INVESTIGATIONS IN THE IMIDAZOLE SERIES

LXX.* SYNTHESIS OF DERIVATIVES OF 1(9)H- AND 1H-IMIDAZO[1,2-*a*]BENZIMIDAZOLES

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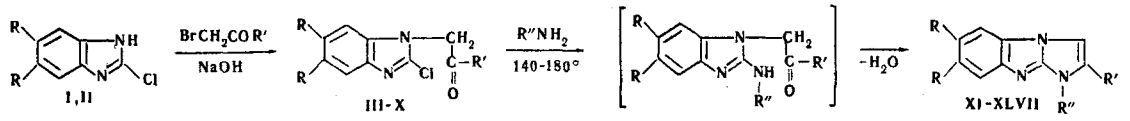
UDC 547.785.5.07

Derivatives of 1(9)H- and 1H-imidazo[1,2-*a*]benzimidazoles were synthesized by the reaction of 1-acylmethyl-2-chlorobenzimidazoles with ammonia and primary amines.

The preparation of 9H-imidazo[1,2-*a*]benzimidazole derivatives by the reaction of 1-alkyl-2-aminobenzimidazoles with α-halo ketones is well-known [2-7]. Heating o-phenylenediamine with 2-chloro-4,5-diphenyloxazole gives a substance of unknown structure, for which the 1(9)H-2,3-diphenylimidazo[1,2-*a*]-benzimidazole structure was proposed on the basis of the results of elementary analysis [8].

We have developed an original method for the synthesis of derivatives of 1(9)H- and 1H-imidazo[1,2-*a*]benzimidazoles, which has been previously reported only in brief publications [9, 10]. 1-Acylmethyl-2-chlorobenzimidazoles (III-X) [9, 14] were obtained by reaction of the accessible 2-chlorobenzimidazole (I) [11, 12] and 2-chloro-5,6-dimethylbenzimidazole (II) [13] with α-halo ketones in alcohol or aqueous alcohol solutions in the presence of an alkaline agent. When these compounds are heated with ammonia or primary amines in lower alcohols or dimethylformamide (DMF) at 140-180°C, not only does the chlorine atom undergo nucleophilic substitution, but the intermediate 1-acylmethyl-2-amino(alkylamino, arylamino)benzimidazoles are simultaneously dehydrated to give 1(9)H-imidazo[1,2-*a*]benzimidazole derivatives (XX, XXXIV, XXXVII, and XLII) and 1H-imidazo[1,2-*a*]benzimidazole derivatives (XI-XIX, XXI-XXXIII, XXXV, XXXVI, XXXVIII-XLI, and XLIII-XLVII, Table 1). All of the indicated compounds were synthesized in order to study the dependence between their structure and biological activity.



R = H, Alk; R' = Alk, Ar; R" = H, Alk, Ar

The structures of the three-ring compounds were confirmed by the IR spectra, in which the absorption bands of the CO group that are present in the IR spectra of the starting 1-acylmethyl-2-chlorobenzimidazoles (III-X) are absent.

EXPERIMENTAL

2-Chlorobenzimidazole (I) [11, 12], 2-chloro-5,6-dimethylbenzimidazole (II) [13], and 1-acetonyl-(p-methoxyphenacyl, p-bromophenacyl, α-acetothienyl)-2-chlorobenzimidazoles (III-VI) [14] were prepared by known methods.

1-Phenacyl-2-chlorobenzimidazole (VII). A solution of 3 g (0.02 mole) of I, 4 g (0.02 mole) of phenacyl bromide, and 0.8 g (0.02 mole) of NaOH in 50 ml of 50% methanol was stirred at 35-40° for 30-40 min

* See [1] for communication LXIX.

Zaporozhe Medical Institute. S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 253-256, February, 1972. Original article submitted August 13, 1970.

