REACTIONS OF 6-METHOXY-1,2,3,4-TETRAHYDRO-β-CARBOLIN-1-ONES AND THEIR DICHLOROPHOSPHORYL-SUBSTITUTED DERIVATIVES WITH ACETIC ANHYDRIDE

SYNTHESIS OF 5-ACETYL DERIVATIVES OF THE β-CARBOLINE SERIES

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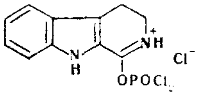
2-Benzyl-, 9-benzyl-, and 2,9-dibenzyl-6-methoxy-1,2,3,4-tetrahydro-β-carbolin-1-ones were synthesized. It is shown that 6-methoxy-1,2,3,4-tetrahydro-β-carbolin-1-one and its 2- and 9-monobenzyl-substituted derivatives react with phosphorus oxychloride to give dichlorophosphoryl derivatives in which the dichlorophosphoryl residue enters into the composition of the cation and is bonded to the oxygen in the 1 position or (in the case of the pyrrole-nitrogen-unsubstituted compounds) the nitrogen atom in the 9 position. The possibility of acetylation of the dichlorophosphoryl compounds in the 5 position with acetic anhydride under mild conditions to give high yields of products was observed. The regularities in the mass spectra and PMR spectra of the β-carbolinone derivatives were exposed.

Activation of the carbonyl group in the 1 position of the tetrahydro-β-carbolinone system seems of considerable interest for the development of synthetic research involving substituted β-carbolinones. The formation of a complex in the reaction of 1,2,3,4-tetrahydro-β-carbolin-1-one with phosphorus oxychloride, to which structure A [2], B, or C [3] was subsequently assigned, was described in a German patent [1] in 1958, but the possibility of the formation of an N-dichlorophosphoryl derivative was not excluded [4]. As a result of synthetic investigations, it was found that the complex reacts readily with nucleophilic agents (alcohols and amines) to give the corresponding 1-alkoxy- and 1-alkyl(or dialkyl)amino derivatives of β-carbolines.



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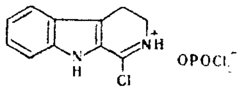

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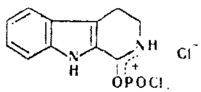

C

It seemed of interest to us to make a more detailed study of the reaction of phosphorus oxychloride with tetrahydro-β-carbolin-1-ones having different degrees of substitution of the hydrogens attached to both nitrogen atoms and also to investigate the reactions of dichlorophosphoryl derivatives and the starting tetrahydro-β-carbolin-1-ones with electrophilic agents, for example, with acetic anhydride.

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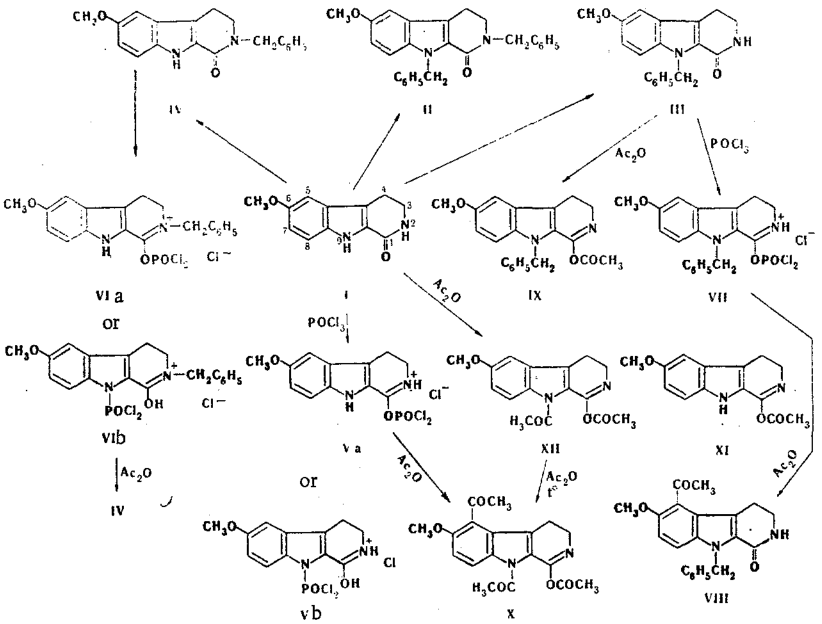
These investigations were conducted most conveneintly on the basis of the accessible 6-methoxy-1,2,3,4-tetrahydro-β-carbolin-1-one (I), which is an intermediate in the synthesis of the medicinal preparation mexamine (5-methoxytryptamine hydrochloride) [5]. Carbolinone II, with both nitrogen atoms substituted by benzyl residues, was obtained by conversion of carbolinone I in liquid ammonia to the disodium derivative and treatment of the latter with benzyl chloride in refluxing toluene. The N-benzyl derivative with respect to the indole nitrogen atom (III) was synthesized by treatment of the monosodium derivative with benzyl chloride in dimethylformamide (DMF).



