Chemistry of Heterocyclic Compounds, Vol. 30, No. 8, 1994

SYNTHESIS AND SOME REACTIONS OF INDOLO[2,1-c]-1,4-OXAZINIUM PERCHLORATES

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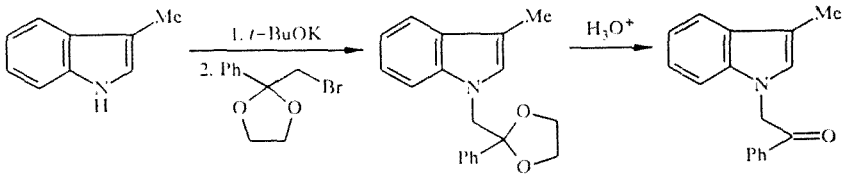
The reaction of acyl perchlorates with 1-phenacylskatole affords the previously unknown 1-R-10-methyl-3-phenylindolo[2,1-c]-1,4-oxazinium salts, which undergo recyclization by the action of ammonia to the corresponding indolo[2,1-a]pyrazines. It is found that the salts (R = CH_3, C_2H_5) also form dimers of their anhydro bases. The perchlorate (R = Ph) is converted to indolo[2,1-d]-1,2,5-triazepine by the action of hydrazine.

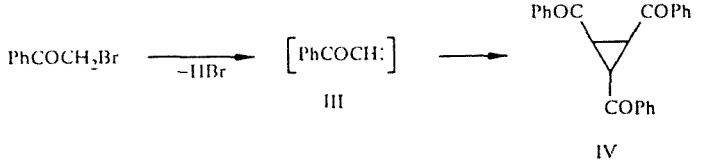
The method, which we developed previously, for the ring fusion of the pyrylium nucleus to π-excess heterocycles consists of the acid-catalyzed ortho-acylation of their β-oxoalkyl derivatives [1]. In the indole series, this route was utilized to obtain indolo[2,3-c]- and indolo[3,2-c]pyrylium salts which, in their turn, have served as convenient intermediates for the synthesis of biologically active β- and γ-carbolines [2-7]. In the cases indicated, the β-oxoalkyl substituents occurred correspondingly at positions 3 and 2 of the indole nucleus.

With the object of studying the possibility of the ring fusion of the pyrylium cation at the 1-2 side of indole by this method, 1-phenacyl-3-methylindole (II) was synthesized. The last is formed with a good yield as a result of the sequential treatment of the solution of skatole in DMSO with potassium tert-butoxide and the ethyleneketal of phenacyl bromide and the subsequent hydrolysis of the resulting ketal (I).



I II

Attempts to isolate the ketone (II) by the alkylaton of the N-sodium or potassium salts of skatole directly with phenacyl halides were unsuccessful. This was probably caused by the high availability of the hydrogen atom in the halogenomethyl group of the α-halogenoketone, leading to undesired processes. Thus, when phenacyl bromide was utilized as the alkylating agent, 1,2,3-tribenzoylcyclopropane (IV), which is formed as a result of the cleavage of hydrogen bromide by the action of the base and the trimerization of the resulting ketocarbene (III), was found in the products of the reaction besides the initial skatole.

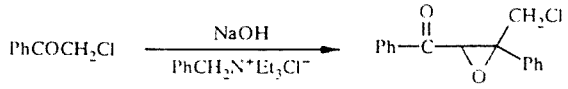


III IV

Institute of Physico-Organic Chemistry and Carbon Chemistry, NAN of the Ukraine, Donetsk 340114. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1041-1047, August, 1994. Original article submitted September 5, 1994.

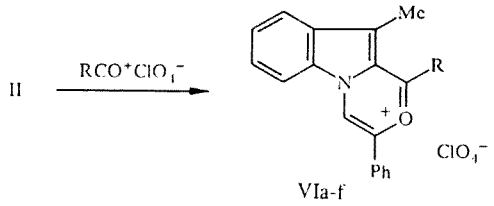
0009-3122/94/3008-0895 $12.50

In the case of phenacyl chloride, the main process is also not the alkylation of skatole, but the formation of the epoxyketone (V) by the Darzens reaction.



