UDC 447.789.5 + 543.422

SYNTHESIS OF SUBSTITUTED DERIVATIVES OF IMIDAZO [5, 1-b] BENZIMIDAZOLE

I. 3-(Pyrid-4'-yl)- and 3-Phenyl-4-methylimidazo [5,1-b] benzimidazoles

V. M. Aryuzina and M. N. Shchukina

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 2, No. 4, pp. 605-610, 1966

Heating, either molten or in high-boiling solvents, 1-methyl-2-{[(N-phenylthiocarbamoyl) amino] (pyrid-4'-yl)}- methylbenzimidazole, or refluxing with phosphorus oxychloride in benzene acyl derivatives of 1-methyl-2-[(pyrid-4'-yl)(amino)]- and 1-methyl-2[(phenyl)(amino)]-methylbenzimidazoles, gives the corresponding derivatives of the imidazo [5,1-b] benzimidazole system, hitherto undescribed in the literature.

The present work aimed to synthesize some derivatives of the system, hitherto not described in the literature, imidazo [5,1-b]-benzimidazole, with a view to investigating their biological activities.

Condensing 2-aminomethylbenzimidazole with benzylidenacetophenone gave a compound [1] whose composition corresponded to that of an imidazo [5,1-b] benzimidazole.* However, IR and PMR spectra showed that the compound was not derived from that system. An attempt to synthesize imidazo [5,1-b] benzimidazole by reacting 2-aminomethylbenzimidazole with orthoformic ester was further unsuccessful [1].

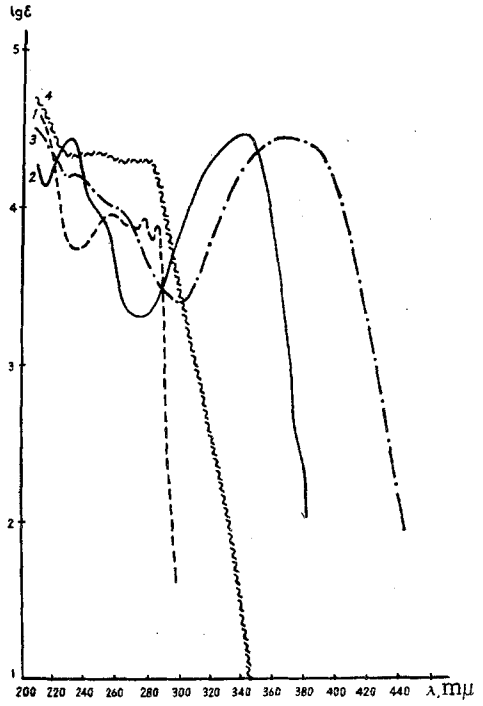


Fig. 1. UV spectra. 1) 1-Methyl-2-[(pyrid-4'-yl) (formylamino) methyl] benzimidazole (VII); 2) 3-(pyrid-4'-yl)-4-methylimidazo [5,1-b] benzimidazole (VIII); 3) 1-mercapto-3-(pyrid-4'-yl)-4-methylimidazo [5,1-b] benzimidazole (X); 4) 1-methyl-2-{[(N-phenylthiocarbamoyl) amino] (pyrid-4'-yl) methyl}-benzimidazole (IX).