Isomeric mono-N-benzyl derivatives III (ν_{CO} 1668, ν_{NH} 3320, 3220, and 3100 cm^{-1}) and IV (ν_{CO} 1640 and ν_{NH} 3225 cm^{-1}) have different IR spectra. The frequencies of the stretching vibrations of the carbonyl groups in III and in nonbenzylated I (ν_{CO} 1666 cm^{-1}) are similar but differ from the frequencies for IV. It is well known that the ν_{CO} frequencies (1670 cm^{-1}) are higher for cyclic lactams having a secondary nitrogen atom than for lactams with a tertiary nitrogen atom (ν_{CO} 1640 cm^{-1}), and this is in agreement with the attachment of the benzyl residue to $N_{(9)}$ in III and to $N_{(2)}$ in IV. As one should have expected, the bands characteristic for NH groups are absent in the IR spectra of dibenzyl derivative II, and the ν_{CO} band is observed at 1644 cm^{-1}. To obtain dichlorophosphoryl derivatives, we heated I, II, III, and IV with excess freshly distilled phosphorus oxychloride. The reaction with phosphorus oxychloride did not occur only in the case of dibenzyl derivative II, and starting tetrahydro-β-carbolinone II was recovered from the reaction mixture in high yield. In all of the remaining cases we obtained dichlorophosphoryl derivatives V-VII, and the substances were isolated immediately from the reaction mixtures and were suitable for elementary analysis and spectral investigations without additional purification. In addition, one should note that dichlorophosphoryl compounds V-VII are extremely unstable and are converted to the corresponding tetrahydrocarbolinones (I, III, and IV) by the action of water or alcohol containing even traces of water.

Inasmuch as the dichlorophosphoryl residue in the investigated compounds is not replaced by $SbCl_6^-$ on reaction with antimony pentachloride via the Arnold-Holy method [6], it can be asserted that the dichlorophosphoryl portion of these molecules is not an anion. The disappearance in the IR spectra of intense absorption bands at 1640-1670 cm^{-1} on passing from carbolinones I, III, and IV to their dichlorophosphoryl derivatives (V-VII) attests to the absence of amide carbonyl groups in the reaction products, and the appearance of a band at 1610 cm^{-1} can be ascribed to the absorption of a strongly polarized $\overset{+}{N}=C-O$ double bond. In the case of VII, the data obtained make it possible to unambiguously establish its structure. In the case of V and VI, in which the pyrrole nitrogen atom is not blocked by a benzyl group, in addition to the structure of dichlorophosphoryl derivatives Va and VIa, alternative dichlorophosphamide structures Vb and VIb are not excluded.

Interesting results were obtained by reaction of dichlorophosphoryl compounds V-VII with acetic anhydride. In VII, in which the 1, 2, and 9 positions are blocked with respect to attack by an electrophilic reagent, acetylation proceeds selectively in the 5 position under mild conditions to give 5-acetyl-6-methoxy-

TABLE 1. PMR Spectra of the Synthesized Compounds in Deuterodimethyl Sulfoxide

Compound	Chemical shifts									Spin-spin coupling constants, Hz		
	1-R	2-R	3-H_2	4-H_2	5-R	6-R	7-H	8-H	9-R	$J_{3,4}+J_{3,4}$	$J_{5,6}$	$J_{7,8}$
I	—	7,47	3,53	2,90	7,00	3,77	6,84	7,29	11,4	~13	2,5	9
III	—	7,58	3,42	2,92	7,0—7,2	3,75	6,87	7,31	5,81 (CH_2) 7,0—7,2 (Ph)	~13	2,5	9
VIII	—	7,67	3,32	2,72	2,56	3,85	7,07	7,48	5,86	~13	—	9
IX	2.46	—	4,18	3,01	7,1—7,2	3,77	7,00	7,39	5,80 (CH_2) 7,1—7,2 (Ph)	~13	2,5	9
X	2,53—2,59	—	4,16	2,76	2,53—2,59	3,91	7,35	8,15	2,53—2,59	~13	—	9
XI*	2,66	—	4,34	3,03	6,99	3,84	7,03	7,29	—	~13	2,5	9
XII	2,55—2,61	—	4,23	2,98	7,18	3,83	7,13	7,99	2,55—2,61	~13	2,5	9

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*The spectrum was recorded in deuterochloroform.