TABLE 1. 1H-Imidazo[1,2-*a*]benzimidazoles (XI-XLVII)[a]

Compound	R	R′	R″	Mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
						C	H	N	C	H	N	
XI	H	CH_3	CH_2CH_2OH	167—169	$C_{12}H_{13}N_3O$	67,0	6,0	19,9	66,9	6,1	19,5	87
XII	H	CH_3	$CH_2CH{=}CH_2$	224—226	$C_{13}H_{13}N_3 \cdot C_6H_3N_3O_7$	51,9	4,0	19,2	51,8	3,7	19,1	67
XIII	H	CH_3	$CH_2C_6H_5$	128—130	$C_{17}H_{15}N_3$	78,0	6,0	16,3	78,1	5,8	16,1	93
XIV	H	CH_3	C_6H_5	143—145	$C_{16}H_{13}N_3$	77,4	5,4	17,3	77,7	5,3	17,0	57
XV	H	CH_3	$C_6H_4CH_3$-*m*	204—206	$C_{17}H_{15}N_3 \cdot C_6H_3N_3O_7$	56,2	3,7	17,3	56,3	3,7	17,1	54
XVI	H	CH_3	$C_6H_4CH_3$-*p*	111—113	$C_{17}H_{15}N_3 \cdot H_2O$	73,4	6,1	15,0	73,1	6,1	15,0	64
XVII	H	CH_3	$C_6H_4OCH_3$-*p*	113—115	$C_{17}H_{15}N_3O \cdot H_2O$	69,5	5,6	14,9	69,1	5,8	14,3	85
XVIII	H	CH_3	$C_6H_4OC_2H_5$-*p*	122—124	$C_{18}H_{17}N_3O \cdot H_2O$	70,0	5,9	13,4	69,9	6,2	13,6	53
XIX	H	CH_3	α-$C_{10}H_7$	180—182	$C_{20}H_{15}N_3 \cdot C_6H_3N_3O_7$	59,4	3,7	15,6	59,3	3,4	15,9	47
XX	H	C_6H_5	H	285—287[b]	$C_{15}H_{11}N_3$	77,3	4,9	18,1	77,2	4,7	18,0	87
XXI	H	C_6H_5	CH_3	238—240[b]	$C_{16}H_{13}N_3 \cdot HCl$[c]	67,4	5,0	14,9	67,7	5,0	14,8	88
XXII	H	C_6H_5	CH_2CH_2OH	166—168	$C_{17}H_{15}N_3O$	73,5	5,6	14,8	73,6	5,5	15,1	83
XXIII	H	C_6H_5	$CH_2CH_2N(C_2H_5)_2$	192—194	$C_{21}H_{24}N_4 \cdot 2C_6H_3N_3O_7$	50,2	3,7	17,3	50,1	3,8	17,7	70
XXIV	H	C_6H_5	*i*-C_4H_9	207—209	$C_{19}H_{19}N_3 \cdot C_6H_3N_3O_7$	58,0	4,2	15,9	57,9	4,3	16,2	82
XXV	H	C_6H_5	C_6H_{11}	203—205	$C_{21}H_{21}N_3 \cdot C_6H_3N_3O_7$	59,7	4,7	15,5	59,5	4,4	15,4	66
XXVI	H	C_6H_5	$CH_2C_6H_5$	130—132	$C_{22}H_{17}N_3$	81,6	5,3	12,9	81,7	5,3	13,0	92
XXVII	H	C_6H_5	C_6H_5	204—206	$C_{21}H_{15}N_3$	81,7	5,0	13,9	81,5	4,9	13,6	71
XXVIII	H	C_6H_5	$C_6H_4CH_3$-*m*	188—190	$C_{22}H_{17}N_3$	81,7	5,2	13,2	81,7	5,3	13,0	71
XXIX	H	C_6H_5	$C_6H_4CH_3$-*p*	188—190	$C_{22}H_{17}N_3$	82,1	5,1	12,8	81,7	5,3	13,0	65
XXX	H	C_6H_5	C_6H_4OH-*p*	348—350[b]	$C_{21}H_{15}N_3O$	77,8	4,8	12,7	77,5	4,6	12,9	50
XXXI	H	C_6H_5	$C_6H_4OCH_3$-*p*	205—207	$C_{22}H_{17}N_3O$	77,8	5,1	12,2	77,9	5,0	12,4	88
XXXII	H	C_6H_5	$C_6H_4OC_2H_5$-*p*	149—151	$C_{23}H_{19}N_3O \cdot H_2O$	74,0	5,3	11,2	74,4	5,7	11,3	87
XXXIII	H	C_6H_5	α-$C_{10}H_7$	212—214	$C_{25}H_{17}N_3$	83,8	4,6	11,7	83,5	4,8	11,7	45
XXXIV	H	$C_6H_4OCH_3$-*p*	H	295—297[b]	$C_{16}H_{13}N_3O$	72,7	4,8	15,9	73,0	5,0	16,0	83
XXXV	H	$C_6H_4OCH_3$-*p*	CH_2CH_2OH	188—190	$C_{18}H_{17}N_3O_2$	70,0	5,7	14,0	70,3	5,6	13,7	80
XXXVI	H	$C_6H_4OCH_3$-*p*	C_6H_5	125—127	$C_{22}H_{17}N_3O \cdot H_2O$	73,8	5,2	12,2	73,9	5,4	11,8	82
XXXVII	H	C_6H_4Br-*p*	H	316—318[b]	$C_{15}H_{10}BrN_3$[d]	57,8	3,3	13,4	57,7	3,2	13,5	64
XXXVIII	H	C_6H_4Br-*p*	CH_2CH_2OH	184—186	$C_{17}H_{14}BrN_3O$[e]	57,4	3,8	11,9	57,3	4,0	11,8	87
XXXIX	H	C_6H_4Br-*p*	*i*-C_4H_9	225—227	$C_{19}H_{18}BrN_3 \cdot C_6H_3N_3O_7$[f]	50,5	3,9	13,9	50,3	3,5	14,1	77
XL	H	C_6H_4Br-*p*	C_6H_5	182—184	$C_{21}H_{14}BrN_3$[g]	65,1	3,7	11,0	65,0	3,6	10,8	72
XLI	H	C_6H_4Br-*p*	$C_6H_4CH_3$-*p*	188—190	$C_{22}H_{16}BrN_3 \cdot H_2O$[h]	62,7	4,1	9,9	62,9	4,3	10,0	85
XLII	H	2-Thienyl	H	281—283[b]	$C_{13}H_9N_3S$[i]	64,9	3,8	17,5	65,2	3,8	17,6	34
XLIII	CH_3	CH_3	$CH_2C_6H_5$	192—194	$C_{19}H_{19}N_3$	79,3	6,9	14,4	78,9	6,6	14,5	83
XLIV	CH_3	CH_3	C_6H_5	198—200	$C_{18}H_{17}N_3$	78,5	6,4	15,3	78,5	6,2	15,3	75
XLV	CH_3	C_6H_5	CH_2CH_2OH	163—165	$C_{19}H_{19}N_3O$	74,7	5,9	13,8	74,7	6,3	13,8	59
XLVI	CH_3	C_6H_5	*n*-C_4H_9	211—213	$C_{21}H_{23}N_3 \cdot C_6H_3N_3O_7$	59,5	4,9	15,4	59,3	4,8	15,4	54
XLVII	CH_3	C_6H_5	C_6H_5	154—156	$C_{23}H_{19}N_3$	81,9	5,4	12,4	81,9	5,7	12,5	51