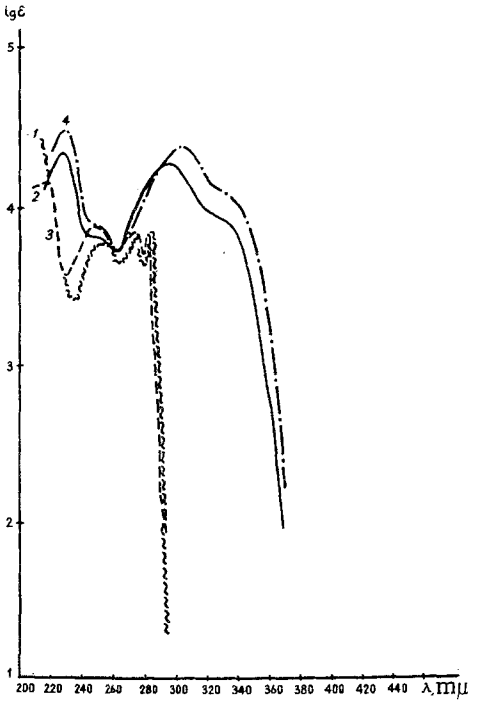


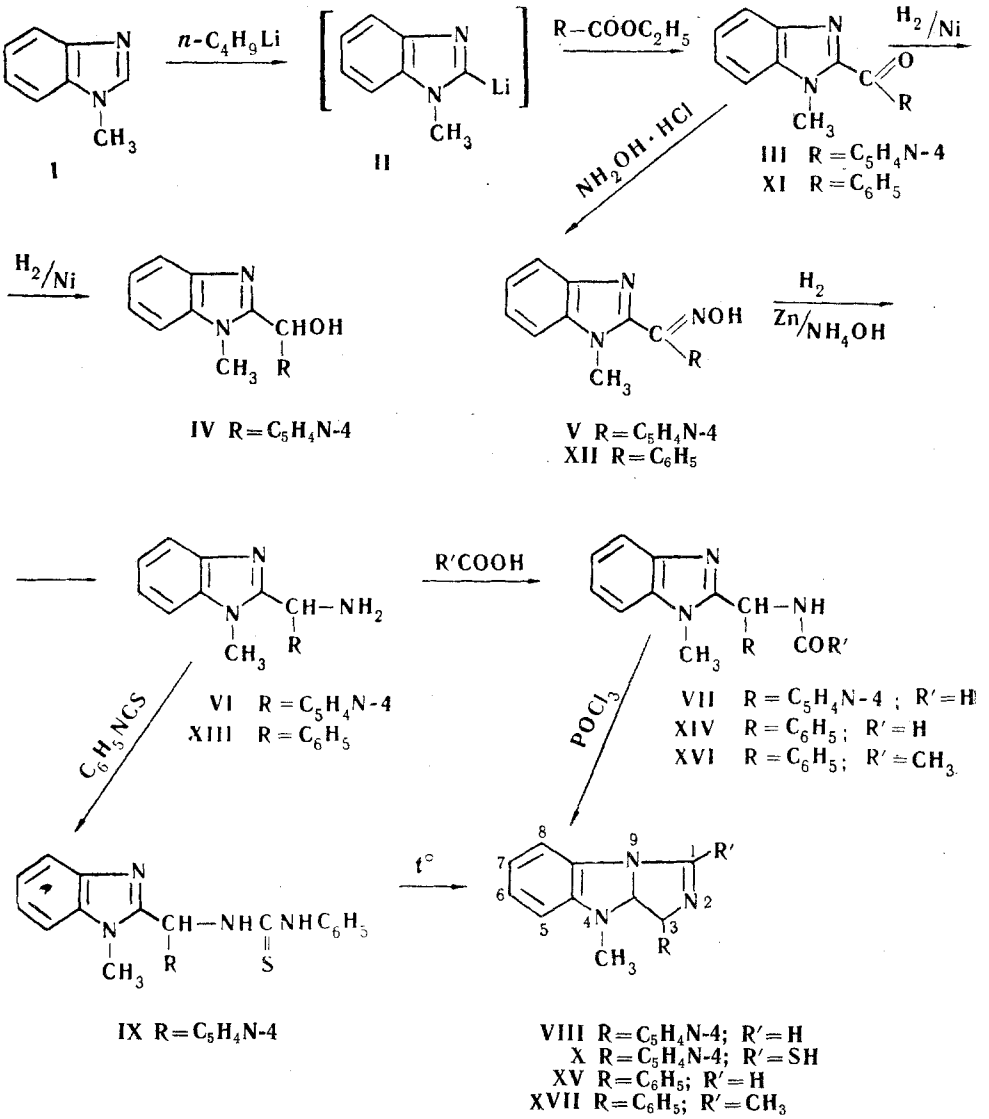
Fig. 2. UV spectra. 1) 1-Methyl-2-[(phenyl) (formylamino) methyl] benzimidazole (XIV); 2) 3-phenyl-4-methylimidazo [5,1-b] benzimidazole (XV); 3) 1-methyl-2-[(phenyl)(acetylamino) methyl] benzimidazole (XVI); 4) 1, 4-dimethyl-3-phenylimidazo [5,1-b] benzimidazole (XVII).

*The authors called the system the imidazo [3,4-a] benzimidazole system.

The present research deals with the possibility of synthesizing some imidazo [5, 1-b] benzimidazole derivatives by heating, either molten or in high-boiling solvents, 1-methyl-2-[(N-phenylthiocarbamoyl) amino] methylbenzimidazole, or by heating formyl or acetyl derivatives of 1-methyl-2-aminomethylbenzimidazole with phosphorus oxychloride.

