

HETARENES WITH A NITROGEN BRIDGING ATOM

1.* PHENACYLATION OF 2-SUBSTITUTED

6-METHYLPYRIDINES

E. V. Babaev, A. V. Efimov, and D. A. Maiboroda

The reaction of 2-X-6-methylpyridines (X = Cl, Br, OMe, OH, ONa) with phenacyl bromides has been studied. It was shown that for X = Cl or Br the reaction products unexpectedly proved to be the previously unknown 5-methyl homologs of oxazolo[3,2-a]pyridinium, the structure of which was confirmed by spectral data and by an alternate synthesis using the acid cyclization of N-phenacyl-6-methylpyrid-2-one. The model compound required for the alternate synthesis was obtained by the phenacylation of 2-methoxy-6-methylpyridine, 6-methylpyrid-2-one, and its sodium salt. Competition between N- and O-alkylation was observed in the last two cases. The structures of the N- and O-isomers were assigned on the basis of spectral data and by comparison with the spectra of the lower homologs.

Azolopyridines with a nitrogen bridging atom and their cations represent a class of heteroaromatic structures interesting both from a theoretical point of view and for the study of their pharmacology. The traditional method of synthesizing the simplest representatives of this class, such as the indolizines or imidazo[1,2-a]pyridines, is that of Chichibabin, viz. the reaction of α -substituted (alkyl or amino) pyridines with α -haloketones [1, 2]. The first stage of this reaction is alkylation of the pyridine nucleus with the formation of salt (I), which readily undergoes cyclocondensation. The synthetic principle thought to be at the basis of this method, which consists of the buildup of a 5-membered ring on the N=C-X fragment, is not restricted to α -methyl or α -amino derivatives of pyridine.

The substituent X may, for example, be the oxygen atom of α -pyridones or α -alkoxy-pyridines. The resulting alkylation products (II) serve as precursors of oxazolo[3,2-a]pyridinium cations (III). An interesting variant of this scheme of synthesis is the reaction of α -halopyridines with α -haloketones. The resulting N-(β -oxoalkyl)-2-halopyridinium salts (I) are promising precursors for further heterocyclizations, particularly for the formation of the bridged azolopyridines (III) and their cations [2].

A little studied area of application of this scheme is the reaction of α -haloketones with pyridines containing two α groups. It is natural to expect that the first reaction step, alkylation of a 2,6-disubstituted pyridine, must proceed with difficulty for steric reasons and alkylation at an exocyclic heteroatom in the α position may be a competing process. Theoretically, any α -substituent may participate at the second stage, the cyclocondensation reaction.

There are only individual literature examples of investigations in this area. Low yields of salt (I) are recorded in the Chichibabin synthesis of indolizines from 2,6-lutidine [3]. When using the unsymmetrical 3-nitro-2,6-lutidine cyclocondensation proceeds with the participation of both α -alkyl groups [4]. The expected 5-substituted imidazo[1,2-a]pyridines are formed by the reaction of 2,6-diamino-, 2-amino-6-chloro- [5], and 2-amino-6-methylpyridines [6] with aliphatic haloketones. There are data confirming that 2-amino-6-methylpyridine is capable of competing alkylation at the amino group when using α -chlorocyclohexane [7], but in reactions with phenacyl bromide the alternate cyclocondensation involving the methyl group occurs [8-10]. Reactions of 6-aminopyrid-2-one [5], 6-methyl-2-phenoxy- [11], and 2-arylthio-6-methylpyridines [12] with haloketones were unsuccessful. The O-alkylation of 6-methylpyrid-2-one silver salt with bromo-acetaldehyde acetal has been described [13]. A mixture of N- and O-alkylation products was formed on phenacylation of 3-cyano-4,6-dimethylpyrid-2-one [14].

M. V. Lomonosov Moscow State University, Moscow 119899. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1104-1111, August, 1995. Original article submitted July 9, 1995.