1,2,3,4-tetrahydro-β-carbolin-1-one (VIII) in practically quantitative yield. The 5 position is apparently activated in VII by the dichlorophosphoryl residue, inasmuch as direct acetylation of tetrahydrocarbolinone III gives only 1-acetoxy derivative IX. Reaction in the 5 position of the carboline molecule does not occur in this case. A similar reaction of dichlorophosphoryl compound VI with acetic anhydride is accompanied only by removal of the dichlorophosphoryl grouping, and the starting 2-benzyl-6-methoxy-1,2,3,4-tetrahydro-β-carbolin-1-one (IV), like the analogous 2,9-dibenzyl derivative (II), does not react with acetic anhydride even on refluxing.

On the other hand, in the case of dichlorophosphoryl derivative V, which does not have protective benzyl groups attached to the nitrogen atoms, acetylation with acetic anhydride proceeds extremely vigorously to give triacetyl derivative X, which has acetyl groups attached to the oxygen atom in the 1 position, the nitrogen atom in the 9 position, and the carbon atom in the 5 position, The same triacetyl derivative (X) (containing monoacetate XI) is formed by refluxing carbolinone I with acetic anhydride. Under mild conditions – at room temperature – I gives only O,N-diacetate XII, which is converted to triacetate X on heating with acetic anhydride. In this case, the introduction of two strong electron-acceptor groupings (two acetyl residues in XII or one dichlorophosphoryl group and one acetyl group in the acetylation of V) in the 1 and 9 positions of the carbolinone molecule apparently also activates the 5 position of the molecule, as does the presence of a dichlorophosphoryl substituent in VII.

A mass-spectral study of isomeric VIII and IX showed that both compounds have molecular weights of 348 corresponding to monoacetyl derivatives of 9-benzyl-6-methoxy-1,2,3,4-tetrahydro-β-carbolin-1-one. The presence in both spectra of an intense peak with m/e 91 confirms the presence of a benzyl group. Substantial differences are observed in the high-molecular-weight regions of the spectra of monoacetyl derivatives VIII and IX. In addition to an intense $(M-COCH_2)^{\dot{+}}$ ion peak (m/e 306), the spectrum of IX contains a peak with mass number 289, the assignment of which to the $(M-OCOCH_3\cdot)^{\dot{+}}$ fragment is confirmed by the presence of the corresponding metastable transition. This sort of fragmentation of IX indicates the presence of an acetyl group attached to the oxygen atom in the 1 position. On the other hand, the $(M-COCH_2)^{\dot{+}}$ ion peak in the spectrum of monoacetyl derivative VIII is of low intensity, but an intense $(M-CH_3\bullet)^+$ peak is observed, and this characterizes the fragmentation of the C-acetyl group in the benzene ring.

Pyrrole-nitrogen-unsubstituted monoacetate XI, the spectrum of which contains an intense peak with m/e 199, evidently formed through elimination of $OCOCH_3\cdot$ from the molecular ion and, constituting evidence for the presence of an acetyl group attached to the oxygen atom attached to $C_{(1)}$, also undergoes fragmentation similar to that of monoacetyl compound IX. In addition to this, ions with m/e 216 $([M-COCH_2]^{\dot{+}})$ and ions with m/e 187, 159, etc., characteristic for fragmentation of nonacylated I appear in the spectrum of monoacetate XI.

The molecular weight of X (342) confirms that it is the triacetyl derivative of carbolinone I. Ions with m/e 300 and 258 due to successive elimination of two $COCH_2$ groups from the molecular ion are observed in its mass spectrum. The presence of an ion with m/e 241 attests to detachment of one of the acetyl groups in the $OCOCH_3\cdot$ composition $(M-COCH_2-OCOCH_3)^{\dot{+}}$, and this confirms the presence of an acetyl group attached to the oxygen in the 1 position. The presence in the spectrum of an intense ion peak with m/e 243 corresponding to ejection of a CH_3 group from the $[M-COCH_2-COCH_2]^{+\cdot}$ ion constitutes evidence for the addition of a third acetyl residue to the carbon atom of the benzene ring.