Since closure of those compounds to the imidazo [5, 1-b] benzimidazole system of necessity involves migration of hydrogen linked to carbon in an aminomethyl group, to unsubstituted nitrogen in the imidazole ring, it was considered appropriate to increase the mobility of this hydrogen by introducing a strongly electronegative substituent, e.g., a pyridine group. This substituent is known to increase hydrogen mobility at the carbon of secondary alcohols [2] and aminomethyl group [3] in 2-derivatives of thiazole.

3-(Pyrid-4'-yl)-4-methylimidazo [5, 1-b] benzimidazole (VIII) and its mercapto derivative X were synthesized as follows:



I

II

III R = C_5H_4N-4
XI R = C_6H_5

IV R = C_5H_4N-4

V R = C_5H_4N-4
XII R = C_6H_5

VI R = C_5H_4N-4
XIII R = C_6H_5

VII R = C_5H_4N-4; R' = H
XIV R = C_6H_5; R' = H
XVI R = C_6H_5; R' = CH_3

IX R = C_5H_4N-4

VIII R = C_5H_4N-4; R' = H
X R = C_5H_4N-4; R' = SH
XV R = C_6H_5; R' = H
XVII R = C_6H_5; R' = CH_3

Butyllithium converts 1-methylbenzimidazole (I) [4] to 1-methyl-2-lithiumbenzimidazole (II) [5]. Reaction of II with ethyl isonicotinate gives (1-methylbenzimidazol-2-yl)-(pyrid-4'yl) ketone (III), and for characterization, this is reduced with hydrogen and Raney nickel to (1-methylbenzimidazol-2-yl) (pyrid-4'-yl) carbinol (IV). The latter, like (thiazol-2-yl) (pyrid-4'-yl) carbinol [2] gives free radicals, indicating the mobility of the hydrogen at the carbon atom of the secondary alcohol group. The presence of radicals checks by EPR spectrum data. Reaction of III with hydroxylamine converts it into the corresponding oxime V, reduced by zinc dust in aqueous ammonia to 1-methyl-2-[(pyridyl-4') (amino) methyl] benzimidazole (VI). VI reacts with 88% formic acid to give the formyl derivative VII, converted by phosphorus oxychloride into 3-(pyrid-4'-yl)-4-methylimidazo [5, 1-b] benzimidazole (VIII).

Reaction of VI with phenylisothiocyanate gives 1-methyl-2-{[(N-phenylcarbamoyl) amino](pyrid-4'-yl) methyl} benzimidazole (IX), cyclized by heating in various organic solvents, or in the molten state. Heating in phenetole, or without a solvent, at 175–185° C gives 1-mercapto-3-(pyrid-4'-yl)-4-methylimidazo [5,1-b] benzimidazole (X) in 48–51% yield. Heating in cymene gave a lower yield of X. If the reaction was carried out with the melt at 200–206° C, there was marked resinification, and X could not be isolated.

Table 1

Benzimidazole Derivatives

Compound Number	Mp °C (recrystallization solvent)	Formula	Found, %				Calculated, %				Yield, %
			C	H	N	S	C	H	N	S	
III	134,5—135 (MeOH)	$C_{14}H_{11}N_3O$	71.05	4.63	17.44	—	70.87	4.67	17.71	—	73
IV	158—159 (AcOEt)	$C_{14}H_{13}N_3O$	70.27	5.70	17.20	—	70.27	5.48	17.56	—	73
V	252.5—253, (MeOH)	$C_{14}H_{12}N_4O$	66.79	4.77	22.33	—	66.65	4.79	22.21	—	95
VI	102.5—103.5 (benzene-petrol ether 1:1) : 1)	$C_{14}H_{14}N_4O$	70.44	5.90	23.74	—	70.56	5.92	23.52	—	91
VII	236—238 (dry EtOH)	$C_{15}H_{14}N_4O$	—	—	20.85	—	—	—	21.04	—	71
IX	171.5 (dry EtOH)	$C_{21}H_{19}N_5S$	67.46	5.25	18.45	8.27	67.53	5.13	18.75	8.57	97
XI	70—71* (EtOH)	$C_{16}H_{12}N_2O$	—	—	11.81	—	—	—	11.86	—	69.5
XII	248—248,5, decomp (dry EtOH)	$C_{15}H_{13}N_3O$	71.71	5.09	16.75	—	71.69	5.21	16.72	—	99
XIII	113.5—114 (hexane-benzene 1:1)	$C_{15}H_{15}N_3O$	75.84	6.25	17.73	—	75.92	6.37	17.71	—	95
XIV	185—186 (MeOH)	$C_{16}H_{15}N_3O$	72.37	5.52	15.95	—	72.43	5.70	15.84	—	98.5
XVI	183.5—184.5 (MeOH)	$C_{17}H_{17}N_3O$	73.20	5.99	15.30	—	73.09	6.13	15.04	—	95

* The literature gives mp 66–67°.