[a]The substances were purified for analysis by crystallization: XI from water; XXII, XXVI, and XXVII from aqueous methanol; XV, XIX, XXIV, XXV, XXXI, and XLVI from methanol; XIII, XIV, XVI-XVIII, XXVIII, XXIX, XXXII, XXXIII, XXXV, XXXVI, XXXVIII, XL, XLI, XLIII-XLV, and XLVII from aqueous acetone; XXI from acetone–methanol (11 : 1); XII and XXXIX from dioxane; XX and XXIII from acetic acid; and XXX, XXXIV, XXXVII and XLII from aqueous DMF. [b]With decomposition. [c]Found: Cl 12.6%. Calculated: Cl 12.5%. [d]Found: Br 25.3%. Calculated: Br 25.6%. [e]Found: Br 22.9%. Calculated: Br 22.4%. [f]Found: Br 13.4%. Calculated: Br 13.4%. [g]Found: Br 20.7%. Calculated: Br 20.6%. [h]Found: Br 19.2%. Calculated: Br 19.0%. [i]Found: S 13.6%. Calculated: S 13.4%.

and cooled. The precipitate was removed by filtration and washed with 50% methanol to give 4.5 g (85%) of VII with mp 168-170° (from methanol). Found: C 66.3; H 3.9; Cl 13.3; N 10.4%. $C_{15}H_{11}ClN_2O$. Calculated: C 66.5; H 4.1; Cl 13.1; N 10.3%.