V

As was expected, the acylation of the ketone (II) by acyl perchlorates proceeds at the free position 2 of the indole with the subsequent cyclization under the conditions of the reaction to give the previously unknown indolo[2,1-c]-1,4-oxazinium cations (VIa-f).



VIa-f

VI a R = CH_3; b R = C_2H_5; c R = C_3H_7; d R = *i*-C_3H_7; e R = *t*-C_4H_9; f R = Ph

The perchlorates (VIa-d) were obtained in yields close to quantitative with the utilization of anhydrides of acetic, propionic, butyric, and isobutyric acids in the presence of perchloric acid. Acid chlorides of corresponding acids were utilized as acylating agents in the presence of 70% perchloric acid for the introduction of the tert-butyl and phenyl substituents [the salts (VIe, f)].

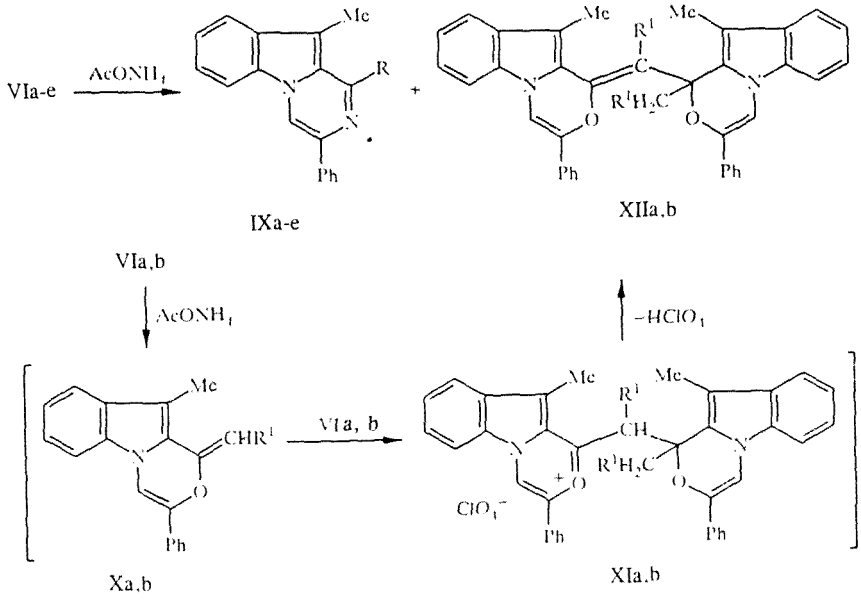
The perchlorates (VIa-f) are crystalline substances stable in air, colored dark violet, and melting with decomposition. The deep color of the compounds obtained is probably determined by the possibility of the occurrence of two main resonance structures with the charge on the oxygen atom in (VII) and on the nitrogen atom in (VIII).

VII VIII

In the IR spectra of the salts (VIa-f), there are absorption bands in the range of 1605-1640 and at 1100 cm^{-1}, characterizing the pyrylium nucleus and the perchlorate anion correspondingly. As an example, we will present the PMR spectrum of 3-phenyl-1,10-dimethylindolo[2,1-c]-1,4-oxazinium perchlorate (VIa), including the singlet of protons of the methyl group at the position 10 at 3.1 ppm, the three-proton singlet of the 1-CH_3 group at 3.4 ppm, the multiplet of nine aromatic protons in the range 7.13-8.10 ppm pertaining to the phenyl group at the position 3 and the benzene part of the molecule, as well as the singlet of the 4-H proton at 8.70 ppm.

Indolooxazinium salts present interest in connection with the possible synthesis, from them, of indolopyrazines, which are analogs of psychotropic preparations (e.g. pyrazidol) applied in therapeutic practice. Moreover, the indolo[1,2-*a*]pyrazine system lies at the basis of some natural compounds, e.g. the antibiotic gliotoxin. Therefore, we investigated the reaction of the salts (VI) with ammonia.

