UDC 542.952.52

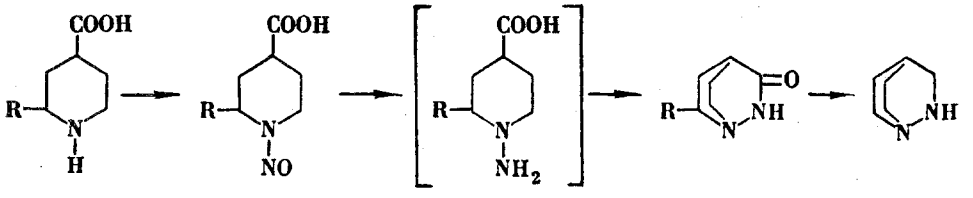
SYNTHESIS OF 1, 2-DIAZABICYCLO [2.2.2] OCTANE, 1, 2-DIAZABICYCLO [3.2.1]-OCTANE, AND THEIR DERIVATIVES

E. E. Mikhlina, N. A. Komarova, and M. V. Rubtsov

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 2, No. 2, pp. 259–265, 1966

1, 2-Diazabicyclo [2.2.2] octane, its 6-methyl homolog, and 1, 2-diazabicyclo [3.2.1] octane are synthesized by a general method involving nitrosation of piperidine carboxylic acids, subsequent reduction to 1-aminopiperidine carboxylic acids, cyclization to 3-keto-1, 2-diazabicycloalkanes, reduction of the latter to 1, 2-diazabicycloalkanes. A number of 2-substituted 1, 2-diazabicyclo [2.2.2] octanes are synthesized.

In a previous communication [1] we described a synthesis of 1, 2-diazabicyclo [4.4.0] decane, one of the representatives of the previously unknown 1, 2,-diazabicycloalkanes. Continuing research on the series, we have effected a synthesis of 1, 2-diazabicyclo- [2.2.2] octane, its isomer 1, 2, -diazobicyclo [3.2.1] octane and some of their derivatives.* These compounds were prepared by a general method which we previously used to synthesize 1, 2-diazabicyclo [4.4.0] decane [1]. This scheme for synthesis of 1, 2-diazabicyclo [2.2.2] octanes is represented by the following series of conversions:



I II III IV V

a R=H; b R=CH_3

1-Nitrosoisonipecotinic acid (IIa), prepared from isonipecotinic acid (Ia), is reduced by zinc in acetic acid at 25–35° C to 1-aminoisonipecotinic acid (IIIa). A higher temperature promotes reductive deamination of the amino acid IIIa. Without being isolated this latter is converted, by heating in a vacuum, to 3-keto-1, 2-diazabicyclo [2.2.2)-octane (IVa). The process of splitting off water starts at 190–200° C, and proceeds more completely at 250–255° C. Formation of IVa is also observed when ethyl 1-aminoisonipecotinic acid (XI) is heated to 250° C. However, the reaction is accompanied by marked resinification, and the yield of IVa is considerably lower (25–30%) than by cyclizing the appropriate amino acid IIIa (55–57%). Introduction of a methyl group at position 2 in the piperidine ring lowers the temperature of cyclization. Thus, 1-amino-2-methylisonipecotinic acid (IIIb) prepared by the same method, is converted at 210–220° C to 3-keto-6-methyl-1, 2-diazabicyclo [2.2.2] octane (IVb).

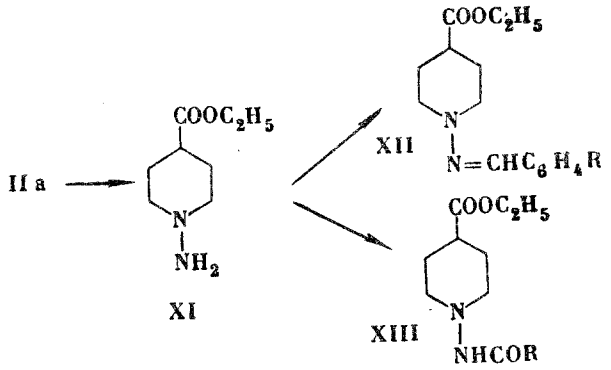
The cyclic hydrazide IVa forms salts with mineral acids, and quaternary salts with alkyl halides, and it is acylated with acetic anhydride, and by benzoyl chloride. Reduction of IVa and IVb by lithium aluminum hydride gives 1, 2-diazabicyclo [2.2.2] octane (Va), and its 6-methyl homolog (Vb).