TABLE 1. Characteristics of Compounds (IIa-d), (IIIa-d), (VII)

Compound	Empirical formula	Calculated %			mp, °C	Yield, %	Method	UV Spectrum (ethanol) λ_{\max} nm (log ϵ)	PMR Spectrum δ , ppm (TMS)	IR spectrum, cm^{-1}	
		Found %	C	H						N	ν C=O (phen-acyl)
IIa	$\text{C}_{13}\text{H}_{11}\text{NO}_2$	—	—	—	—	—	203 (4,31), 234 (4,15), 301 (3,71)	5.4 (2H, s, CH_2); 6.2 (1H, t, H-5); 6.6 (1H, d, H-3); 7.1-8.1 (7H, m, Ph, H-4, H-6)	1719	1677	
IIb	$\text{C}_{13}\text{H}_{10}\text{BrNO}_2$	—	—	—	—	—	200 (4,37), 256 (4,12), 307 (3,49)	—	1707	1675	
IIc	$\text{C}_{14}\text{H}_{13}\text{BrNO}_2$	—	—	—	96...97	C	204 (4,24), 235 (4,17), 307 (3,85)	2.23, (3H, s, CH_3); 5.53 (2H, s, CH_2); 6.1 (1H, d, H-5); 6.5 (1H, d, H-3); 7.1-8.1 (6H, m, Ph, H-4)	1708	1670	
IIId	$\text{C}_{14}\text{H}_{12}\text{BrNO}_2$	54.9 54.8	4.0 4.1	4.6 4.5	131...132	C D	197 (4,3), 256 (3,95), 311 (3,41)	2.2 (3H, s, CH_3); 5.4 (2H, s, CH_2); 6.07 (1H, d, H-5); 6.4 (1H, d, H-3); 7.3 (1H, q, H-4); 7.77 (4H, m, Ar)	1702	1675	
VII	$\text{C}_{14}\text{H}_{12}\text{BrNO}_2$	54.9 55.5	4.0 4.1	4.6 4.3	100...101	D E	200 (4,3), 256 (4,16)	CDCl ₃ : 2.30 (3H, s, CH_3); 5.50 (2H, s, CH_2); 6.70 (2H, d, H-3, H-5); 7.47 (1H, t, H-4); 7.62 (2H, d, Ph); 7.88 (2H, d, Ph). CF_3COOH : 2.80 (3H, s, CH_3); 5.90 (2H, s, CH_2); 7.26 (1H, d, H-5); 7.40 (1H, d, H-3); 8.40 (1H, t, H-4); 7.75-7.95 (4H, m, Ar)	1725	—	
IIIa	$\text{C}_{13}\text{H}_{10}\text{ClNO}_5$	—	—	—	218...219	B	205 (4,31), 297 (4,31)	H-3: 8.63 (s); H-5: 8.97 (d); H-6: 7.91 (t); H-7: 8.44 (t); H-8: 8.16 (d); H-9: 9.0 (d)	J ₅₇ : 1.3	J ₆₈ : —	
IIIb	$\text{C}_{13}\text{H}_6\text{ClNO}_5$	—	—	—	259...260	B	204 (4,46), 245 (3,95), 302 (4,42)	H-3: 8.7 (s); H-5: 9.00 (d); H-6: 7.92 (t); H-7: 8.44 (t); H-8: 8.14 (d); H-9: 8.9 (d)	J ₅₆ : 6.5	J ₇₈ : 0.8	
IIIc	$\text{C}_{14}\text{H}_{12}\text{ClNO}_5$	54.3 54.5	4.5 4.3	3.9 3.98	216...217	A B	205 (4,34), 298 (4,31)	H-3: 8.48 (s); H-5: —; H-6: 7.70 (d); H-7: 8.33 (d); H-8: 8.01 (d); H-9: 9.0 (d)	J ₅₆ : —	J ₇₈ : 0.8	
IIIId	$\text{C}_{14}\text{H}_{11}\text{BrClNO}_5$	43.3 42.9	2.9 2.9	3.6 3.1	308...309	B	205 (4,46), 242 (4,03), 302 (4,41)	H-3: 8.52 (s); H-5: —; H-6: 7.70 (d); H-7: 8.33 (d); H-8: 8.00 (dd); H-9: 8.8 (dd)	J ₅₆ : —	J ₇₈ : —	

The phenacylation of the simplest 2-X-6-methylpyridines, where X is a heteroatom of halogen, an oxo, or an alkoxy group has not been reported. On the other hand quaternary N-phenacyl salts containing α -halo and α -methyl groups in the pyridine ring simultaneously may serve as interesting subjects for studying ambident cyclization. In particular the cyclocondensation products of such compounds might be hitherto unknown representatives of 5-substituted indolizines. It is difficult to imagine that steric-electronic reasons serve as a dramatic obstacle to the first reaction step in the case of 2-halo-6-picolines. The methylation of 2-chloro(bromo)-6-methylpyridines is well known [15]. Study of the reaction kinetics unexpectedly showed a higher alkylation rate for the chloro than for the bromo derivative [16], in contrast to the basicities of these halopicolines.