It was established that the heating of the perchlorates (VIa-e) with ammonium acetate in acetic acid leads to the expected 1-alkyl-3-phenyl-10-methylindolo[1,2-*a*]pyrazines (IXa-e). In the case of the salts (VIa, b), the formation of the products (IXa, d) and (XIIa, b) correspondingly is observed. The share of the second product also decreases in the case of the salts (VIc-e) with the increase in the length of the alkyl substituent at the position 1; only the indolopyrazines (IXc-e) are isolated from the reaction mixtures



IX a R = CH_3; b R = C_2H_5; c R = C_3H_7-n; d R = i-C_3H_7; e R = i-C_4H_9;
X—XII a R^1 = H; b R^1 = CH_3

The structures of the compounds (XIIa, b) was established using the mass spectrometric determination of the molecular mass and the data of the IR and PMR spectra. Their formation can be described as the result of the reaction of the anhydro bases (Xa, b) with the molecule of the salt, and the deprotonation of the adducts (XIa, b) obtained.

The formation of the same product was noted by the action of sodium acetate or triethylamine in acetic acid, and ammonia in alcohol, on the salts (VIa, b), as well as by the attempt to recrystallize these salts from nitromethone, acetic acid, or acetonitrile.

For the compounds (XIIa) and (XIIIb), the values obtained for the masses of the molecular ions were 546.2273 and 574.2615 correspondingly: the calculated values were 546.2307 and 575.2620. Their IR spectra contain absorption bands at 1710-1695 and 1670-1650 cm^{-1}, characteristic of α-methylenepyrans. The PMR spectrum of compound (XIIa), for example, consists of three singlets of methyl groups at 1.98, 2.68, and 2.81 ppm, a singlet of two vinyl protons at 5.42 ppm, a broadened singlet of one vinyl proton at 6.52 ppm, and the multiplet of 18 aromatic protons at 6.92-8.05 ppm.

When the salt (VIf), which has two phenyl substituents, is acted on by water or ammonia in alcohol, the product of ring opening – the 1,5-diketone (XIII) – is formed quantitatively; (XIII) undergoes ready cyclization to the initial indolooxazinium cation (VIf) in the presence of acetyl perchlorate. Both the perchlorate (VIf) and the diketone (XIII) give the indolopyrazine (XIV) when they are heated in acetic acid with ammonium acetate, and the indolotriazepine (XV) is given by the reaction with hydrazine hydrate in alcohol.

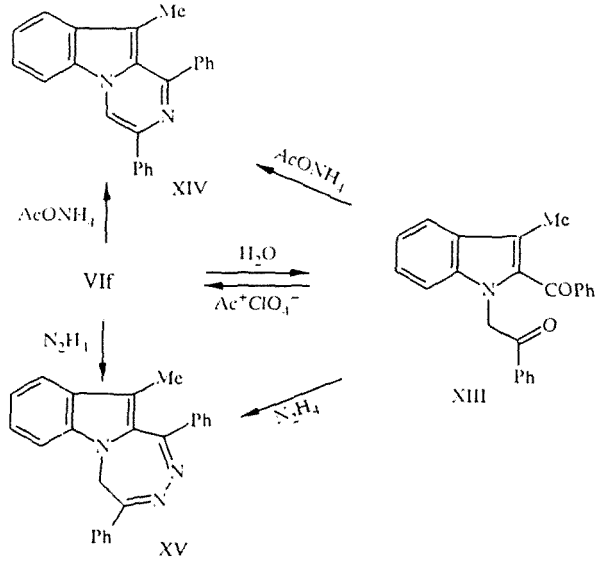


TABLE 1. Characteristics of the Compounds (I), (II), (VIa-f), (IXa-e), (XIIa, b), (XIII), (XIV), and (XV)