A molecular ion with m/e 300 and ions with m/e 258 and 216 formed by successive elimination of two $COCH_2$ residues are observed in the mass spectrum of diacetyl derivative XII. The presence of an intense peak with mass number 199 and of the corresponding metastable transition proves elimination of an $OCOCH_3$ group from the $[M-COCH_2]^{+\cdot}$ ion, and this constitutes evidence for the presence of an acetyl residue attached to the oxygen atom in the 1 position. The second acetyl group is evidently attached to the pyrrole nitrogen atom: the absence in the spectrum of $(M-CH_3^{+\cdot}$ and $(M-COCH_2-CH_3\cdot)^{+\cdot}$ ions makes it possible to assert that diacetate XII does not contain a $C-COCH_3$ grouping. The signal of the 8-H proton in the PMR spectra (Table 1) of X and XII is shifted substantially to weak field as compared with the chemical shift of this proton in the remaining compounds and, in particular, in nonacylated carbolinone I. In addition, the signal of the 9-H proton in acetyl derivatives X and XII is absent (the spectrum of I contains a broad singlet at 11.3 ppm). All of this constitutes evidence for the presence of an acetyl group attached to the pyrrole nitrogen atom in X and XII. The absence of a weak-field shift of the 8-H proton in monoacetyl derivative XI is in agreement with the 1-acetoxy structure of this compound. The presence of an acetyl group attached to $C_{(5)}$ in acetyl derivatives X and VIII is confirmed by the absence of the signal of the 5-H proton and the character of the multiplicity of the signals of the 7-H and 8-H protons (two doublets, $J_{7,8} \sim 9$ Hz). As one should have expected, the signals of the 9-H proton at ~11 ppm are absent in the spectra of III and VIII, but the signal of a proton attached to the nitrogen atom in the 2 position (~7.6 ppm) is observed, and this constitutes evidence for the absence of an acetyl group attached to the nitrogen atom of the six-membered ring in monoacetyl derivative VIII. On the other hand, the signal of a proton attached to $N_{(2)}$ is absent in the spectrum of IX, and the chemical shift of the 8-H proton is close to the analogous characteristic of the 8-H proton in carbolinone III and differs markedly from the corresponding values for $N_{(9)}$-acylated derivatives X and XII. In addition, the signal of the 7-H proton is a quartet with J ~ 9 and 2.5 Hz, which indicates the absence of an acyl substituent attached to $C_{(5)}$. The combination of all of these data is in good agreement with attachment of the acetyl residue in IX to the oxygen atom attached to $C_{(1)}$.

As one should have expected, the NH band is absent in the IR spectra of acetyl derivatives IX, X, and XII, and bands are observed at 1690-1695 cm^{-1}; the ν_{CO} stretching vibrations appear at 1668 cm^{-1} in the spectrum of monoacetyl derivative VIII, and NH bands are present at 3300-3200, and 3100 cm^{-1} in the high-frequency region.

It should be noted that in the case of di- and triacetyl derivatives, the bands of the CO groups in the various positions of the molecule had close values and the corresponding signals in the IR spectra merged into one intense band. The IR spectra of dichlorophosphoryl derivatives V and VII contain bands of NH groups at 2600-2800 cm^{-1}; in the spectrum of V absorption also appears at 3100-3200 cm^{-1}, whereas vibrations of CO groups are absent in the spectra of V and VII. These data are in good agreement with structures V and VII but do not make it possible to choose between structures Va and Vb in the case of V. We were also unable to choose between the two alternative structures (VIa and VIb) in the case of dichlorophosphoryl derivative VI.

EXPERIMENTAL

The mass spectra were recorded with an MKh-1301 spectrometer equipped for direct introduction of the sample into the source. The ionizing-electron energy was 40 eV. The PMR spectra were recorded with a NJM 4H-100 spectrometer (100 MHz) with tetramethylsilane as the internal standard. The IR spectra of crystals and mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer.