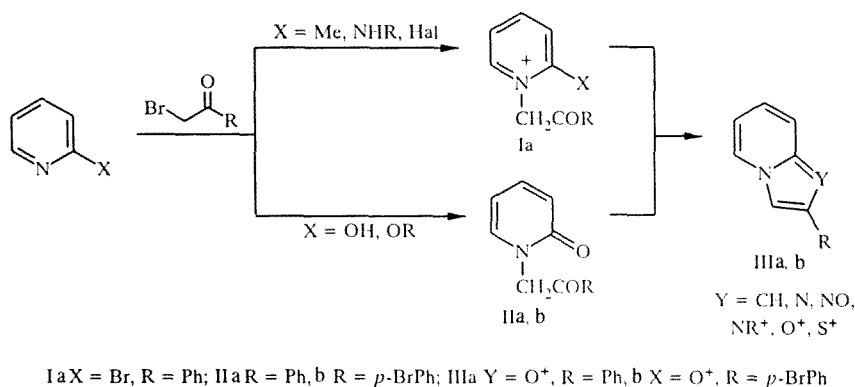
A systematic analysis has been carried out for the first time in the present study of the reaction of 2-substituted 6-methylpyridines (having groups containing oxygen or halogen at position 2) with phenacyl bromides.

As is known, the quaternization of pyridines occurs readily in the cold or on heating in suitable solvents in which the ionic compounds formed are insoluble. It turned out that the reaction of 2-bromo-6-methylpyridine (IVa) with phenacyl bromide (Va) proceeds with difficulty under the usual conditions. The reaction does not proceed in the cold or on boiling in acetone or toluene and in boiling acetone only trace quantities of product were formed even after 40 h. Nonetheless the formation of a significant quantity of crystals was observed on short boiling of a mixture of the reactants in nitrobenzene at 150-190°C.

The reaction product proved to be a mixture of two ionic compounds from which one readily sublimed. Sublimation in vacuum proved to be the only convenient method affording complete separation of the obtained mixture. The volatile component was the hydrobromide (VIa) of the initial 2-bromo-6-methylpyridine. It was converted readily into the initial pyridine by base and was identical with the salt obtained by passing HBr gas into an ether solution of the bromopicoline. The involatile residue differed from the expected N-phenacylpyridinium salt (Ic) in spectral properties, but the expected singlet at 6.5 ppm for the methylene group was absent from the PMR spectrum. This singlet (6.67 ppm) is a characteristic of the lower N-phenacyl-2-bromopyridinium homolog (Ia). Bands for the carbonyl group were generally absent from the IR spectrum. In addition, retention in the spectrum of the singlet signal of the methyl group excluded the products of condensation at the alkyl group, particularly indolizines, from the structures possible. Furthermore, the ionic substance obtained was readily converted into a poorly soluble perchlorate, which contained no covalently bound bromine on elemental analysis. The PMR spectra of the initial bromide and of the obtained perchlorate proved to be identical.

It is known from the literature that N-phenacyl-2-bromopyridinium salts (Ia, b) are able to undergo intramolecular cyclization under the action of tertiary amines with the formation of the oxazolo[3,2-a]pyridinium cation (IIIa, b) [17]. It was assumed correctly that the analogous cyclization also occurs for the homologous salt (Ic), the formation of which we expected. On the same basis the initial pyridine (IVa) may be capable of enolization at the N-phenacyl group bringing about a subsequent cyclization. In this case the reaction product must be the previously unknown homolog 5-methyl-2-phenyloxazolo[3,2-a]pyridinium (IIIc) and the reaction byproduct is the hydrobromide (VIa) of the initial pyridine.