Compound	Empirical formula	mp, °C	PMR spectrum, solvent, δ, ppm, J, Hz (the solvent CF_3CO_2H is not indicated)	Yield, %
I	$C_{19}H_{19}NO_2$	59...60	$CDCl_3$, 2,2 (3H, s, 3-CH_3); 3,4 (4H, d, J = 3,0, CH_2CH_2O); 4,13 (2H, s, 1-CH_2); 6,77 (1H, s, 2-H); 6,85...7,47 (9H,m, H_{arom})	81
II	$C_{17}H_{15}NO$	131...132	$CDCl_3$, 2,2 (3H, s, 3-CH_3); 5,17 (2H, s, 1-CH_2); 6,7 (1H, s, 2-H); 6,92...7,90 (9H, m H_{arom})	91
VIa	$C_{19}H_{16}ClNO_5$	250...251	3,1, s, (10-CH_3); 3,40 (3H, s, 1-CH_2); 7,43...8,10 (9H,m, H_{arom}) 8,70 (1H, s, 4-H)	90
VIb	$C_{20}H_{18}ClNO_5$	250...252	1,95 (3H, s, J = 7; 1-β-CH_3); 3,1 (3H, s, 10-CH_3); 3,88 (2H, q, J = 7, 1-α-CH_2); 7,50...8,18 (9H, m, H_{arom}); 8,78 (1H, s, 4-H)	95
VIc	$C_{21}H_{20}ClNO_5$	230...231	1,32 (3H, t, J = 7; 1-γ-CH_3); 2,27 (2H, m, 1-β-CH_2); 3,17 (3H, s, 10-CH_3); 3,77 (2H, t, J = 8, 1-α-CH_2); 7,53...8,23 (9H, m, H_{arom}); 8,83 (1H, s, 4-H)	90
VId	$C_{21}H_{20}ClNO_5$	238...239	1,66 (6H, d, J = 7; 1-β,β-CH_3); 3,0 (3H, s, 10-CH_3); 4,27 (1H, q, J = 7; 1-α-CH); 7,46...8,03 (9H,m, H_{arom}); 8,70 (1H, s, 4-H)	94
VIe	$C_{22}H_{22}ClNO_5$	168...170	1,27 (9H, s, 1-β,β,β-CH_3); 3,08 (3H, s, 10-CH_3); 7,25...8,20 (9H,m, H_{arom}); 8,9 (1H, s, 4-H)	60
VIf	$C_{24}H_{18}ClNO_5$	250...252	2,67 (3H, s, 10-CH_3); 7,37...8,23 (14H, m, H_{arom}); 8,83 (1H, s, 4-H)	95
IXa	$C_{19}H_{16}N_2 \cdot HCl$	289...290	2,73 (3H, s, 10-CH_3); 3,05 (3H, s, 1-CH_3); 7,17...7,88 (9H,m,H_{arom}); 8,25 (1H, s, 4-H)	37
IXb	$C_{20}H_{18}N_2 \cdot HCl$	186...187	1,37 (3H, t, J = 7,5; 1-β-CH_3); 2,7 (3H, s, 10-CH_3); 3,37 (2H, q, J = 7,5; 1-α-CH_3); 7,20...7,80 (9H, m, H_{arom}); 8,3 (1H, s, 4-H)	52
IXc	$C_{21}H_{20}N_2$	120...121	$CDCl_3$, 1,25 (3H, t, J = 7; 1-γ-CH_3); 1,83...2,38 (2H, m, 1-β-CH_2); 3,02 (2H, s, 10-CH_2); 3,54 (2H, t, J = 7; 1-α-CH_2); 7,43...8,22 (9H, m, H_{arom}); 8,61 (1H, s, 4-H)	90
IXd	$C_{21}H_{20}N_2$	126...127	$CDCl_3$, 1,48 (6H, d, J = 6,8; 1-β,β-CH_3); 2,79 (3H, s, 10-CH_3); 3,82 (1H, q, J = 6,8; 1-α-CH); 7,24...8,10 (9H,m, H_{arom}); 8,37 (1H, s, 4-H)	95
IXe	$C_{22}H_{22}N_2$	136...138	$CDCl_3$, 1,35 (9H, s, 1-β,β,β-CH_3); 2,75 (3H, s, 10-CH_3); 7,21...8,05 (9H, m, H_{arom}); 8,33 (1H, s, 4-H)	57
XIIa	$C_{38}H_{30}N_2O_2$	240...241	$CDCl_3$, 1,98 (3H, s, CH_3), 2,68 (3H, s, CH_3), 2,81 (3H, s, CH_3); 5,42 (2H, s, N—CH); 6,52 (1H, broadsCH); 6,92...8,05 (18H,m, H_{arom})	40
XIIb	$C_{40}H_{34}N_2O_2$	244...245	$CDCl_3$ 1,03 (3H, d, J = 7; β-CH_3); 1,63 (3H, s, CH_3); 1,8 (3H, s, CH_3); 2,62 (3H, s, CH_3); 2,88 (2H, q, J = 7, CH_2); 5,25 (2H, s, N—CH); 6,9...8,0 (18H,m, H_{arom})	20
XIII	$C_{24}H_{19}NO_2$	169...170	$CDCl_3$, 2,01 (3H, s, 3-CH_3); 5,93 (2H, s, 1-CH_2); 7,27...8,17 (14H,m, H_{arom})	78
XIV	$C_{24}H_{18}N_2$	131...132	$CDCl_3$, 2,03 (3H, s, 10-CH_3); 7,08...8,02 (14H, m, H_{arom}) 8,25 (1H, c, 4-H)	97
XV	$C_{24}H_{19}N_3$	254...255	2,33 (3H, s, 5-CH_3); 5,77 (2H, s, 11-CH_2); 7,17...8,23 (14H,m, H_{arom})	—