Similar transformations based on nipecotinic acid (VI) were effected. Nitrosation of VI under the usual conditions gives 1-nitrosonipecotinic acid (VII). VII was reduced with zinc-acetic acid at 20–25° C, raising the temperature to 30–35° C facilitated deamination, to give the 1-aminonipecotinic acid (VIII). Cyclization of VIII to 3-keto-1, 2-diazabicyclo [3.2.1] octane (IX) took place at a higher temperature (260–270° C) than in the previous cases. The total yield of IX was 17%. The indicated yield of cyclic hydrazine IX could not be raised by varying the conditions for reduction of VII or for cyclization of VIII. IX gives 1, 2-diazabicyclo [3.2.1] octane (X), and its N-benzoyl derivative.

2-Nitroso-, 2-acyl-, and 2-alkyl (aralkyl)-1, 2-diazabicyclo- [2.2.2] octane were synthesized from Va. The latter readily undergoes the Mannich reaction with formaldehyde and phthalimide, and with formaldehyde sodium bisulfite and sodium cyanide, and it adds acrylonitrile. Introduction of powerful electron-accepting substituents (nitroso, diphenylacetyl, phthalimidomethyl groups) at position 2 in V, deprives the compounds of their basic properties (hydrochlorides not formed).

2- Cyanomethyl-1, 2-diazabicyclo [2.2.2] octane was converted successively to 2- (β-aminoethyl)- and 2-(β-

*When the present work was finished, there appeared a paper on the symthesis of 1, 2-diazabicyclo [2.2.2] octane and some derivatives of it [2].



XIIa R=H; b R=$N(CH_3)_2$;
XIIIa R=C_6H_5; b R=4-C_5H_4N

guanidoethyl)-1,2-diazabicyclo [2.2.2] octane. The 2-(β-cyanoethyl derivatives gives 2-(β-carboxyethyl)-1,2-diazabicyclo [2.2.2] octance.

Ethyl 1-aminoisonipecotinate (XI), prepared from acid IIa, was converted by reaction with aromatic aldehydes to the benzal derivatives (XII), while the acyl derivatives (XIII) were synthesized by treating it with the acid chlorides.

Experimental

1-Nitroso-2-methylisonipecotinic acid (IIb). A solution of 4.35 g (0.063 mole) $NaNO_2$ in 15 ml water, was added to a solution of 10 g (0.055 mole) 2-methylisonipecotinic acid hydrochloride in 16 ml water at 70° C. An acid reaction to congo red was maintained by periodically adding 2 N HCl. The reaction mixture was held for 2 hr at 70°C, cooled, and extracted with $CHCl_3$, to give 7.8 g (81.2%) IIb, colorless crystals, mp 108-110° C (ex benzene). Found: C 48.80; H6.88; N 16.01%. Calculated for $C_7H_{12}N_2O_3$: C 48.83; H 7.02; N 16.27%.

1-Nitrosonipecotinic acid (VII). Nitrosation of 37 g (0.22 mole) nipecotinic acid hydrochloride as described above, gave 9.3 g (33%) VII. Colorless crystals, mp 104-106° C (ex benzene). Found: C 45.50; H 6.36; N 17.68%. Calculated for $C_6H_{10}N_2O_3$: C 45.56; H 6.37; N 17.71%.

3-Keto-1,2-diazabicyclo [2.2.2] octane (IVa). 80 ml 85% AcOH was added to a suspension of 20 g (0.127 mole) 1-nitrosoisonipecotinic acid and 50.5 g (0.8 g at) Zn dust in 175 ml water, at 25-30° C. The mixture was held at the latter temperature for 2 hr more, filtered, and the solution evaporated under reduced pressure. After removing AcOH and water, the residue was heated at 5-10 mm for 1 hr 30 min at 250-255° C (Wood's metal bath). The reaction products were dissolved in water, made alkaline with K_2CO_3, and extracted with $CHCl_3$, to give 9.1 g (57%) IVa, as colorless crystals, readily soluble in $CHCl_3$ and water, sparingly soluble in benzene, AcOEt, Me_2CO. Mp 171-173° C (ex benzene). Found: C 57.14; H 7.94; N 22.20%. Calculated for $C_6H_{10}N_2O$: C 57.12; H 7.98; N 22.20%.