9-Benzyl-6-methoxy-1,2,3,4-tetrahydro-β-carbolin-1-one (III). A solution of 1 g (4.5 mmole) of carbolinone I in 40 ml of distilled dimethylformamide (DMF) was added dropwise to a suspension of 0.15 g (6.2 mmole) of sodium hydride in 50 ml of DMF. The reaction mixture was stirred at room temperature for 1 h, after which 0.5 g (4.5 mmole) of benzyl chloride was added dropwise. The mixture was then stirred at 18-20° for 16 h, after which it was evaporated to dryness, and the residue was extracted with boiling chloroform to give 1.1 g (77.5%) of colorless crystals of III with mp 169-170° (from alcohol). The product was insoluble in ether and petroleum ether, only slightly soluble in benzene, acetone, alcohols, and water, and soluble in chloroform. Found: C 74.3; H 5.8; N 9.3%. $C_{19}H_{18}N_2O_2$. Calculated: C 74.5; H 5.9; N 9.2%.

2,9-Dibenzyl-6-methoxy-1,2,3,4-tetrahydro-β-carbolin-1-one (II). A solution of 1 g (4.5 mmole) of carbolinone I in 50 ml of anhydrous toluene was added to a solution of 0.21 g (0.1 g-atom) of sodium in 75 ml of liquid ammonia, and the mixture was then stirred until the ammonia had evaporated completely, after which 1.16 g (9.5 mmole) of benzyl chloride was added, and the mixture was refluxed for 3 h. The resulting solution was filtered to remove the precipitated inorganic salts, and the filtrate was vacuum evaporated. The residue was crystallized from alcohol to give 1.2 g (65.5%) of colorless crystals of II with mp 130-131°. The product was quite soluble in acetone, benzene, toluene, and chloroform, but only slightly soluble in alcohols, water, heptane, and ether. Found: C 79.1; H 6.2; N 7.3%. $C_{26}H_{24}N_2O_2$. Calculated: C 78.8; H 6.1; N 7.1%.

1-Dichlorophosphoryloxy-6-methoxy-3,4-dihydro-β-carbolinium Chloride (V). A 0.2-g (0.9 mmole) sample of carbolinone I was heated at 60-70° with 2 ml (8 mmole) of phosphorus oxychloride for 15 min, after which the mixture was cooled to 18-20° and diluted with 5-7 ml of anhydrous ether. The resulting light-yellow crystalline substance was removed by filtration and dried in a vacuum desiccator to give 0.2 g (83%) of V with mp 169-170° (dec.). Found: C 38.9; H 3.6; Cl 28.6; N 7.4; P 8.5%. $C_{12}H_{12}Cl_3N_2O_3P$. Calculated: C 39.0; H 3.3; Cl 28.9; N 7.6; P 8.4%.

Carbolinone I was formed in quantitative yield in the reaction of V with water or alcohol.

1-Dichlorophosphoryloxy-2-benzyl-6-methoxy-3,4-dihydro-β-carbolinium Chloride (VI). This compound was obtained as in the preceding experiment from 0.2 g (0.65 mmole) of carbolinone IV and 2 ml (8 mmole) of phosporus oxychloride. The yield of light-yellow crystals with mp 164-165° (dec.) was 0.2 g (66.7%). Found: C 49.2; H 4.0; Cl 22.9; N 6.2; P 6.8%. $C_{19}H_{18}Cl_3N_2O_3P$. Calculated: C 49.4; H 4.2; Cl 23.2; N 6.1; P 6.8%.

A 0.2-g (0.43 mmole) sample of dichlorophosphoryl derivative VI was triturated with 2 ml of water, and the solid material, which had become white, was removed by filtration and dried to give 0.13 g (quantitative yield) of carbolinone IV with mp 198-199°. The product was identical to a genuine sample of IV with respect to a mixed-melting-point determined and its IR spectrum. Found: C 74.6; H 5.8; N 9.4%. $C_{19}H_{18}N_2O_3$. Calculated: C 74.5; H 5.9; N 9.2%.

1-Dichlorophosphoryloxy-9-benzyl-6-methoxy-3,4-dihydroxo-β-carbolinium Chloride (VII). This compound was similarly obtained as light-yellow crystals with mp 134-135° in 66.7% yield from 0.2 g (0.65 mmole) of carbolinone III. Found: C 94.4; H 4.2; Cl 23.1; N 6.2; P 6.9%. $C_{19}H_{18}Cl_3N_2O_3P$. Calculated: C 49.4; H 4.2; Cl 23.2; N 6.1; P 6.8%.