The structure of the indolotriazepine (XV) is confirmed by the PMR spectrum in which the following signals are observed: the three-proton singlet of the methyl group at 2.33 ppm, the singlet of the protons of the methylene group at 5.77ppm, and the multiplet of 14 aromatic protons in the range 7.17-8.23 ppm. Its IR spectrum contains absorption bands of the C=N bonds at 1585-1560 cm^{-1}.

The characteristics of the compounds synthesized are presented in Table 1.

EXPERIMENTAL

The PMR spectra were recorded on the Tesla BS-467 instrument (60 MHz); chemical shifts of protons were measured in relation to TMS. The IR spectra were taken on the UR-20 instrument in mineral oil. The molecular weight was determined on the MS-902 high-resolution mass spectrometer of the firm AEI.

The data of the elemental analysis of the compounds synthesized for C, H, Cl, and N correspond with the calculated data.

The ethyleneketal of phenacyl bromide was synthesized from phenacyl bromide and ethylene glycol according to the method of the work [9].

Attempts to Alkylate Skatole with Phenacyl Halides. A. To 6.55 g (0.05 mole) of skatole in 50 ml of DMF are added 1.3 g (0.055 mole) of sodium hydride. At the completion of the release of hydrogen, the solution of 10 g (0.05 mole) of phenacyl bromide in 50 ml of DMF is added dropwise with stirring; the mixture is boiled for 1 h and poured into water. The mixture is extracted with benzene, and the extract is washed with water. After the distillation of the solvent, the residue is extracted with hexane. The hexane is evaporated prior to the isolation of 4 g of the initial skatole. The residue which was insoluble in hexane is crystallized from carbon tetrachloride prior to the isolation of 0.6 g (10%) of 1,2,3-tribenzoylcyclopropane (IV) with the mp 219-220°C; according to the data of [8], the mp is 215°C, and according to [10], the mp is 215-220°C.

B. Skatole (6.55 g, 50 mmole) and 10 g (50 mmole) of phenacyl bromide are dissolved in 50 ml of benzene; 1.5 g (0.5 mmole) of triethylbenzylammonium bromide are added. To the mixture obtained are added, with stirring, 25 ml of the 50% solution of NaOH. The stirring is continued at room temperature for 8 h; the mixture is left overnight. The benzene layer is separated and washed with water. After the removal of the solvent, the residue is crystallized by treatment with 20 ml of alcohol. The 1,2,3-tribenzoylcyclopropane obtained after crystallization from CCl_4 has mp 219-220°C. The yield is 0.5 g (8%).