Hydrochloride. Colorless crystals, mp 220-222° C (decomp, ex EtOH). Found: Cl 22.10; N 17.53%. Calculated for $C_6H_{10}N_2O \cdot HCl$: Cl 21.80; N 17.23%.

Methiodide. Colorless crystals, mp 214-215° C (decomp, ex EtOH). Found: I 47.79; N 10.49%. Calculated for $C_7H_{13}IN_2O$: I 47.33; N 10.44%.

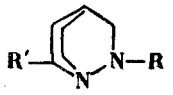
3-Keto-6-methyl-1,2-diazabicyclo [2.2.2] octane (IVb). 9.5 g (0.055 mole) IIb in 78 ml water was reduced with 22.5 g Zn dust and 36 ml 85% AcOH, at 25-30° C. Cyclization was effected at 210-220° C, to give 4.4 g (57% IVb), colorless crystals, mp 111-113° C (ex benzene-petrol ether). Found: C 59.85; H 8.53; N 19.97%. Calculated for $C_7H_{12}N_2O$: C 59.97; H 8.63; N 19.98%.

3-Keto-1,2-diazabicyclo [3.2.1] octane (IX). 10 g (0.065 mole) VII in 80 ml water was reduced with 25 g Zn dust and 40 ml 85% AcOH, at 15-20° C. Cyclization was effected at 260-270° C, to give 1.7 g (17%) IX, colorless crystals, mp 172-173° C (ex AcOEt). Found: C 57.37; H 8.17; N 22.03%. Calculated for $C_6H_{10}N_2O$: C 57.12; H 7.98; N 22.20%.

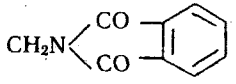
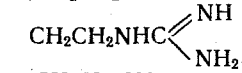
Hydrochloride: mp 172-174° C.

2-Acetyl-3-keto-1,2-diazabicyclo [2.2.2] octane. Prepared by heating together 2.4 g (0.019 mole) IVa and 15 ml Ac_2O, yield 2.75 g (84%), colorless crystals, readily soluble in ether, benzene, alcohols, sparingly soluble in petrol ether. Mp 124-126° C (ex petrol ether + benzene). Found: C 57.07; H 7.05; N 16.89%. $C_8H_{12}N_2O_2$: C 57.13; H 7.19; N 16.66%.

2-Benzoyl-3-keto-1,2-diazabicyclo [2.2.2] octane. 3 g (0.024 mole) IVa, 3.35 g (0.024 mole) benzoyl



