REACTIONS OF CYCLOAMMONIUM CATIONS

XI.* HETARYLATION OF KETONES WITH N-ACYLBENZOPYRIDINIUM SALTS

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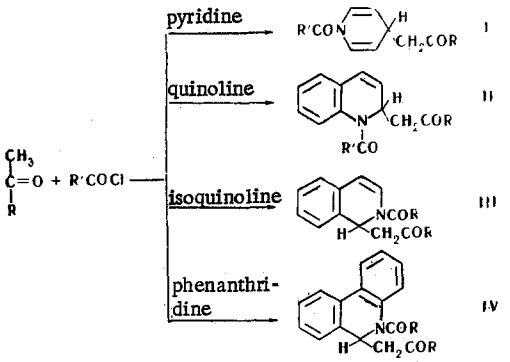
UDC 547.831.3.8+547.833.1+547.836

2-Keto derivatives of N-acyl-1,2-dihydroquinoline and isoquinoline were obtained by the reaction of quinoline and isoquinoline with ketones and β-dicarbonyl compounds in the presence of acyl halides. Under similar conditions, 9-phenacylacridines are formed by the reaction of acridine with acetophenones and acyl halides, while 5-acyl-6-phenacyl-5,6-dihydrophenanthridines are formed in the reaction of phenanthridine.

The reaction of ketones and β-dicarbonyl compounds with acyl halides in the presence of tertiary amines proceeds in different ways, depending on the nature of the amine and the carbonyl component. The N-acylammonium salts formed in situ as active intermediates in these reactions are acylating agents only when tertiary aliphatic amines are used, and O- and C-acylation of carbonyl compounds proceed to an equal extent [2-4]. In the presence of pyridine there is either predominant O-acylation (in reactions with β-dicarbonyl compounds) or pyridylation (in reactions with ketones), depending on the nature of the carbonyl component [5-7].

N-Acylquinolinium salts under similar conditions generally quinolinate both mono- and β-dicarbonyl compounds [4-5]. 1-Acyl-1,4-dihydropyridine derivatives are always formed in reactions with N-acylpyridinium salts, while 2-substituted 1-acyl-1,2-dihydroquinolines are formed with quinolinium salts.

The behavior of other six-membered nitrogen heterocycles in these reactions has not been sufficiently investigated up to now. We studied the reaction of various acetophenones and some other mono- and β-dicarbonyl compounds with benzoyl chloride in the presence of quinoline, isoquinoline, phenanthridine, and acridine. We found that predominant hetarylation of the carbonyl compounds to form N-acyldihydro derivatives of these heterocycles occurs in all cases.



*See [1] for communication X.

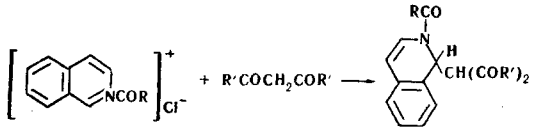
Donets State University, Donets Branch, Academy of Sciences of the Ukrainian SSR. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 643-647, May, 1971. Original article submitted March 10, 1970.

TABLE 1. Substituted N-Benzoyl-1,2-dihydroquinolines (II) and N-Benzoyl-1,2-dihydroisoquinolines (III)