C. The alkylation of skatole with phenacyl chloride by the method B led to the isolation of 2-benzoyl-3-chloromethyl-3-phenyloxirane (V) having mp 149-150°C (benzene–hexane); according to the data of [10], the mp is 145-150°C.

1-Phenacylskatole Ethyleneketal (I). The solution of 32.8 g (0.25 mole) of skatole and 36 g (0.3 mole) of potassium tert-butoxide in 250 ml of dimethylsulfoxide is stirred for 1 h at 50-60°C. To the resulting solution are added, at room temperature in the course of 1 h, 68 g (0.28 mole) of phenacyl bromide ethyleneketal, and the mixture is stirred for 16 h at 80-100°C. The red-brown solution which formed is poured into 1.5 liters of water, and the mixture is extracted with 3 × 200 ml of the 1:1 mixture of benzene–hexane. The extract is washed with water. After the removal of the solvents, the residue is distilled *in vacuo*. After a small predistillation, the product is distilled at 170-180°C/0.66 GPa. The yield is 59.4 g (81%); the mp is 59-60°C (methanol).

1-Phenacylskatole (II). The ethyleneketal (I) (59 g, 0.2 mole) is dissolved in 1.1 liters of methanol prior to the addition of 5 ml of concentrated hydrochloric acid in 250 ml of water. The mixture is boiled with a reflux condenser for 5 h and cooled to room temperature. After the completion of crystallization, the colorless residue is filtered off. The yield is 45.4 g (91%). The mp is 131-132°C (methanol). The IR spectrum is characterized at 1685 cm^{-1} (C=O).

1-Alkyl-10-methyl-3-phenylindolo[2,1-c]-1,4-oxazinium Perchlorates (VIa-d). Into the solution of 1.2 g (5 mmole) of 1-phenacylskatole (II) in 5 ml of methylene chloride is poured the mixture of 50 mmole of the carboxylic acid anhydride and 0.4 ml of 70% perchloric acid. After 0.5-2 h, the precipitated residue is filtered off, washed with ether, and dried *in vacuo*.

1-tert-Butyl-3-phenyl-10-methylindolo[2,1-c]-1,4-oxazinium Perchlorate (VIe). To a solution of 3.6 ml (0.03 mole) of pivaloyl chloride and 1 g (0.01 mole) of pivalic acid in 10 ml of methylene chloride are added 0.4 ml (0.05 mole) of 70% perchloric acid and 1.25 g (5 mmole) of 1-phenacylskatole. The mixture is left for 10 h at room temperature. After the addition of 20 ml of dry ether, the precipitated product is filtered off, washed with 30 ml of ether, and dried *in vacuo*.

1,3-Diphenyl-10-methylindolo[2,1-c]-1,4-oxazinium Perchlorate (VIf). To the solution of 11.5 ml (0.1 mole) of benzoyl chloride and 0.8 ml (0.01 mole) of 70% perchloric acid in 20 ml of methylene chloride are added 2.5 g (0.01 mole) of 1-phenacylskatole. The mixture is left for 1 day at room temperature. The precipitated residue is filtered off, washed with 50 ml of ether, and dried *in vacuo*.

General Method for the Reaction of Indolo[2,1-c]-1,4-oxazinium Perchlorates (VIa-f) with Ammonium Acetate. To the suspension of 10 mmole of the perchlorates (VIa-f) in 50 ml of acetic acid are added 4 g (53 mmole) of ammonium acetate. The mixture is shaken until the solution of the indolooxazinium salt is effected; the mixture is then boiled for 2 h. Into the solution are poured 10 ml of water, and the mixture is cooled. In the case of the salts (VIa, b), the residue of the dimers of the anhydro bases (XIIa) and (XIIb) is thereby precipitated. The reaction mass [for (VIc-f)] or the filtrates [for (VIa,b)] are

rendered alkaline with ammonia, and the indolopyrazines (IXa-f) which separated out are filtered off. The compounds (IXa,b) were characterized in the form of their hydrochlorides, synthesized by the treatment of the solutions of the bases in acetone with a saturated solution of hydrogen chloride in ether.