2-Substituted 1, 2-diazabicyclo [2.2.2] octanes

R'	R	Bp, °C (mm Hg) Mp, °C	Hydrochloride, mp, °C	Formula	Found, %			Calculated, %			Yield, %
					C	H	N	C	H	N	
H	CH_3	96—97 (85)	230—232	$C_7H_{14}N_2 \cdot HCl$	22.04**		17.24	21.79**		17.22	73.3
H	$COCH_3$	65—67	176—178	$C_8H_{14}N_2O$	62.23	9.06	17.98	62.31	9.15	18.17	84.3
H	COC_2H_5	57—60	163—165	$C_9H_{16}N_2O \cdot HCl$	17.41**		13.88	17.31		13.68	82.2
H	COC_6H_5	159—160	168—170	$C_{13}H_{16}N_2O$	72.54	7.38	12.76	72.19	7.46	12.96	72.5
H	$COC_6H_2(OCH_3)_3$-3′,4′,5′	129—131	185—187	$C_{16}H_{22}N_2O_4 \cdot HCl$	10.44**		8.21	10.35**		8.14	87.2
H	$COCH(C_6H_5)_2$	144—146	—	$C_{20}H_{22}N_2O$	78.63	6.94	9.28	78.48	7.24	9.14	78.8
H	NO	86—87	—	$C_6H_{11}N_3O$	51.02	7.88	30.04	51.05	7.85	29.77	85.4
H		amorphous powder	—	$C_{15}H_{17}N_3O_2$	66.80	6.08	15.20	66.40	6.32	15.48	66.5
H	CH_2C	117—119 (6)	181—183	$C_8H_{13}N_3$	63.21	8.61	27.62	63.54	8.66	27.79	73
H	$CH_2CH_2NH_2$	89 (5)	—	$C_8H_{17}N_3$	61.29	10.90	27.23	61.89	11.04	27.07	91
H		—	208—210*	$C_9H_{19}N_5 \cdot 2HCl$	39.71	7.90	25.81	40.00	7.83	25.92	46.1
H	CH_2CH_2CN	122—124 (4)	180—182	$C_9H_{15}N_3$	65.13	8.95	25.17	65.42	9.15	25.42	78.2
H	$CH_2CH_2COOC_2H_5$	162—164 (28)	—	$C_{11}H_{20}N_2O_2$	62.04	9.53	13.05	62.23	9.49	13.20	24.6
H	CH_2CH_2COOH	—	204—206	$C_9H_{16}N_2O_2 \cdot HCl$	48.96	7.62	13.04	48.98	7.76	12.70	64
H	C_2H_5	103 (45)	116—118	$C_8H_{16}N_2 \cdot HCl$	54.12	9.50	16.02	54.35	9.69	15.85	76.5
H	C_3H_7	88—90 (17)	131—133	$C_9H_{18}N_2 \cdot HCl$	18.53**		15.00	18.59**		14.69	66.6
H	$CH_2C_6H_5$	152—153 (9)	225—227	$C_{13}H_{18}N_2 \cdot HCl$	15.06**		11.65	14.85**		11.74	54.7
H	$CH_2CH(C_6H_5)_2$	—	228—231	$C_{20}H_{24}N_2 \cdot HCl$	10.64**		8.50	10.78**		8.52	92.3
CH_3	$COCH_3$	130—131 (5)	—	$C_9H_{16}N_2O$	64.20	9.43	16.44	64.25	9.59	16.64	78.8
CH_3	C_2H_5	86—87 (29)	—	$C_9H_{18}N_2$	70.40	11.50	18.50	70.08	11.76	18.16	78.5

* Dihydrochloride mp

** Chlorine figure.

chloride, and 30 ml benzene were refluxed together for 6 hr. The solution was then evaporated under reduced pressure, the residue triturated with ether, filtered, washed with ether, and treated with 40 ml 4% K_2CO_3 solution. The precipitate was filtered off, washed with water, dried, and recrystallized from benzene, to give 1.4 g (25.6%) compound mp 183–185° C. Found: C 67.76; H 5.87; N 12.48%. Calculated for $C_{13}H_{14}N_2O_2$: C 67.81; H 6.13; N 12.17%.

1, 2-Diazabicyclo [2.2.2] octane (Va). 20 g (0.16 mole) IVa was added gradually to a suspension of 12.06 g (0.32 mole) $LiAlH_4$ in a mixture of 200 ml dry ether and 300 ml dry benzene. Then the mixture was refluxed for 20 hr, cooled, and treated with 25 ml water. The hydroxides were filtered off, washed with benzene, then with benzene-ether, and evaporated under reduced pressure, to give 12 g Va, as pale yellow volatile crystals with a sharp amine odor. Mp 130–133° C (after distilling under reduced pressure). Acidification of the benzene distillate gave 5.3 g hydrochloride of Va. Total yield of base 16 g (90%). Found: N 25.34%. Calculated for $C_6H_{12}N_2$: N 24.96%.

Hydrochloride: mp 256–258° C (ex EtOH-ether). Found: C 48.87; H 8.62; Cl 24.15; N 18.91%. Calculated for $C_6H_{12}N_2 \cdot HCl$: C 48.48; H 8.82; Cl 23.85; N 18.84%.

6-Methyl-1, 2-diazabicyclo [2.2.2] octane (Vb). Colorless liquid, bp 92–93° C (25 mm). Found: C 66.22; H 11.19; N 22.10%. Calculated for $C_7H_{14}N_2$: C 66.62; H 11.18; N 22.20%.

Hydrochloride: mp 170–172° C (ex EtOH-ether). Found: N 17.31%. Calculated for $C_7H_{14}N_2 \cdot HCl$: N 17.22%.

1, 2-Diazabicyclo [3.2.1] octane (X). Transparent, extremely hygroscopic plates, mp 86–88° C. Found: N 24.62%. Calculated for $C_6H_{12}N_2$: N 24.96%.