It was also established that N-acyl derivatives of 1-methyl-2-[(phenyl)(amino)] methylbenzimidazole can be cyclized to a tricyclic system. Reaction of II with ethyl benzoate gives ketone XI, previously synthesized by another route [6]. Reaction of XI with hydroxylamine converts it into the corresponding oxime XII, reduced as described above to amine XIII. Reaction of the formyl derivative XIV of the amine with phosphorus oxychloride gives 3-phenyl-4-methylimidazo [5, 1-b] benzimidazole (XV). 1, 4-Dimethyl-3-phenylimidazo [5, 1-b] benzimidazole (XVII) is similarly obtained from 1-methyl-2-[(phenyl) (acetylamino) methyl]-benzimidazole (XVI). All the imidazo [5, 1-b] benzimidazole derivatives prepared are characterized by IR and UV absorption spectra.

The UV spectra of derivatives VII, X, XV, and XVII of imidazo [5,1-b]-benzimidazole differ sharply from those of the corresponding starting compounds VII, IX, XIV, and XVI. The absorption maxima of imidazo-[5,1-b] benzimidazole derivatives are shifted towards the long-wave region, indicating increase in the system of conjugated double bonds (Figs. 1 and 2).

The IR spectra of imidazo [5,1-b] benzimidazole derivatives VII, XV, and XVII lack absorption bands of the NH group (3300 cm^{-1}) and carbonyl group (1680 cm^{-1}) which are present in the IR spectra of starting compounds VII (3300 cm^{-1}, 1655 cm^{-1}), XIV 3310 cm^{-1}, 1678 cm^{-1}, and XVI 3260 cm^{-1}, 1680 cm^{-1}, and a characteristic absorption band appears at respectively 1585, 1595, and 1600 cm^{-1}.

Experimental

(1-Methylbenzimidazol-2-yl)(pyrid-4'-yl) ketone (III). A solution of BuLi was prepared from 2.16 g (0.312 mole) Li and 11.6 g (0.125 mole) BuCl in 76 ml dry ether [7]. It was cooled to −60° C and kept there while a

solution of 13.22 g (0.1 mole) 1-methylbenzimidazole in 400 ml dry ether was gradually added. The reaction products were stirred for 3 hr at −60° C, and a solution of 15.12 g (0.1 mole) ethyl isonicotinate in 40 ml dry ether added gradually. Then the mixture was stirred for 2 hr at a temperature not exceeding −45° C, carefully poured into 360 ml HCl (1:1), the acid aqueous layer separated off, treated with active charcoal, and then, with cooling, made alkaline with aqueous NH_4OH. The precipitate which formed was filtered off, washed with water, and dried. Yield 17.33 g III as colorless long needles, soluble in $CHCl_3$, EtOAc, and EtOH (Table 1).

Table 2

Imidazo [5,1-b] benzimidazole Derivatives

Compound number	Mp °C (recrystallization solvent)	Formula	Found, %				Calculated, %				Yield, %
			C	H	N	S	C	H	N	S	
VIII	204.5—206 (EtOH-H_2O, 1:1)	$C_{15}H_{12}N_4S$	72.87	4.80	22.32	—	72.56	4.87	22.57	—	94
X	215.5—216 (dimethylformamide-H_2O, 1:1)	$C_{15}H_{12}N_4S$	64.47	4.62	20.32	11.43	64.26	4.31	19.99	11.44	48.5—51
XV	130.5—131 (benzene)	$C_{16}H_{13}N_3S$	77.61	5.38	17.09	—	77.71	5.30	17.00	—	89
XVII	133—135 (EtOAc)	$C_{17}H_{15}N_3S$	77.90	5.86	16.03	—	78.13	5.80	16.08	—	99 5

(1-Methylbenzimidazol-2-yl) (pyrid-4'-yl) carbinol (IV). A solution of 2 g (0.00845 mole) III in 270 ml dry EtOH was hydrogenated at ordinary temperature and atmospheric pressure, using Raney nickel catalyst. After the calculated amount of H_2 had been absorbed, the catalyst was filtered off, the filtrate vacuum-evaporated, and the residue ground up with dry ether. Yield of IV 1.62 g, a white crystalline compound, soluble in $CHCl_3$, benzene, and hot EtOH (Table 1). On heating with an ethanolic solution of NaOEt, a pale blue color appears, and disappears on cooling (on standing), reappearing on reheating. The EPR spectrum has a complex ultra-fine structure.