Scheme 1



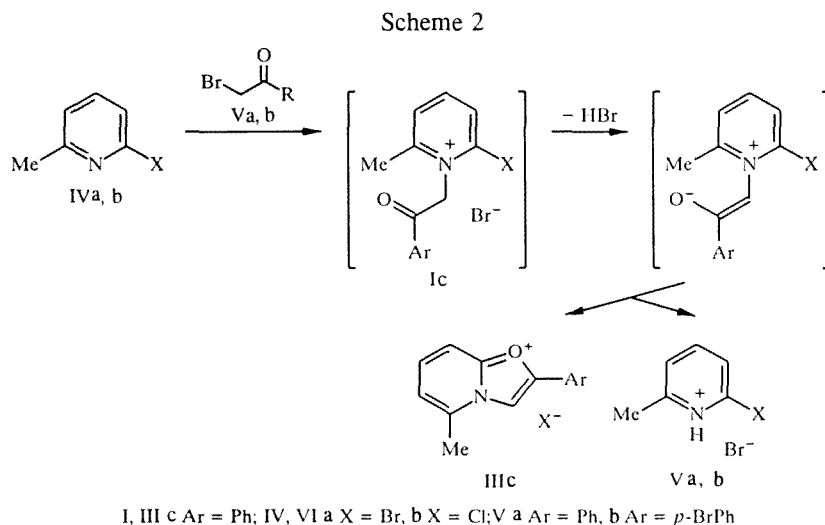
In reality the spectral properties of the involatile compound were in accordance with this hypothesis. The UV spectrum of compound (IIIc) proved to be practically identical with the spectrum of the lower homolog, the oxazolopyridinium salt (IIIa) (Table 1). It is seen by comparing the PMR spectra (Table 1) of the cations that on going from the lower (IIIa) to the higher (IIIc) homolog the doublet at low field for the 5-H proton (8.97 ppm) disappears with the simultaneous appearance of a singlet

for the position 5 methyl group at 3.01 ppm. A singlet for the 3-H proton of the oxazole fragment was observed at 8.6-8.7 ppm in the spectra of both homologs.

It follows from the scheme that the reaction result may be similar when using picolines with other α substituents, which act as leaving groups at the cyclization stage. In fact, when using another halopicoline, viz. 2-chloro-6-methylpyridine (IVb), as initial reactant the same oxazolopyridine (IIIc) was formed with phenacyl bromide and was characterized as the perchlorate. On reacting both halopicolines with a different haloketone, *p*-bromophenacyl bromide (Vb), a mixture of salts was formed. In this case however, the resulting oxazolopyridinium salt (IIId) failed to be purified by sublimation. The salt proved to be thermally unstable and on heating the mixture decomposed significantly.

For final confirmation of the structure of cation (IIIc), and also for the purpose of investigating the effect of other α substituents on the course of the reaction, we studied the interaction of haloketones with α -picolines containing an oxygen-containing substituent at the α position. It is known from the literature [18] that oxazolopyridinium salts such as (IIIa, b) are obtained conveniently by the acid cyclization of *N*-phenacylpyrid-2-ones (IIa, b). It is evident that the precursor of salt (IIIc) must be *N*-phenacyl-6-methylpyrid-2-one (IIc), which in its turn might be obtained by the *N*-phenacylation of 6-methylpyrid-2-one (IVc) or its sodium salt.

It turned out that phenacyl bromide (Va) reacts with the methylpyridine (IVc) and its sodium salt (IVb) in a complex manner. The formation of a large number of resinous products was observed. Nevertheless, in similar reactions of another haloketone, *p*-bromophenacyl bromide (Vb), with the pyridone (IVc) in acetonitrile [or with the pyridone sodium salt (IVb) in DMF] we successfully isolated and preparatively separated two substances, the spectral properties of which corresponded to the products of *O*- and *N*-phenacylation.

