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THIN-LAYER CHROMATOGRAPHY OF ENAMINO KETONES. II*

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SUMMARY

The synthesis of sixteen enamino ketones by reaction of 2,4-pentanedione, ethyl 3-oxobutanoate and 3-phenylazo-2,4-pentanedione with variously substituted aromatic amines is described. The compounds were separated by thin-layer chromatography and the R_F values were determined on pre-coated silica gel plates and on commercially available ready-coated Silufol sheets using four developing systems. The spots were detected with three reagents and under UV light. Some R_F values were dependent on the structure of the substances. The purity of the prepared enamino ketones was controlled by the diagonal technique, the detection being carried out by application of two different reagents in succession.

INTRODUCTION

In Part I¹, the development of a method for the separation of enamino ketones (derivatives of 2,4-pentanedione and ethyl 3-oxobutanoate) on thin layers was reported.

The purpose of this work was to investigate a further series of enamino ketones, *viz.*, the N-aryl-substituted derivatives of 2,4-pentanedione and ethyl 3-oxobutanoate, which are of importance for the synthesis of medicaments, pesticides and dyes and as intermediates in different organic syntheses. Within the scope of studies of azo coupling reactions of 2,4-pentanedione, we prepared several of its 3-phenylazo derivatives which, to our knowledge, had not previously been described. We also studied their thin-layer chromatographic (TLC) behaviour in order compare them with unsubstituted and 3-alkyl-substituted 2,4-pentanediones¹. An attempt was made to develop a satisfactory method for the separation of all those compounds whose R_F values differed only slightly and to find new solvent systems, because those applied in our previous study¹ were not suitable for these compounds. TLC was carried out on pre-coated silica gel plates and on ready-coated Silufol sheets in four different

* For Part I, see ref. 1

solvent systems. We also tested the purity and the degree of decomposition of the above-mentioned substances by application of the diagonal technique, the spots being detected by treatment of each chromatogram successively with two different reagents. Thus, in addition to enamino ketones, the decomposition products arising during the development of the chromatogram could be demonstrated.

EXPERIMENTAL

The proton NMR spectra were measured on a Tesla BS 487 B spectrometer (Tesla, Brno, Czechoslovakia) at 80 MHz. For the measurements, saturated solutions of substances in hexadeuteriodimethyl sulphoxide (DMSO- d_6), deuteriochloroform (CDCl₃) and tetrachlormethane (CCl₄) with hexamethyldisiloxane (HMDS) as internal standard ($\delta = 0.05$) were used. The melting points were determined on a Kofler block and were not corrected.

Preparation of the compounds

4-Amino-3-pentene-2-one. A 10-ml volume (0.1 mol) of 2,4-pentanedione was treated with 60 ml of a 25% solution of ammonia and the mixture was allowed to stand at room temperature for 24 h. The solution was then extracted three times with 50-ml volumes of chloroform and the organic layers were combined and dried over anhydrous sodium sulphate. The solvents were removed by distillation to yield a crude product, which was then distilled *in vacuo*. On cooling, the mixture in the flask solidified. Recrystallization from *n*-hexane gave 8.5 g (86%) of a crystalline substance, m.p. 39–41°C, which was consistent with that reported in ref. 2.

4-Phenylamino-3-pentene-2-one (I). In a flask, 9.3 g (0.1 mol) of redistilled aniline were mixed with 9.75 g (0.1 mol) of 2,4-pentanedione and 40 ml of benzene. The mixture was boiled on an oil-bath and the distilled-off azeotropic mixture (benzene-water) was replaced with benzene until all the water (1.8 ml) separated. Then the surplus solvent was removed by distillation. The crude product was redistilled *in vacuo* [b.p. 75–76°C (30 Torr), lit.³, 74–75°C (30 Torr)] to give a crystalline substance, which was recrystallized from *n*-hexane to yield 15 g (86%) of fine yellowish crystals, m.p. 46–48°C (lit.⁴, 47–48°C).

Enamino ketones II–VI. 2,4-Pentanedione was treated^{5,6} with solutions of substituted derivatives of aniline in a molar ratio of 1:1. The crude crystalline substances III–VI were purified by recrystallization from *n*-hexane and the liquid compound II by distillation *in vacuo* (Table I). The structure and the purity of the compounds were examined by ¹H NMR spectrometry.

