII) was 0.41 g (67%). The pale-yellow needles had mp 193-194°C (from alcohol). PMR spectrum ($CDCl_3$) 2.75 (3H, s, 2-CH_3), 4.85 (2H, s, 3-$COCH_2Br$), 7.15 (1H, d, J = 7.5 Hz, 6-H), 7.62 (3H, m, 7-9-H), 8.59 (1H, m, 10-H), and 9.25 ppm (1H, d, J = 7.55 Hz, 5-H). IR spectrum: 1645 cm^{-1} (C=O). Found: C 55.2; H 3.4; Br 25.9%. $C_{14}H_{11}BrN_2O$. Calculated: C 55.4; H 3.6; Br 26.3%.

B) With Bromine in Glacial Acetic Acid. A solution of 0.1 ml (2 mmole) of bromine in 3 ml of acetic acid was added gradually with stirring to a heated (to 90°C) solution of 0.45 g (2 mmole) of acetyl derivative IId in 10 ml of glacial acetic acid. After 45 min, the mixture was cooled and poured into 30 ml of water, and the precipitate was removed by filtration. Treatment of the latter with chloroform separated 0.15 g of the hydrobromide of IId, and a

mixture of mono- and dibromo ketones VII and VIII was separated by chromatography as described above. The yield of bromo derivative VII was 0.28 g (46%), while the yield of the dibromo derivative was 0.16 g (20%). With respect to their physicochemical characteristics, the compounds were identical to the compounds described in experiment A.

3-Bromoacetyl-2-phenylimidazo[2,1-a]isoquinoline and 3-Dibromoacetyl-2-phenylimidazo-[2,1-a]isoquinoline. These compounds were synthesized by method B. The yield of the monobromo ketone was 43%. The colorless needles had mp 201-203°C (dec., from alcohol). IR spectrum: 1640 cm^{-1} (C=O). Found: C 62.2; H 4.1; Br 21.6%. $C_{19}H_{13}BrN_2O$. Calculated: C 62.4; H 4.3; Br 21.9%. The yield of the dibromo ketone was 17%. The colorless needles had mp 205-207°C (dec., from butanol). IR spectrum: 1640 cm^{-1} (C=O). Found: C 51.0; H 2.7; Br 36.2%. $C_{19}H_{12}Br_2N_2O$. Calculated: C 51.3; H 2.7; Br 36.2%.

2-Methyl-3-(2-quinoxalyl)imidazo[2,1-a]isoquinoline. A solution of 0.38 g (1 mmole) of dibromo ketone VIII and 0.21 g (2 mmole) of o-phenylenediamine in 10 ml of alcohol was refluxed for 30 h, after which it was evaporated to dryness, and the residue was chromatographed with a column filled with Al_2O_3 by elution with chloroform. The first fraction was separated and worked up to give yellow needles with mp 232-233°C (from butanol). Found: C 77.1; H 4.5; N 17.9%. $C_{20}H_{14}N_4$. Calculated: C 77.4; H 4.5; N 18.2%.

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ACETALS OF LACTAMS AND ACID AMIDES.

38.* SYNTHESIS OF PYRIMIDINE AND PYRIDINE DERIVATIVES ON THE BASIS OF THE REACTION OF ENAMINO AMIDES WITH AMIDE ACETALS

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Derivatives of 1-benzyl-4-pyrimidinones and 1-benzyl-6-pyrimidinones were synthesized by the reaction of α-cyano-β-N-benzylaminocrotonamide and α-cyano-β-aminocrotonic acid N-benzylamine with dimethylformamide diethylacetal. When 1-benzyl-5-cyano-6-(β-dimethylamino)vinyl-1,6-dihydro-4-pyrimidinone is heated in an alkaline medium, it is converted to 3-cyano-4-benzylamino-2-pyridone, from which a pyrido[1,2-a]pyrimidine derivative was synthesized. When 1-benzyl-5-cyano-4-(β-dimethylamino)vinyl-1,6-dihydro-6-pyrimidinone is heated in alkaline solution, it is converted to α-cyano-β-hydroxycrotonic acid N-benzylamide.

We have previously established [2, 3] that condensed pyrimidines are formed in the reaction of cyclic enamino amides with amide acetals. In a continuation of these investiga-

*See [1] for Communication 37.

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