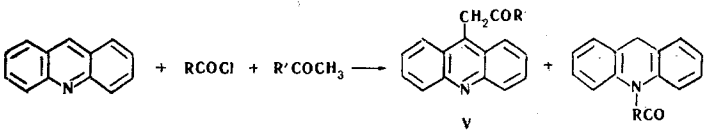
Compound	R	mp	Empirical formula	Found, %			Calc., %			Yield, %	Phenylhydrazones							
				C	H	N	C	H	N		mp	empirical formula	found, %			calc., %			yield, %
													C	H	N	C	H	N	
IIa	C_6H_5	148—149 [b]	$C_{24}H_{19}NO_2$	81,5	5,4	4,1	81,6	5,4	3,9	20	156—157 [c]	$C_{30}H_{25}N_3O$	81,4	5,5	9,5	81,2	5,7	9,5	91
IIb	p-$C_6H_4CH_3$	142—143 [a]	$C_{25}H_{21}NO_2$	81,5	5,7	4,1	81,7	5,8	3,8	31	—	—	—	—	—	—	—	—	—
IIc	m-$C_6H_4NO_2$	171—172 [a]	$C_{24}H_{18}N_2O_4$	72,3	4,5	7,1	72,4	4,5	7,0	12	—	—	—	—	—	—	—	—	—
IId	2-Ketocyclopentyl	150—151 [a]	$C_{21}H_{19}NO_2$	79,3	6,1	4,3	79,5	5,9	4,4	17	—	—	—	—	—	—	—	—	—
IIe	2-Thienyl	163—164 [a]	$C_{22}H_{17}NO_2S$	74,0	5,0	4,0	73,5	4,7	3,9	20	145—146 [c]	$C_{28}H_{23}N_3OS$	74,9	5,3	9,6	74,8	5,1	9,3	93
IIIa	C_6H_5	131—132 [d,e]	$C_{24}H_{19}NO_2$	81,9	5,7	3,7	81,6	5,4	4,0	45	210—212 [f]	$C_{30}H_{25}N_3O$	81,0	5,5	9,2	81,2	5,7	9,5	60
IIIb	p-$CH_3OC_6H_4$	108—109 [g]	$C_{25}H_{21}NO_3$	77,9	5,3	3,8	78,3	5,5	3,6	60	228—230 [f]	$C_{31}H_{27}N_3O_2$	78,5	5,6	8,7	78,6	5,7	8,9	75
IIIc	p-$CH_3C_6H_4$	78—79 [g]	$C_{25}H_{21}NO_2$	81,4	5,6	3,3	81,7	5,8	3,8	76	184—186 [f]	$C_{31}H_{27}N_3O$	81,1	5,8	9,0	81,4	5,9	9,2	80
IIId	p-$C_6H_5C_6H_4$	98—99 [g]	$C_{30}H_{23}NO_2$	83,8	5,7	3,3	83,9	5,4	3,3	83	180—182 [f]	$C_{36}H_{29}N_3O$	83,8	5,8	7,9	83,2	5,6	8,1	80
IIIe	2-Thienyl	130—131 [d]	$C_{22}H_{17}NO_2S$	73,1	4,5	3,9	73,5	4,8	3,9	80	208—210 [f]	$C_{28}H_{23}N_3OS$	75,0	5,1	9,6	74,8	5,2	9,3	80
IIIf	CH_3	104—105 [a]	$C_{19}H_{17}NO_2$	78,0	5,9	5,0	78,3	5,9	4,8	52	174—176 [f]	$C_{25}H_{23}N_3O$	78,6	5,9	10,9	78,7	6,1	11,0	85
IIIg	2-Ketocyclohexyl	112—113 [d]	$C_{22}H_{21}NO_2$	79,7	6,8	4,1	79,7	6,4	4,2	66	208—210 [f]	$C_{28}H_{27}N_3O$	79,5	6,7	9,9	79,8	6,5	10,0	80
IIIh	2-Ketocyclopentyl	140—141 [a]	$C_{21}H_{19}NO_2$	79,8	6,1	4,4	79,5	6,0	4,4	86	203—205 [f]	$C_{27}H_{25}N_3O$	79,3	6,4	10,0	79,6	6,2	10,3	75

[a] From ethanol.
[b] mp 149-150° [4].
[c] From butanol.
[d] From methanol.
[e] 2,4-Dinitrophenylhydrazone, mp 178-180°. Found %: C 67.8; H 4.1; N 13.4. Calculated %: C 67.5; H 4.3; N 13.1.
[f] From hexanol.
[g] From petroleum ether.