Ethyl 3-phenylamino-2-butenolate (VII). A 9.3-g (0.1-mol) amount of redistilled aniline, 13.0 g (0.1 mol) of ethyl 3-oxobutanoate, 1 ml of acetic acid and 30 ml of benzene were boiled for 3.5 h on an oil-bath. The separated azeotropic mixture (benzene-water) was replaced with benzene until all the water (1.8 ml) was removed. The remaining solvent was distilled off and the crude product was purified by distillation *in vacuo* to yield 15.6 g (76%) of VII, b.p. 132–136°C (2.5 Torr) (lit.⁷, 128–130°C at 2 Torr).

Enamino ketones VIII–XI. The compounds were prepared^{8,9} by reaction of ethyl 3-oxobutanoate with solutions of the corresponding substituted aniline derivatives in a molar ratio of 1:1. The products were isolated in the same manner as VII.

The crude liquid substances VIII–X were purified by distillation *in vacuo* and the crystalline compound XI by recrystallization from alcohol (Table I). The structure and the purity of the compounds were examined by ^1H NMR spectrometry.

3-Phenylazo-4-amino-3-pentene-2-one (XII). A 4.65-g (0.05-mol) amount of aniline was diazotized with 50 ml of 2.5 *M* hydrochloric acid and 20 ml of 2.5 *M* sodium nitrite at 0°C. To the solution of the diazonium salt, 8.2 g (0.1 mol) of molten sodium acetate were added. The refiltered solution of the diazonized aniline in an acetate buffer was added to a solution of 4.75 g (0.05 mol) of 4-amino-3-pentene-2-one in 50 ml of acetone with stirring. Immediately, a product precipitated that was filtered off after several minutes. The further precipitated portion was already contaminated by a product of the hydrolysis of XII. The first obtained product was dried at laboratory temperature and crystallized first from *n*-hexane and then from chloroform to yield 8.3 g (82%) of XI, m.p. 128–128.5°C (lit.¹⁰, 125°C).

3-(4-Chlorophenylazo)-4-amino-3-pentene-2-one (XIII). This was prepared in the same manner as XII from 6.4 g (0.05 mol) of 4-chloroaniline diazotized as above, and from a solution of 4.75 g (0.05 mol) of 4-amino-3-pentene-2-one in 50 ml of acetone. Crystallization from chloroform gave 9.5 g (80%) of XIII, m.p. 185–186°C. For $\text{C}_{11}\text{H}_{12}\text{N}_3\text{ClO}$ (mol.wt. 237.7): calculated, C 55.58, H 5.09, N 17.68%; found, C 55.35, H 4.77, N 17.50%. ^1H NMR spectrum (DMS- d_6 , 25°C): δ (NH) = 12.29, δ (Ar) = 7.69–7.31, δ (CH_3) = 2.44.

3-(4-Chlorophenylazo)-4-phenylamino-3-pentene-2-one (XIV). A solution of 8.75 g (0.05 mol) of 4-phenylamino-3-pentene-2-one in 50 ml of acetone was mixed with a solution of diazotized 4-chloroaniline. The first precipitated product was crystallized from *n*-hexane to yield 11.1 g (71%) of XIV, m.p. 120–122°C. For $\text{C}_{17}\text{H}_{16}\text{N}_3\text{ClO}$ (mol.wt. 313.8): calculated, C 65.07, H 5.13, N 13.39%; found, C 65.71, H 5.42, N 13.54%. ^1H NMR spectrum (C^2HCl_3 , 50°C): δ (NH) = 15.60, δ (ArCl) = 7.18, δ (Ar) = 7.46–6.66, δ (CH_3) = 2.45, 2.24.

3-(4-Chlorophenylazo)-4-(4-methylphenylamino)-3-pentene-2-one (XV). This was prepared in the same manner as XIV from an equal amount of diazotized 4-chloroaniline and 9.45 g (0.05 mol) of 4-(4-methylphenylamino)-3-pentene-2-one. Crystallization from *n*-hexane gave 10.6 g (65%) of XV, m.p. 130–131°C. For $\text{C}_{18}\text{H}_{18}\text{N}_3\text{ClO}$ (mol.wt. 327.8): calculated, C 65.95, H 5.53, N 12.82%; found, C 65.62, H 5.42, N 12.88%. ^1H NMR spectrum: (C^2HCl_3 , 50°C): δ (NH) = 15.77, δ (ArCl) = 7.25, δ (Ar) = 7.31–6.62, δ (CH_3) = 2.50, 2.29.