(1-Methylbenzimidazol-2-yl) (pyrid-4'-yl) ketoxime (V). A mixture of 6 g (0.0253 mole) III, 6 g (0.0865 mole) $NH_2OH \cdot HCl$, 30 ml dry EtOH, and 30 ml dry pyridine was heated for 2 hr on a boiling water-bath. After vacuum-distilling off the EtOH and pyridine, the residue was ground with 30 ml water. Yield 6.05 g V (Table 1).

1-Methyl-2 [(pyrid-4'-yl) (amino) methyl] benzimidazole (VI). 15.2 g (0.0604 mole) V in 175 ml EtOH was heated on a boiling water bath for 2 hr with 15.2 g Zn dust, 15.2 g NH_4OAc, and 750 ml aqueous NH_4OH. Then at 2 hr intervals, a further 15 g Zn dust and 300 ml aqueous NH_4OH were added, each in 3 equal portions. The Zn dust was filtered off hot, the filtrated treated with 200 ml 50% NaOH, and extracted with benzene. The benzene extract was dried over $MgSO_4$, the solvent vacuum-distilled off, and the residue triturated with petrol ether. Yield of VI 13.12 g, a pink solid, soluble in EtOH, dichloroethane, and dilute mineral acids (Table 1).

1-Methyl-2-[(pyrid-4'-yl) (formylamino) methyl] benzimidazole (VII). 1.5 g (0.0063 mole) VI and 2.1 ml 88% HCOOH were heated together for 3 hr on a boiling water bath. The reaction products were cooled and made alkaline with aqueous NH_4OH, the precipitate filtered off, washed, and dried. Yield of VII 1.2 g, soluble in water on heating, insoluble in ether (Table 1).

3-(Pyrid-4'-yl)-4-methylimidazo [5,1-b] benzimidazole (VIII). 0.9 g (0.0034 mole) VII in 12 ml dry benzene, and 2.8 ml $POCl_3$ were refluxed together for 4 hr. Excess $POCl_3$ and benzene were vacuum-distilled off, the residue treated with ice-water, and made alkaline with Na_2CO_3. The precipitate formed was filtered off, washed with water, and dried. Yield of VIII 0.79 g, a light yellow solid, soluble in benzene, AcOEt, dichloroethane, insoluble in water and ether (Table 2).

Picrate. Yellow crystals, insoluble in water and organic solvents, decomp 264–264.5° C. Found: N 20.61%. Calculated for $C_{15}H_{12}N_4 \cdot C_6H_3N_3O_7$: N 20.54%.

1-Methyl-2-{[(N-phenylthiocarbamoyl) amino](pyrid-4'-yl) methyl}-benzimidazole (IX). A solution of 1 g (0.0042 mole) VI in 16 ml dry benzene and 1 g (0.0074 mole) phenylisothiocyanate was refluxed for 4 hr. The reaction products were cooled, the precipitate filtered off, washed with benzene, then with ether, and dried. Yield of IX 1.51 g, a yellow solid, mp 171.5° C (ex dry EtOH), immediately solidified, and remelted at 185.5–187° C. The

compound dissolved when heated with benzene, and did not dissolve in ether (Table 1).

1-Mercapto-3-(pyrid-4'-yl)-4-methylimidazo [5, 1-b] benzimidazole (X). a) 0.8 g (0.00241 mole) IX was boiled for 5 min with 4 ml phenetole, when IX completely dissolved. The precipitate formed on cooling was filtered off, washed with ether, and dried. Yield of X 0.29 g, a bright yellow solid, soluble in dilute alkalies, insoluble in organic solvents (Table 2).

Picrate. Brick-red crystals, insoluble in water and organic solvents, decomp 235.5–237°. Found: N 19.29%. Calculated for $C_{15}H_{12}N_4S \cdot C_6H_3N_3O_7$: N 19.25%.

b) 0.26 g (0.0007 mole) IX was heated molten at 175–185° C for 7 min. The precipitate which formed after cooling was ground with ether, and the solid filtered off. Yield, 0.1 g compound, identical with X prepared as in a).