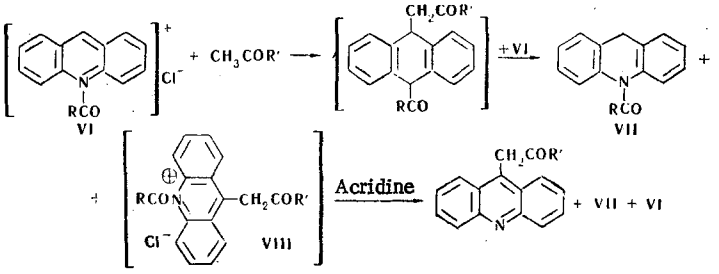
Compounds I-IV do not give picrates and display a double bond (tests with Br_2 and $KMnO_4$), and the IR spectra of all of the compounds have intense absorption bands at 1680 cm^{-1}, which are characteristic for the valence vibrations of the C=O group of aryl ketones, or at 1730 cm^{-1}, which are characteristic for alkyl ketones and cyclohexanone, and at 1650 cm^{-1}, which correspond to the valence vibrations of the C=O group of tertiary amides. In addition, there is an intense band from a C=C bond conjugated with the benzene ring at 1620 cm^{-1} in the IR spectra of these compounds. All of the compounds readily form phenylhydrazones. The hetarylation of β-dicarbonyl compounds proceeds just as readily.



In contrast to this, we unexpectedly obtained 9-phenacylacridines and other ketones of the acridine series in the reaction of acridine and acyl halides with acetophenones and other ketones, even though there is a widespread opinion in the literature that such reactions do not occur with acridine [5].



This sort of method for the preparation of ketones of the acridine series (V) is considerably more convenient than that recently proposed by Hayashi and Nakura [8], and can be recommended as a preparative method. The mechanism of this interesting reaction is apparently similar to the one we described in [9] for the reaction of acridine and acyl halides with dialkyl anilines and consists in the following: the initially formed 9-phenacyl-10-acyl-9,10-dihydroacridine, as a result of removal of a hydride ion by the N-acylacridinium cation in the reaction medium, is converted to the unstable N-acyl salt (VIII), which is decomposed by acridine to form once again the N-acylacridinium salt and V. 10-Benzoylacridine (VII) was isolated along with V.

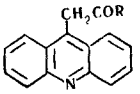


Some of the ketones that we synthesized were identical to those described in [8]. The IR and UV spectra of the unreported V were similar to the spectra of known ketones, which confirms their structure. An intense band at 1700 cm^{-1}, characteristic for the valence vibrations of the C=O group of aryl ketones, is observed in the IR spectra of these compounds. All ketones V form picrates and hydrochlorides with greater difficulty than is the case of I-IV and react with phenylhydrazine. The methylene group in the 9-phenacylacridines and other V ketones, which is activated by the proximity to the carbonyl group and acridine ring, readily reacts with aldehydes to form chalcones. The reaction proceeds smoothly in acetic anhydride, apparently as a consequence of the intermediate formation of an N-acyl salt (VIII) in which the activation of the methylene group is intensified as compared with V [10].

EXPERIMENTAL

The purity of the coal-tar by-products quinoline, isoquinoline, phenanthridine, and acridine was checked by gas-liquid chromatography (with a UKh-1 chromatograph with a 6-m long column, 4 mm in diameter with 0.4% of an ethylene oxide–tetrahydrofuran copolymer on salt as the stationary phase and helium as the gas carrier) and was no lower than 98-99%. A benzene–hexane–chloroform (6 : 1: 30) mixture was used as the eluant in all cases for chromatography in a loose thin layer of activity II aluminum oxide, and the chromatograms were developed with iodine vapors and in UV light. The UV spectra of ethanol solutions were ob-

TABLE 2.