5-Acetyl-6-methoxy-9-benzyl-1,2,3,4-tetrahydro-β-carbolin-1-one (VIII). A 0.5-g (1.6 mmole) sample of light-yellow dichlorophosphoryl derivative VII was heated at 50° for 15 min with 6 ml (5.5 mmole) of acetic anhydride, after which the mixture was allowed to stand at room temperature for 48 h. It was then vacuum evaporated to dryness, and the residual acetic anhydride was removed by distillation with benzene. The residue was triturated with alcohol to give 0.3 g (79%) of VII as colorless crystals with mp 199-200°. The product was quite soluble in acetone and chloroform, slightly soluble in benzene and alcohols, and insoluble in water and ether. Found: C 72.4; H 5.9; N 8.3%. $C_{21}H_{20}N_2O_3$. Calculated: C 72.3; H 5.8; N 8.1%.

1-Acetoxy-6-methoxy-9-benzyl-3,4-dihydro-β-carboline (IX). A 0.3-g (0.98 mmole) sample of carbolinone III was refluxed for 1 h with 3 ml (27 mmole) of acetic anhydride, after which the mixture was vacuum evaporated to give 0.32 g (100%) of acetyl derivative IX as colorless crystals with mp 139-140° (from alcohol). The product was quite soluble in benzene and chloroform, less soluble in acetone and alcohols, and slightly soluble in water and ether. Found: C 72.3; H 5.9; N 8.3%. $C_{21}H_{20}N_2O_3$. Calculated: 72.3; H 5.8; N 8.1%.

1-Acetoxy-5,9-diacetyl-6-methoxy-3,4-dihydro-β-carboline (X). A) A 0.3-g (1.35 mmole) sample of carbolinone I was refluxed for 1 h with 3 ml (27 mmole) of acetic anhydride, after which the mixture was vacuum evaporated, and the residual acetic anhydride was removed by distillation with benzene. The residue was triturated with ether and recrystallized from alcohol to give 0.28 g (59%) of colorless crystals of X with mp 176-177°. The product was slightly soluble in water and ether and more soluble in benzene, acetone, and chloroform. Found: C 63.1; H 5.1; N 8.3%. $C_{18}H_{18}N_2O_5$. Calculated: C 63.1; H 5.3; N 8.2%. Prior to recrystallization from alcohol, the product, according to the mass spectroscopic data, was a mixture of X and 1-acetoxy-6-methoxy-3,4-dihydro-β-carbolinone (XI).

B) A 0.4-g (1.1 mmole) sample of dichlorophosphoryl derivative V was refluxed for 1 h with 3 ml (27 mmole) of acetic anhydride, after which the mixture was vacuum evaporated, and the residual acetic anhydride was removed by distillation with benzene. The residue was extracted with boiling hexane and crystallized from alcohol to give 0.25 g of X with mp 176-177°. No melting-point depression was observed for a mixture of this product with a sample of X obtained by method A, and the two samples had identical IR and mass spectra.

1-Acetoxy-6-methoxy-9-acetyl-3,4-dihydro-β-carboline (XII). A mixture of 0.3 g (1.35 mmole) of carbolinone I and 10 ml (90 mmole) of acetic anhydride was held at 18-20° for 30 days until I had dissolved completely. The resulting solution was vacuum evaporated, and the residual acetic anhydride was removed by distillation with benzene. The residue was triturated with ether to give 0.28 g (64%) of colorless crystals of XII with mp 141-142°. The product was soluble in benzene and chloroform, less soluble in ether and alcohol, and only slightly soluble in water. Found: C 64.0; H 5.5; N 9.3%. $C_{16}H_{16}N_2O_4$. Calculated: C 64.0; H 5.3; N 9.3%.

LITERATURE CITED

1. H. Henecka, R. Lorenz, and H. Timmler, West German Patent No. 1045411 (1958); Chem. Abstr., 55, 5543 (1961).
2. R. A. Abramovitch and D. Spencer, Adv. Heterocycl. Chem., 3, 117 (1964).
3. R. G. Glushkov and V. G. Granik, Usp. Khim., 38, 1989 (1969).
4. R. G. Glushkov, V. A. Volskova, and O. Yu. Magidson, Khim.-Farmats. Zh., No. 9, 25 (1967).
5. N. N. Suvorov and V. S. Murashova, Med. Prom., No. 1, 6 (1961).
6. L. Arnold and A. Holý, Coll. Czech. Chem. Commun., 27, 2886 (1962).