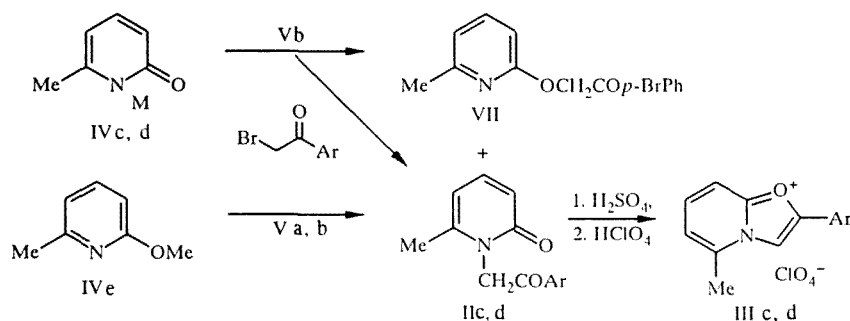


The data of the PMR spectra (Table 1) did not permit unequivocal assignment of the isomers as the products of *O*- or *N*-phenacylation. An effective means of distinguishing the isomers proved to be the IR and UV spectra in juxtaposition with the spectra of the lower homolog *N*-(*p*-bromophenacyl)pyrid-2-one (IIb) synthesized by the known method of [18]. The UV spectrum of one of the obtained isomers (IIc) was practically identical with the spectrum of the lower homolog (IIb) (see Table 1) which points in favor of the phenacyl group being located on the nitrogen atom. This same isomer displayed in the IR spectrum two characteristic frequencies for the vibrations of both the pyridone amide group (1675) and the carbonyl group (1702 cm^{-1}). In the lower homolog these values were 1675 and 1707 cm^{-1} respectively. In the spectrum of compound (VII), assigned as the *O*-isomer, the only frequency observed was for vibrations of a carbonyl group (1726 cm^{-1}). In the PMR spectrum of the *O*-isomer (VII) (in CDCl_3) a remarkable effect was observed in the superposition of two doublets for the H-3 and H-5 protons, leading to an unusually clearly expressed pseudo-doublet of doubled intensity. The signals of the H-3 and H-5 protons in the simpler prototype model of *O*-alkylation, 2-methoxy-6-picoline, also differed insignificantly. Recording of the spectrum of the *O*-isomer (VII) in trifluoroacetic acid enabled spreading of the single signal into two overlapping doublets.

The results obtained showed that phenacylation of the pyridone occurs nonselectively and is not a preparative reaction. This stimulated us to study the phenacylation of 2-methoxy-6-picoline (IVe) which may be expected to form *N*-phenacylpyridones exclusively. It was shown previously that 2-methoxypyridines give *N*-phenacylpyridones with phenacyl bromide [18].

Steric difficulties probably do not have a serious effect. In particular 2-methoxyquinoline, resembling 2-methoxy-6-picoline in the steric environment of the nitrogen atom, is phenacylated in 38% yield [18]. It turned out that the methoxypicolone (IVe) reacted with p-bromophenacyl bromide (Vb) in acetonitrile in acceptable yield forming a substance identical in properties with isomer (IIc) to which we assigned above the structure of N-(p-bromophenacyl)-6-methylpyrid-2-one. As was shown the unsubstituted phenacyl bromide (Va) reacts similarly forming the described N-phenacyl-6-methylpyrid-2-one (IIc). The IR and UV spectra of the latter again proved to be extremely similar to the spectra of the corresponding lower homolog (IIa) (see Table 1).

Scheme 3



Finally we were able to effect an alternate synthesis of the oxazolopyridinium salts (IIIc, d) with the desired alternative precursors of the homologs. Cyclization of the phenacylpyridones (IIc, d) was carried by analogy with the procedure for the lower homologs (IIa, b) [18], by the sequential action of sulfuric and then perchloric acids. In its turn 5-methyl-2-phenyloxazo[3,2-a]pyridinium bromide (IIIc) [obtained previously from the bromopicoline (IVa)] was converted into the poorly soluble perchlorate, proving to be identical in melting point and IR spectral data (fingerprint region) with the perchlorate obtained by the cyclization of the corresponding phenacylpyridone (IIc). The characteristics of the perchlorates (IIIa-d), including their UV and PMR spectra, are given in Table 1.

The data presented therefore indicate that on phenacylation of 2-halo-6-methylpyridines the sequences of a slow step of quaternization and rapid steps of deprotonation and condensation of the yield generally exclude the possibility of isolating salts of type (Ic) and studying their reactivity. The available N-phenacyl-6-methylpyrid-2-ones may therefore be the only reasonable precursors for the class of 5-substituted indolizines when using the Chichibabin scheme. Preparative experiments showed that intensely fluorescent products are formed on reacting both pyridones (IIc, d) and oxazolopyridinium salts (IIIc, d) with bases. Study of the nature of such conversions will be the subject of a separate communication.