Dimers of the Anhydro Bases (XIIa, b). To the suspension of 0.01 mole of the perchlorates (VIa, b) in 30 ml of acetic acid are added 2.5 g (0.03 mole) of sodium acetate, after which the mixture is boiled for 3 h. The solution is diluted with water and extracted with 3 × 50 ml of chloroform. The extract is washed with sodium carbonate solution and water, and is dried with calcium chloride prior to the passage through a column with 20 g of aluminum oxide. The filtrate is evaporated to the volume of 20 ml and cooled; residues of the dimers (XIIa) (the yield 66%) and (XIIb) (the yield 50%) are filtered off.

1-Phenacyl-2-benzoyl-3-methylindole (XIII). The suspension of 2.2 g (5 mmole) of the perchlorate (VIf) in 50 ml of alcohol is saturated with ammonia, and the mixture is boiled with a reflux condenser for 1 h. The yellow crystalline residue which thereby forms if filtered off, washed with water, and dried. The IR spectrum is characterized at 1700 cm^{-1} (C=O).

When the diketone XIII is treated with the solution of the equimolar amount of 70% perchloric acid in an excess of acetic anhydride, the initial indolooxazinium salt (VIf) is isolated with a yield close to quantitative.

1,4-Diphenyl-5-methylindolo[2,1-c]-1,2,5-triazepine (XV). A. The perchlorate (VIf) (4.4 g, 0.01 mole) is dissolved in 150 ml of alcohol prior to the addition of 5 ml (0.1 mole) of hydrazine hydrate. The solution is boiled with a reflux condenser for 20 h. The reaction mass is cooled, and the residue is filtered off and washed with alcohol and water. Compound (XV) is isolated with the yield of 1.8 g (51%).

B. The compound 1-phenacyl-2-benzoyl-3-methylindole (XIII) (1.93 g, 5 mmole) is dissolved in 30 ml of butanol prior to the addition of 2 ml (40 mmole) of hydrazine hydrate, and the mixture is boiled with a reflux condenser for 10 h. The solvent is distilled off *in vacuo*, and the residue is crystallized from toluene. The yield of compound (XV) is 1.4 g (80%).

REFERENCES

1. Ya. P. Stradyn', Khim. Geterotsikl. Soedin., No. 10, 1415 (1981).
2. A. S. 194093. G. N. Dorofeenko and L. V. Dulenko, B. I., No. 8, 23 (1967).
3. G. N. Dorofeenko and V. I. Dulenko, Khim. Geterotsikl. Soedin., No. 3, 417 (1969).
4. V. I. Dulenko, N. S. Semenov,, Yu. A. Nikolyukin, S. N. Baranov, and G. N. Dorofeenko, Khim. Geterotsikl. Soedin., No. 4, 568 (1971).
5. I. V. Komissarov, V. I. Dulenko, A. T. Dolzhenko, L. Ya. Zin'kovskaya, Yu. A. Nikolyukin, M. Z. Nizharadze, O. G. Obraztsova, A. V. Kibal'nyi, and V. I. Luk'yanenko, Khim.-farm. Zh., No. 3, 172 (1985).
6. V. I. Dulenko, I. V. Komissarov, A. T. Dolzhenko, and Yu. A. Nikolyukin, β-Carbolines: Chemistry and Nuerobiology [in Russian], Nauk. Dumka, Kiev (1992), p. 76.
7. G. I. Zhungietu, Zh. Org. Khim., No. 3, 716 (1969).
8. C. Paal and H. Schulze, Ber., **36**, 2425 (1903).
9. M. Kuhn, J. Prakt. Chem., **156**, 103 (1940).
10. D. Pasto, K. Garves, and L. Sevenair, J. Org. Chem., **33**, 2975 (1968).