(1-Methylbenzimidazol-2-yl)(phenyl) ketone (XI). The reaction was carried out as for ketone III, but after adding Et benzoate, the reaction mixture was held for 3 hr at −54° C. 4.5 g (0.65 mole) Li 23.2 g (0.25 mole) n-BuCl, and 156 ml dry ether, 26.44 g (0.02 mole) I in 800 ml dry ether, and 30.2 g (0.2 mole) Et benzoate gave 32.82 g XI (Table 1).

(1-Methylbenzimidazol-2-yl-2)(phenyl) ketoxime (XII). The reaction was carried out as for oxime V. 15.02 g (0.0635 mole) XI and 15.02 g (0.216 mole) $NH_2OH \cdot HCl$ in 65 ml dry EtOH plus 65 ml dry pyridine gave 15.79 g XII (Table 1).

1-Methyl-2-[(phenyl)(amino) methyl] benzimidazole (XIII). The reaction was carried out as for compound VI. 12 g (0.0478 mole) XII, 24 g Zn, 12 g $AcONH_4$ in 150 ml EtOH, and 1100 ml aqueous NH_4OH, gave 10.7 g XIII. Soluble in EtOH, benzene, and insoluble in ether and hexane (Table 1).

1-Methyl-2-[(phenyl)(formylamino) methyl] benzimidazole (XIV). Reaction carried out as for compound VII. 5 g (0.0211 mole) XIII and 6.5 ml 88% HCOOH gave 5.5 g XIV (Table 1).

3-Phenyl-4-methylimidazo [5, 1-b] benzimidazole (XV). Prepared similarly to imidazole VIII. 2 g (0.0075 mole) XIV in 26 ml dry benzene, and 6.6 ml $POCl_3$ were taken for reaction. Upon boiling, the solution turned dark-green and a precipitate formed. The reaction products were worked up as for VIII. Yield of a dark-green solid, decomp 227.5–229.5° C, 2.62 g. It gave qualitative reactions for P and Cl. After prolonged, careful grinding with 10% Na_2CO_3 solution, 1.66 g solid was obtained, not containing Cl and P. The substance was heated with EtOH to dissolve it, cooled, the flocculent precipitate filtered off, the filtrate treated with charcoal, evaporated to dryness, and the residue recrystallized from benzene. Yield of XV, 1.25 g. A pink solid, soluble in $CHCl_3$, the dichloroethane, insoluble in ether (Table 2).

1-Methyl-2-[(phenyl)(acetylamino)] methylbenzimidazole (XVI). A mixture of 3 g (0.0127 mole) XIII, 5 ml AcOH, and 2 ml Ac_2O was heated on a boiling water bath for 2 hr, when XIII dissolved completely, and the solution turned dark green. Excess Ac_2O and AcOH were vacuum-distilled off, the residue ground with water, the solid filtered off, washed with water, and recrystallized from MeOH. Yield of XVI, 3.36 g (Table 1).

1, 4-Dimethyl-3-phenylimidazo [5, 1-b] benzimidazole (XVII). Prepared similarly to VIII. No coloring of the solution observed. After 2 hr, a pale yellow oil formed. 1.5 g (0.00545 mole) XVI in 20 ml dry benzene, and 5 ml $POCl_3$ gave 1.4 g XVII, a white solid with a slight yellowish reflex, soluble in dichloroethane, EtOH, and benzene, insoluble in ether (Table 2).

REFERENCES

1. W. Ried and F. Grull, Chem. Ber., 96, 130, 1963.
2. V. G. Ermolaeva and M. N. Shchukina, ZhOKh, 32, 2664, 1962.
3. V. V. Avidon and M. N. Shchukina, KhGS [Chemistry of Heterocyclic Compounds], 1, 64, 1965.
4. A. F. Pozharskii and A. M. Simonov, ZhOKh, 33, 179, 1963.
5. P. W. Alley and D. A. Shirley, J. Org. Chem., 23, 1791, 1958.
6. British Patent no. 885 520; C. A., 57, P7428, 1962.
7. H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, J. Am. Chem. Soc., 71, 1499, 1949.

8 February 1965

Ordzhonikidize All-Union Scientific Research Chemical and Pharmaceutical Research Institute, Moscow