3-(4-Chlorophenylazo)-4-(4-chlorophenylamino)-3-pentene-2-one (XVI). This was prepared by the same technique as for XIV from diazotized 4-chloroaniline and 10.5 g (0.05 mol) of 4-(4-chlorophenylamino)-3-pentene-2-one. Crystallization from *n*-hexane yielded 11.8 g (68%) of XVI, m.p. 118–119.5°C. For $\text{C}_{17}\text{H}_{15}\text{N}_3\text{Cl}_2\text{O}$ (mol.wt. 348.2): calculated, C 58.63, H 4.34, N 12.07%; found, C 58.36, H 4.41, N 12.02%. ^1H NMR spectrum (C^2HCl_3 , 50°C): δ (NH) = 15.44, δ (ArCl) = 7.24, δ (Ar) = 7.39–6.66, δ (CH_3) = 2.50, 2.26.

Thin-layer chromatography

Use was made (also for the diagonal technique) of commercially available 20 × 20 cm plates pre-coated with silica gel 60 F₂₅₄, (E. Merck, Darmstadt, F.R.G.) and Silufol UV₂₅₄ sheets, 20 × 20 cm (Kavalier, Votice, Czechoslovakia). The chromatograms were developed with different solvent systems: S1 = cyclohexane-ethyl

acetate (9:1), S2 = benzene-chloroform (2:1), S3 = benzene-cyclohexane-methanol (4.5:5:0.5) and S4 = benzene-chloroform-methanol (8.5:1:0.5). The compounds were dissolved in methanol to give a 0.5–0.8% solution, and volumes of 1 μ l were applied to the chromatogram. The development of the chromatograms, the preparation of the reagents and the detection were carried out as described previously^{1,11}.

RESULTS AND DISCUSSION

The enamino ketones were separated by TLC on different adsorption layers using several solvent systems. Table I lists the R_F values found and the modes of detection for ready-coated plates with silica gel 60 F₂₅₄. Because on pre-coated plates of the Silufol type analogous values were obtained, but which were *ca.* 15% lower, in Table I only the results obtained on silica gel 60 F₂₅₄ are reported. The order of the R_F values of the analysed compounds did not depend on the type of adsorbent applied but in some instances they did depend on the components of the developing system.

The analysed compounds were subdivided into three groups, *viz.*, derivatives of 2,4-pentanedione (I–VI), ethyl 3-oxobutanoate (VII–XI) and 3-phenylazo-2,4-pen-

TABLE I
ENAMINO KETONES $\text{CH}_3\text{C}(\text{R}_1)=\text{CCOR}_2$ PREPARED BY THE REACTION OF DIKETONES AND KETONES WITH AMINES

Compound	R_1	R_2	R_3	Yield (%)	B.p. ($^{\circ}\text{C}/\text{Torr}$)		M.p. ($^{\circ}\text{C}$)	
					Found	Literature	Found	Lit
I	H	CH ₃	C ₆ H ₅	86.0	75–76/30	74–75/30 ³	46–48	47
II	H	CH ₃	3-CH ₃ C ₆ H ₄	76.0	146–148/5	—	—	—
III	H	CH ₃	4-CH ₃ C ₆ H ₄	77.0	—	—	65–67	68
IV	H	CH ₃	3-ClC ₆ H ₄	79.0	—	—	39–40	42
V	H	CH ₃	4-ClC ₆ H ₄	83.0	—	—	60–62	60
VI	H	CH ₃	3-NO ₂ C ₆ H ₄	65.0	—	—	76–78	78
VII	H	OCH ₂ CH ₃	C ₆ H ₅	76.0	132–136/2.5	128–130/2 ⁷	—	—
VIII	H	OCH ₂ CH ₃	3-CH ₃ C ₆ H ₄	79.0	136–139/4	144–144.5/4 ⁸	—	—
IX	H	OCH ₂ CH ₃	4-CH ₃ C ₆ H ₄	75.0	128–130/2	146–147.5/4 ⁸	—	—
X	H	OCH ₂ CH ₃	3-ClC ₆ H ₄	73.0	146–149/1	145–148/1 ⁹	—	—
XI	H	OCH ₂ CH ₃	4-ClC ₆ H ₄	78.0	—	—	53–54	55 ⁵
XII	Phenylazo	CH ₃	H	82.0	—	—	128–128.5	125 ¹
XIII	4-Chloro-phenylazo	CH ₃	H	80.0	—	—	185–186	—
XIV	4-Chloro-phenylazo	CH ₃	C ₆ H ₅	71.0	—	—	120–122	—
XV	4-Chloro-phenylazo	CH ₃	4-CH ₃ C ₆ H ₄	65.0	—	—	130–131	—
XVI	4-Chloro-phenylazo	CH ₃	4-ClC ₆ H ₄	68.0	—	—	118–119.5	—