1-Acetonyl-2-chloro-5,6-dimethylbenzimidazole (VIII). This compound was prepared by a method similar to that used to prepare III-VI [14]. A product with mp 182-184° (from 50% methanol) was obtained in 40% yield. Found: C 61.3; H 6.0; Cl 14.8; N 12.2%. $C_{12}H_{13}ClN_2O$. Calculated: C 60.9; H 5.5; Cl 15.0; N 11.8%.

1-Phenacyl-2-chloro-5,6-dimethylbenzimidazole (IX). This compound was obtained by a method similar to that used to prepare VII. A product with mp 173-175° (from methanol) was obtained in 88% yield. Found: C 68.1; H 5.2; Cl 11.7; N 9.1%. $C_{17}H_{15}ClN_2O$. Calculated: C 68.3; H 5.1; Cl 11.9; N 9.4%.

1-(α-Acetothienyl)-2-chloro-5,6-dimethylbenzimidazole (X). This compound was obtained by a method similar to that used to prepare III-VI [14]. A product with mp 178-180° (from methanol) was obtained in 85% yield. Found: C 59.9; H 4.3; Cl 11.3; N 9.2; S 11.0%. $C_{15}H_{13}ClN_2OS$. Calculated: C 59.1; H 4.3; Cl 11.6; N 9.2; S 10.5%.

1H-Imidazo[1,2-a]benzimidazole Derivatives (XI-XLVII, Table 1). A solution of 0.01 mole of III-X and 0.02-0.021 mole of amine in 50 ml of methanol was heated at 140-160° for 6 h and cooled. The precipitate was removed by filtration and washed with water and ether. Evaporation of the alcohol mother liquor and washing of the residue with water and ether gave an additional amount of product. In some experiments, the reaction mass was cooled and poured into water, and the precipitate was removed by filtration and washed with water and ether. The ammonia, methylamine, and ethylamine were used in large excess as 20-25% alcohol solutions, and the reactions were carried out at 160-180° (6 h). Compounds XV, XVII, XIX, XXXVI, XL, and XLI were similarly obtained, except that the reactions were carried out by refluxing in DMF for 4 h. The colorless or pale-yellow (XXVII, XXXVI, XLIII, XLIV, and XLVII) crystalline substances were soluble in most organic solvents and insoluble in water. Bases VI, XII, XV, XIX, XXIII-XXV, XXXIX, and XLVI are oily substances and were characterized as picrates or hydrochlorides.

LITERATURE CITED

1. E. G. Knysh, A. N. Krasovskii, and P. M. Kochergin, Khim. Geterotsikl. Soedin., 33 (1972).
2. A. M. Simonov and P. M. Kochergin, Khim. Geterotsikl. Soedin., 316 (1965).
3. L. M. Werbel and M. L. Zamora, J. Heterocycl. Chem., 2, 287 (1965).
4. P. M. Kochergin and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 1, 133 (1967).
5. A. M. Simonov and V. A. Anisimova, Khim. Geterotsikl. Soedin., 1102 (1968).
6. A. M. Simonov, A. A. Belous, V. A. Anisimova, and S. V. Ivanovskaya, Khim.-Farmats. Zh., 3, No. 1, 7 (1969).
7. A. M. Simonov, V. A. Anisimova, and Yu. V. Koshchienko, Khim. Geterotsikl. Soedin., 184 (1969).
8. R. Gompper and F. Effenberger, Ber., 92, 1958 (1959).
9. P. M. Kochergin and V. S. Ponomar', USSR Author's Certificate No. 230,827 (1968); Byull. Izobr., No. 35, 22 (1968).
10. P. M. Kochergin, B. A. Priimenko, V. S. Ponomar', M. V. Povstyanoi, A. A. Tkachenko, I. A. Mazur, A. N. Krasovskii, E. G. Knysh, and M. I. Yurchenko, Khim. Geterotsikl. Soedin., 177 (1969).
11. L. S. Éfros, B. A. Porai-Koshits, and S. G. Farbenshtein, Zh. Obshch. Khim., 23, 1691 (1953).
12. D. Harrison, I. T. Ralf, and A. C. Smith, J. Chem. Soc., 2930 (1963).
13. N. P. Bednyagina, G. N. Tyurenkova, and I. V. Panov, Zh. Obshch. Khim., 34, 1575 (1964).
14. A. N. Krasovskii, P. M. Kochergin, and L. V. Samoilenko, Khim. Geterotsikl. Soedin., 827 (1970).