R	mp	Empirical formula	Found, %			Calc., %			Yield, %	Picrate			
			C	H	N	C	H	N		mp	empirical formula	N, % found	N, % calc.
C_6H_5	240—241[a,b]	$C_{21}H_{15}NO$	85,0	5,1	4,7	84,8	5,1	4,7	68	260—261	$C_{21}H_{15}NO \cdot C_6H_3N_3O_7$	10,4	10,6
p-$CH_3C_6H_4$	200—201[c]	$C_{22}H_{17}NO$	85,2	5,5	4,6	84,9	5,5	4,5	61	268—269	$C_{22}H_{17}NO \cdot C_6H_3N_3O_7$	10,4	10,4
2-Thienyl	227—228[d]	$C_{19}H_{13}NOS$	75,4	4,3	4,4	75,2	4,3	4,6	36	261—262	$C_{19}H_{13}NOS \cdot C_6H_3N_3O_7$	11,0	10,5
2-Ketocyclopentyl	208—210[e]	$C_{18}H_{15}NO$	82,4	5,5	6,0	82,7	5,8	5,4	31	280—282	$C_{18}H_{15}NO \cdot C_6H_3N_3O_7$	11,6	11,4

[a]From benzene.
[b]mp 240° [8].
[c]From ethanol.
[d]From amyl alcohol.
[e]From cyclohexane.

tained with an SF-4A spectrometer, while the IR spectra of chloroform solutions or KBr pellets were obtained with a UR-10 spectrometer.

1-Phenacyl-2-(p-phenylbenzoyl)-1,2-dihydroisoquinoline. Diphenyl-4-carboxylic acid chloride [10.8 g (0.05 mole)] was added to a mixture of 12.9 g (0.1 mole) of anhydrous isoquinoline and 6.0 g (0.05 mole) of dry acetophenone, and the mixture was heated at 100° for 5 h. The reaction mass was then steam distilled, and the organic residue was separated and recrystallized from ethanol to give 20.3 g (70%) of substituted 1,2-dihydroisoquinoline with mp 139-140° and R_f 0.26. Found %: C 86.8; H 5.8; N 3.5. $C_{30}H_{23}NO_2$. Calculated %: C 83.9; H 5.4; N 3.3. The phenylhydrazone [mp 195-197° (from hexanol)] was obtained in 70% yield by refluxing a solution of the ketone and phenylhydrazine in glacial acetic acid, and had R_f 0.90. Found %: C 83.2; H 5.6; N 8.2. $C_{36}H_{29}N_3O$. Calculated %: 83.2; H 5.6; N 8.1.

Other keto derivatives of N-benzoyl-1,2-dihydroquinoline and isoquinoline were similarly obtained by the reaction of quinoline and isoquinoline with ketones in the presence of benzoyl chloride (Table 1).

5-Benzoyl-6-phenacyl-5,6-dihydrophenanthridine. This was obtained as described above in 20% yield and had mp 149-150° (from ethanol) and R_f 0.35. Found %: C 82.9; H 5.0; N 3.2. $C_{28}H_{21}NO_2$. Calculated %: C 83.3; H 5.2; N 3.5.

5-Benzoyl-6-acetothienyl-5,6-dihydrophenanthridine. This was similarly obtained in 17% yield and had mp 209-210° (from ethanol) and R_f 0.20. Found %: C 76.4; H 5.0; N 3.6; S 7.8. $C_{26}H_{19}NO_2S$. Calculated %: C 76.3; H 4.7; N 3.4; S 7.8.

9-(2-Ketocyclopentyl)acridine. Cyclopentanone [4.2 g (0.05 mole)] and 7 g (0.05 mole) of benzoyl chloride were added to a solution of 17.9 g (0.1 mole) of acridine in 70 ml of dimethylformamide, and the mixture was heated under nitrogen at 110° for 22 h. The mixture was treated with petroleum ether, washed with ammonia and water, dried, and extracted with ether. The ether-insoluble residue was recrystallized from cyclohexane. Evaporation of the ether yielded 3.1 g of 10-benzoylacridine as colorless crystals with mp 179-181° (from ethanol) [11]. The ketones of the acridine series obtained via the method described above are presented in Table 2.

1-Di(ethoxycarbonyl)methyl-2-benzoyl-1,2-dihydroisoquinoline. Benzoyl chloride [7.0 g (0.05 mole)] was added dropwise to a mixture of 12.9 g (0.1 mole) of isoquinoline and 8.0 g (0.05 mole) of malonic ester, and the mixture was heated at 100° for 3 h. The residue after steam distillation was extracted with ether, the ether extract was dried, and the ether was evaporated to give 11.8 g (60%) of a product with mp 86-87° (from petroleum ether) and R_f 0.32 (mp 87° [5]).