tanedione (XII–XVI). The first two groups include substances containing an unsubstituted phenylamino group (I and VII), a methylphenylamino group (II, III and VIII, IX), a chlorophenylamino group (IV, V and X, XI) and a nitrophenylamino group (VI). The substances in the third group include derivatives with an unsubstituted amino group (XII, XIII) and those with an arylamino group (XIV, XV, XVI). Compound I served as reference sample.

The compounds in the first group (I–VI) were well separated in systems S2 and S4, containing benzene and chloroform. The compounds were detected with iodine vapour or by spraying with iodine-iodide reagent or with $K_3Fe(CN)_6-FeCl_3$. With the latter they gave a marked green-blue colour.

The substances in the second group (VII–XI) did not separate so readily. The best separation was achieved with systems S1 and S3 (containing cyclohexane). In almost all systems, decomposition occurred to various extents during the development of the chromatograms. The decomposition products were best detectable when the chromatogram was first exposed to iodine vapour and then sprayed with $K_3Fe(CN)_6-FeCl_3$. The spots of enamino ketones, which are readily detectable by exposure to iodine vapour or by spraying with iodine-iodide reagent, are blue-grey with $K_3Fe(CN)_6-FeCl_3$. The spot of ethyl acetoacetate (white with a brown back-

<i>R_F</i> values on silica gel 60 F ₂₅₄				Detection			
S1	S2	S3	S4	UV light		Iodine (brown background)	Iodine-iodide reagent (brown background)
				254 nm	366 nm		
0.25	0.26	0.34	0.48	Light violet	—	White	White→yellow
0.32	0.33	0.37	0.51	Dark violet	—	White	White→beige
0.23	0.23	0.32	0.41	Dark violet	—	Light greyish	White→yellow
0.29	0.39	0.42	0.57	Dark violet	—	Light greyish	White→light yellow
0.19	0.29	0.28	0.49	Dark violet	—	Light grey-yellow	Light yellow→beige
0.11	0.17	0.23	0.45	Dark violet	—	Light grey-yellow	White→light yellow
0.52	0.56	0.56	0.72	Pink	—	White	White
0.60	0.64	0.64	0.76	Pink	—	White	White
0.56	0.59	0.58	0.73	Pink	—	White	White
0.64	0.67	0.66	0.78	Pink	—	White	White
0.58	0.60	0.61	0.75	Pink	—	Light grey-violet	White
0.37	0.45	0.49	0.64	Dark violet	Violet	Yellow	Light yellow
0.34	0.48	0.47	0.69	Blue-violet	Violet	Yellow	Deep yellow
0.46	0.60	0.56	0.75	Grey-violet	Violet	Yellow	Light brown→orange
0.53	0.66	0.60	0.78	Grey-violet	Violet	Brown	Brown→red-brown
0.48	0.72	0.64	0.83	Grey-violet	Violet	Brown	Brown→beige

ground in iodine vapour) produces a light blue colour, whereas that of arylamine (yellow in iodine vapour) gives a dark green-blue colour. This mode of detection was applied to advantage when the diagonal technique was used to control the degree of decomposition of the compounds.

The compounds in the third group (XII–XVI) separated well in systems S1 and S2 but poorly in system S4. They could not be detected with the $K_3Fe(CN)_6-FeCl_3$ reagent, as the colour of the spots was only slightly blue. These compounds are, however, visible on the chromatogram even before detection, as light yellow spots.