EXPERIMENTAL*

The IR spectra were recorded on a UR 20 instrument in Nujol, the UV spectra were taken on a Varian K325 instrument, and the PMR spectra were obtained on Tesla 467 (60 MHz) and Bruker AM 400 (400 MHz) instruments, the internal standard being tetramethylsilane. Solvents were CCl₄, CDCl₃, and CF₃COOH. A check on the progress of reactions was effected by TLC on Silufol UV 254 plates. Chromatographic separation was carried out on Silpearl columns. The characteristics of the compounds obtained are given in Table 1.

Preparation of Oxazolo[3,2-a]pyridines

A. Reaction of Phenacyl Bromides with 2-Halo-6-methylpyridines. A mixture of 2-bromo-6-picoline (IVa) (0.1 mole) and phenacyl bromide (Va) (0.12 mole) in absolute nitrobenzene (30 ml) was heated for 1 h at 170-190°C. The solution dark

*A. Kaznacheev, a student, participated in this.

ened and a significant quantity of greenish crystals was formed. Benzene (200 ml) was added to the mixture, which was then left overnight. The resinous solid was filtered off, washed with benzene, then with a small amount of ethanol. The resulting mixture of salts was dried and heated under vacuum in a sublimation apparatus at 150-250°C. Crystals of the hydrobromide of the initial 2-bromo-6-picoline sublimed. The residue from the sublimation was recrystallized from ethanol. The 5-methyl-2-phenyloxazolo[3,2-a]pyridinium bromide obtained (11%, mp 218-220°C) was converted into the perchlorate (73%) with perchloric acid. The PMR spectra of the bromide and perchlorate in CF₃COOH were identical.

Replacement of the solvent by acetonitrile (50 h boiling) reduced the resinification of the reaction mixture. After similar processing 5-methyl-2-phenyloxazolo[3,2-a]pyridinium bromide was obtained in 6% yield.

A similar reaction of 2-chloro-6-picoline (78 mmole) and phenacyl bromide (80 mmole) in acetonitrile gave 1.34 g involatile residue (mp 238°C) after work-up and sublimation. This residue was converted with perchloric acid into 5-methyl-2-phenyloxazolo[3,2-a]pyridinium perchlorate, identical with that obtained in the previous experiments.

In the similar reaction of 2-bromo-6-picoline and p-bromophenacyl bromide the resulting crystalline product decomposed completely on sublimation.

B. Acid Cyclization of N-Phenacylpyrid-2-ones. A solution of N-phenacylpyridone (1 mmole) in concentrated sulfuric acid (1 ml) was kept overnight. Dry diethyl ether (20-30 ml) was then added with cooling. The precipitated solid was filtered off, dissolved in water (5-10 ml), and excess HClO₄ was added to the solution. The precipitated perchlorate was recrystallized from an ethanol-water (4:1) mixture.

Preparation of N-Phenacylpyrid-2-ones

C. Phenacylation of 2-Methoxy-6-methylpyridine. N-(p-Bromophenacyl)-6-methylpyrid-2-one. A mixture of 2-methoxy-6-methylpyridine (19.5 mmole) and p-bromophenyl bromide (19.6 mmole) was dissolved in acetonitrile (20 ml). The solution was boiled for 24 h and the solvent then evaporated under vacuum. The brown resinous residue obtained was chromatographed on a column of Silpearl. Initial elution with 1,2-dichloroethane removed a fraction containing the starting materials, resinification products, and a little N-(p-bromophenacyl)-6-methylpyrid-2-one. On subsequent elution with a mixture of acetone and petroleum ether (1:1) a bright yellow fraction was obtained which contained mainly N-(p-bromophenacyl)-6-methylpyrid-2-one. After evaporation, the residue was washed with petroleum ether.

N-Phenacyl-6-methylpyrid-2-one was obtained similarly by the reaction of phenacyl bromide with 2-methoxy-6-methylpyridine by boiling for 48 h in acetone. Yield was 14%. mp 96°C.