Picrate: yellow crystals, mp 203–205° C (ex EtOH-ether). Found: C 42.08; H 4.27; N 20.77%. Calculated for $C_6H_{12}N_2 \cdot C_6H_3N_3O_7$: C 42.20; H 4.43; N 20.52%.

2-Benzoyl-1, 2-diazabicyclo [3.2.1] octane. 1.5 g (65%) compound was prepared from 1.2 g (0.0107 mole) X and 1.51 g (0.0107 mole) benzoyl chloride in 15 ml benzene, using the method described below. Colorless crystals, mp 81–83° C. Found: C 72.11; H 7.60; N 12.82%. Calculated for $C_{13}H_{16}N_2O$: C 72.19; H 7.46; N 12.95%.

Below are given brief experimental results relating to preparation of 2-substituted 1, 2-diazabicyclo [2.2.2] octanes. Yields, constants, and analytical data for these compounds are given in the table.

2-Methyl-1, 2-diazabicyclo [2.2.2] octane. 2 g (0.018 mole) Va, 1.7 g 35% formalin (0.02 mole) and 2.5 g (0.055 mole) formic acid were heated together on a water bath for 20 hr. The products were evaporated, made alkaline with K_2CO_3, and extracted with ether.

2-Benzoyl-1, 2-diazabicyclo [2.2.2] octane. 1 g (0.009 mole) Va, 1.26 g (0.009 mole) benzoyl chloride, and 10 ml benzene, were mixed with cooling, then refluxed for 1 hr. The reaction products were cooled, treated with 50% K_2CO_3 solution, then extracted with benzene.

The other 2-acyl derivatives of V were prepared similarly. Reduction of the acyl derivatives with $LiAlH_4$ gave a series of 2-alkyl (aralkyl) substituted compounds (Va).

2-Nitroso-1, 2-diazabicyclo [2.2.2] octane. A solution of 1.36 g (0.02 mole) $NaNO_2$ in 5 ml water was added, with cooling, to a solution of 2 g (0.018 mole) Va in 25 ml 2N HCl, the mixture stirred for 2 hr at 20° C, then extracted with benzene, the benzene solution evaporated under reduced pressure, and the residue recrystallized from ether-petrol ether.

2-Phthalimidomethyl-1, 2-diazabicyclo [2.2.2] octane. 1.12 g (0.01 mole) Va, 1 g 35% formalin (0.012 mole), 1.47 g (0.01 mole) phthalimide, and 8 ml EtOH were refluxed together for 4 hr, the products evaporated under reduced pressure, and the residue triturated with ether.

2-Cyanomethyl-1, 2-diazabicyclo [2.2.2] octane. 6 g (0.053 mole) Va, 16.4 ml 48.5% aqueous formaldehyde sodium bisulfite (0.059 mole), 2.9 g (0.059 mole) NaCN, and 18 ml H_2O were heated for 4 hr at 55–60° C. The reaction mixture was cooled, and extracted with $CHCl_3$.

2-(β-Aminoethyl)-1, 2-diazabicyclo [2.2.2] octane. 5.3 g (0.035 mole) 2-cyanomethyl-1, 2-diazabicyclo [2.2.2] octane was reduced with 4 g $LiAlH_4$ in a mixture of 60 ml benzene and 100 ml ether. The reaction was run as described above.

2-(β-Guanidoethyl)-1, 2-diazabicyclo [2.2.2] octane. 1.5 g (0.015 mole) 2-(β-aminoethyl)-1, 2-diazabicyclo [2.2.2] octane, 1.34 g (0.015 mole) S-methylthiourea, and 8 ml water were refluxed together for 4 hr. The reaction products were treated with 40% NaOH solution, extracted with $CHCl_3$, and the dihydrochloride prepared from the extracts.

2-(β-Cyanoethyl) 1, 2-diazabicyclo [2.2.2] octane. 1.12 g (0.01 mole) Va, 0.95 g (0.018 mole) acrylonitrile, and 10 ml 90% EtOH, were refluxed for 5 hr, the products evaporated under reduced pressure, made alkaline with 50%

K_2CO_3, and extracted with ether.

2-(β-Carboethoxylethyl)-1,2-diazabicyclo [2.2.2] octane. 3.8 g (0.023 mole) 2-(β-cyanoethyl)-1,2-diazabicyclo [2.2.2] octane, 76 ml AcOH, and 38 ml concentrated HCl, were refluxed together for 20 hr, the products evaporated under reduced pressure, and the residue dried and esterified.