The results show that the R_F values of the ethyl 3-oxobutanoate derivatives are higher than those of the 2,4-pentanedione derivatives with the same amino group. The 3-phenylazo-2,4-pentanediones show the highest R_F values in all the solvent systems. This is consistent with our previous conclusions¹ where the R_F values of the 3-alkyl-substituted derivatives of 2,4-pentanedione were higher than those of the unsubstituted compounds.

We also studied the dependence of the R_F values on the type of amino group. As all the compounds (except XII and XIII) contained arylamino groups, an attempt was made to find a dependence between the R_F values and the type of the substituent and its position on the benzene ring.

Of compounds I–VI, III and V show surprisingly lower R_F values than those of I (unsubstituted phenylamino group). Of the compounds in the second (VII–XI) and third groups (XII–XVI), the compound with the unsubstituted phenylamino group (VII or XIV) shows the lowest R_F values in all solvent systems.

In the first two groups, the R_F values of the compounds with the phenylamino group substituted in position 3 on the ring are higher than those of the corresponding 4-substituted derivatives, in all systems.

Of compounds I–VI (in systems S2 and S4), the compounds containing a chlorophenylamino group migrate more rapidly than the methylphenylamino derivatives (the R_F values of IV and V are higher than those of II and III). In system S1 (containing cyclohexane) the order is reversed, and in system S3 (also containing cyclohexane) IV migrates more rapidly than II, but III has a higher R_F value than V. Compound VI (4-nitrophenylamino-) has the lowest R_F value of all the compounds of this group in systems S1, S2 and S3, but in system S4 it shows a comparatively high R_F value.

In compounds VII–XI, such deviations were not observed in connection with the components of the developing systems. In all the solvents, the compounds containing a chlorophenylamino group migrated more rapidly than those with a methylphenylamino group. Compound X had the highest and IX the lowest R_F values.

The derivatives of 3-phenylazo-2,4-pentanedione showed a similar dependence to those of I–VI. Compound XVI (4-chloro-) had the highest R_F value in systems S2, S3 and S4 and XV (4-methyl-) in system S1. The R_F values of XII and XIII, *i.e.*, of the substances with an unsubstituted amino group, were lowest in systems S2 and S4 (XII) and S1 and S3 (XIII). In all the systems, these compounds showed higher R_F values than the 3-unsubstituted or the 3-methyl-substituted derivatives of 2,4-pentanedione with an unsubstituted amino group¹.

On detection, the substances of the second group gave three spots, of which the two smaller ones of lower R_F were situated closely above each other. In order to confirm our assumption that decomposition of compounds of this group had oc-

curred during the development of the chromatogram, we applied the diagonal technique¹². The sample was placed at the left lower margin of the plate and the chromatogram was developed ascendingly in solvent S1. After drying, it was developed vertically in the same solvent. Detection showed that both the spots of lower R_F value appeared in the chromatogram twice, once on the diagonal of the chromatogram and once off-diagonally at the upper margin. The spot with the highest R_F value appeared in the chromatogram only once, on the diagonal. When the whole procedure was repeated using system S4, the same results were obtained.

On the basis of a comparison of the R_F values of the authentic ketoester and amine with those of the enamino ketone, it is assumed that the spot with the highest R_F value belongs to the enamino ketone and the two spots with lower R_F values to the products of decomposition. In order to confirm this assumption, a small amount of the ketoester or the amine was added to the sample of the enamino ketone on the start of the two-dimensional chromatogram. After addition of the ketoester, the spot with the lower R_F value on the diagonal was enlarged, whereas the spot situated above it off-diagonally remained unchanged. After addition of the amine, the second spot with a lower R_F value behaved in a similar manner. For the detection of the spots, the chromatogram was first exposed to iodine vapour, revealing the spots of the ketoester (white), amine (yellow) and enamino ketone (white), and then sprayed with $K_3Fe(CN)_6-FeCl_3$. The colour of the spot of the ketoester was light blue and thus it differed significantly from the adjacent dark green-blue spot of the amine. The colour of the enamino ketone was grey-blue.

The derivatives of ethyl 3-oxobutanoate are probably sensitive to moisture in the adsorbent, and they hydrolyse during development of the chromatogram. This can be demonstrated by application of the diagonal technique and detection as described above. Further, this method can be used for the determination of the purity of enamino ketones and the determination of the degree of decomposition during the so-called "ageing" of the compound.

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