D. Reaction of p-Bromophenacyl Bromide with 6-Methylpyrid-2-one Sodium Salt. p-Bromophenacyl bromide (6 g) was added to a solution of 6-methylpyrid-2-one sodium salt (3 g) (obtained by the reaction of the pyridone with sodium ethylate in ethanol and separation of the precipitated solid) in DMF (20 ml). After 5 min the reaction mixture was poured into dilute HCl (pH 3: 60 ml) and the precipitated solid filtered off. The mother liquor was made alkaline to pH 11 and the precipitated solid separated off. The solid was dried and chromatographed on a column with benzene, then with a benzene-acetone (2:1) mixture. 2-(p-Bromophenacyloxy)-6-methylpyridine (0.32 g: 5%) of mp 100°C was isolated from the first fraction (benzene) and N-(p-bromophenacyl)-6-methylpyrid-2-one (0.1 g: 1.5%) of mp 123°C from the second. The second substance was identical in properties (IR and PMR spectra, chromatographic mobility) with the compound obtained from the reaction of p-bromophenacyl bromide with 2-methoxy-6-methylpyridine.

E. Reaction of p-Bromophenacyl Bromide with 6-Methylpyrid-2-one. 6-Methylpyrid-2-one (0.5 g: 4.6 mmole) and p-bromophenacyl bromide (1 g: 3.6 mmole) were dissolved in acetonitrile (20 ml), and the solution boiled for 33 h. The acetonitrile was evaporated, the residue was treated with saturated sodium bicarbonate solution (5 ml), and the solid residue was washed with water. It was then chromatographed on a column with benzene, and then with a benzene-acetone (1:1) mixture. The crude product (0.2 g: 20%) of N-phenacylation was isolated from the second and was identical on TLC with the product from the previous experiment. The reaction yields were not optimized.

REFERENCES

1. A. E. Tschitschibabin, Chem. Ber., **59**, 2084 (1926).
2. A. R. Katritzky and C. W. Rees (eds.), Comprehensive Heterocyclic Chemistry, Vols. 1-7, Pergamon, Oxford (1984).

3. D. O. Holland and J. H. C. Nayler, *J. Chem. Soc.*, No. 6, 1657 (1955).
4. S. I. Bobrovskii, E. V. Babaev, and Yu. G. Bundel', *Khim. Geterotsikl. Soedin.*, No. 2, 203 (1987).
5. J. P. Paolini and R. K. Robins, *J. Heterocycl. Chem.*, No. 2, 53 (1965).
6. L. Almirante, A. Mugnaini, L. Polo-Fritz, and E. Provincial, *Boll. Chim. Farm.*, **105**, 32 (1966).
7. A. J. Eliot, H. Guzik, and J. R. Soler, *J. Heterocycl. Chem.*, No. 19, 1437 (1982).
8. F. Mattu and E. Marongiu, *Rend. Seminario Fac. Sci. Univ. Cagliari*, **34**, 190 (1964).
9. F. Mattu and E. Marongiu, *Rend. Seminario Fac. Sci. Univ. Cagliari*, **34**, 291 (1964).
10. F. Mattu, *Ann. Chim. (Rome)*, **54**, 496 (1964).
11. C. K. Bradsher, L. D. Quin, and R. E. Leblen, *J. Org. Chem.*, **21**, 3273 (1961).
12. C. K. Bradsher and J. W. McDonald, *J. Org. Chem.*, **27**, 4478 (1962).
13. P. I. Abramenko and V. G. Zhiryakov, *Khim. Geterotsikl. Soedin.*, No. 11, 1544 (1972).
14. K. Gewald and H. J. Jansch, *J. Prakt. Chem.*, **318**, 313 (1966).
15. G. V. Boyd and N. Singer, *J. Chem. Soc. B*, 1017 (1966).
16. K. Waisser, F. Rubacek, R. Karlicek, J. Sova, M. Celednik, and K. Palat, *Pharmazie (Berlin)*, **34**, 197 (1979).
17. C. K. Bradsher, R. D. Brandau, J. E. Boliek, and T. L. Hough, *J. Org. Chem.*, **34**, 2129 (1969).
18. C. K. Bradsher and M. F. Zinn, *J. Heterocycl. Chem.*, No. 4, 66 (1967).