1-Diacetylmethyl-2-benzoyl-1,2-dihydroisoquinoline. This was similarly obtained in 70% yield by the reaction of isoquinoline with acetylacetone and benzyl chloride in a ratio of 2 : 1 : 1 and had mp 92-93° (from methanol) and R_f 0.18. Found %: C 75.7; H 5.8; N 4.4. $C_{21}H_{19}NO_3$. Calculated %: C 75.7; H 5.7; N 4.2.

1-(Acetylethoxycarbonylmethyl)-2-benzoyl-1,2-dihydroisoquinoline. This was similarly obtained in 45% yield and had mp 120-122° (from methanol) and R_f 0.22. Found %: C 72.2; H 5.3; N 3.5. $C_{22}H_{21}NO_4$. Calculated %: C 72.7; H 5.8; N 3.8.

1-(Cyanoethoxycarbonylmethyl)-2-benzoyl-1,2-dihydroisoquinoline. This was obtained as described above in 75% yield and had mp 111-112° (from methanol) and R_f 0.52. Found %: C 73.0; H 5.0; N 8.3. $C_{21}H_{18}N_2O_3$. Calculated %: C 72.8; H 5.2; N 8.1.

1-Benzoyl-2-diacetylmethyl-1,2-dihydroquinoline. This was similarly obtained in 35% yield by the reaction of quinoline with acetylacetone and benzoyl chloride and had mp 136-137° (from ethanol) (mp 138° [5]).

1-Benzoyl-2-(cyanoethoxycarbonylmethyl)-1,2-dihydroquinoline. This was obtained as described above in 15% yield and had mp 149-150° (from butanol). Found %: C 73.0; H 5.3; N 8.2. $C_{21}H_{18}N_2O_3$. Calculated %: C 72.8; H 5.2; N 8.1.

1-Benzoyl-2-di(ethoxycarbonyl)methyl-1,2-dihydroquinoline. This was similarly obtained in 21% yield and had mp 116-117° (from ethanol) and R_f 0.82 (mp 117° [5]).

9-[α-Benzoyl-(p-dimethylaminostyryl)]acridine. A solution of 0.72 g (2.5 mmole) of 9-phenacylacridine and 0.4 g (2.5 mmole) of p-dimethylaminobenzaldehyde in 15 ml of acetic anhydride was refluxed for 4 h, after which the acetic anhydride was removed by steam distillation. The precipitated red crystals were filtered and recrystallized from ethanol to give 0.78 g (72%) of a product with mp 253-254° and R_f 0.7. Found %: C 83.7; H 6.2; N 6.6. $C_{30}H_{24}N_2O$. Calculated %: C 84.1; H 5.7; N 6.5.

LITERATURE CITED

1. A. K. Sheinkman, A. K. Tokarev, and S. N. Baranov, Khim. Geterotsikl. Soedin., 82 (1971).
2. L. Cleisen and E. Haase, Ber., 33, 1242 (1900).
3. S. McElvain and D. Kundiger, J. Am. Chem. Soc., 64, 254 (1942).
4. P. Wright and W. McEwen, J. Am. Chem. Soc., 76, 4540 (1959).
5. H. V. Dobeneck and W. Joltzsche, Chem. Ber., 95, 1484 (1962).
6. W. V. Doering and W. McEwen, J. Am. Chem. Soc., 73, 2104 (1951).
7. E. Ghigi, Ber., 73, 677 (1940); 75, 764 (1942).
8. E. Hayashi and T. Nakura, J. Pharm. Soc. Japan, 87, 570 (1967).
9. A. K. Sheinkman, S. G. Potashnikova, and S. N. Baranov, Zh. Organ. Khim., 6, 614 (1970).
10. A. N. Kost, A. K. Sheinkman, and A. N. Rozenberg, Zh. Obshch. Khim., 34, 4046 (1964).
11. K. Bauer, Ber., 83, 10 (1950).