Ethyl 1-aminoisonipecotinate (XI). A solution of 20 g (0.127 mole) IIa and 176 ml water was reduced with 50 g Zn dust and 70 ml 95% AcOH, following the procedure used above. The reduction products were evaporated under reduced pressure, dried, and twice esterified with ethanolic HCl, to give 12.44 g mixed ethyl esters of isonipecotinic acid and 1-aminoisonipecotinic acid. Careful fractionation gave 9.5 g (43.8%) XI, as a colorless mobile liquid, readily soluble in water and in organic solvents. Bp 90° C (1 mm), n_D^{20} 1.4742. Found: C 55.97; H 9.24; N 15.66%. Calculated for $C_8H_{16}N_2O_2$: C 55.78; H 9.36; N 16.30%.

1-Aminoisonipecotinic acid (IIIa). 0.45 g (0.0026 mole) XI and 8 ml 17% HCl were refluxed together for 4 hr, the products evaporated under reduced pressure, and the residue recrystallized from EtOH, to give 0.4 g (84.7%) hydrochloride, mp 195–197° C. Found: C 39.80; H 7.31; Cl 20.05; N 15.52%. Calculated for $C_6H_{12}N_2O_2 \cdot HCl$: C 39.89; H 7.25; Cl 19.62; N 15.51%.

1-Benzalamino-4-carboethoxypiperidine (XIIa). 0.53 g (0.0031 mole) XI, 0.33 (0.0031 mole) benzaldehyde, and 3 ml EtOH were refluxed together for 3 hr, the products evaporated under reduced pressure, the residue triturated with water, filtered, washed with water, and dried, to give pale yellow crystals, mp 40–43° C. Found: C 69.04%; H 7.62; N 10.57%. Calculated for $C_{15}H_{20}N_2O_2$: C 69.20; H 7.74; N 10.76%.

1-(p-Dimethylaminobenzal) amino-4-carboethoxypiperidine (XIIb). 1 g (0.0058 mole) XI and 0.8 g (0.0058 mole) p-dimethylaminobenzaldehyde in 10 ml EtOH gave 1.3 g (73.6%) XIIb, pale yellow crystals, mp 83–85° C (ex petrol ether-ether). Found: C 67.24; H 8.19; N 14.07%. Calculated for $C_{17}H_{25}N_3O_2$: C 67.30; H 8.30; N 13.85%

1-Benzoylamino-4-carboethoxypiperidine (XIIIa). 1 g (0.0058 mole) XI, 0.82 g (0.0058 mole) benzoyl chloride, and 10 ml dry benzene were refluxed together for 3 hr, the products cooled, diluted with 10 ml ether, and the precipitate formed filtered off, to give 1.4 g (77%) XIIIa hydrochloride, colorless crystals, mp 216–217° C (ex Me_2CO-EtOH). Found: Cl 11.51; N 8.94%. Calculated for $C_{15}H_{20}N_2O_3 \cdot HCl$: Cl 11.56; N 9.13%.

1-Isonicotinoylamino-4-carboethoxypiperidine (XIIIb). 2 g (0.016 mole) XI, 1.65 g (0.016 mole) isonicotinoyl chloride, and 20 ml benzene were refluxed together for 3 hr, the reaction product cooled, the precipitate filtered off with suction, washed with benzene, and treated with 20 ml 50% K_2CO_3 solution. The alkaline solution was extracted with $CHCl_3$, and $CHCl_3$ solution dried over K_2CO_3, evaporated, and the residue recrystallized from benzene-petrol ether, to give 2.5 g (77.5%) XIIIb, colorless glistening crystals, mp 142–144° C. Found: C 60.38; H 6.90; N 15.13%. Calculated for $C_{14}H_{19}N_3O_3$: C 60.64; H 6.90; N 15.15%.

REFERENCES

1. E. E. Mikhlina, N. A. Komarova, and M. V. Rubtsov, KhGS [Chemistry of Heterocyclic Compounds], no. 1, 91, 1966.

2. P. U. Carabateas, A. R. Surrey, and L. S. Harris, J. Med. Chem., 7, 293, 1964.

28 November 1964

Ordzhonikidze All-Union Pharmaceutical Chemistry Scientific Research Institute, Moscow