RESEARCH IN THE IMIDAZOLE SERIES

LXVIII.* SYNTHESIS OF 2-ACYL DERIVATIVES OF NAPHTH[1',2' : 4,5]IMIDAZO[2,1-b]THIAZOLE

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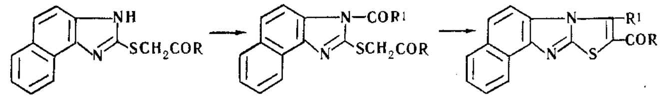
The synthesis of 9-acyl- and 8-alkyl-9-acyl-substituted naphth[1',2' : 4,5]imidazo[2,1-b]thiazoles was accomplished by the reaction of 2-acylmethylthionaphth[1,2-d]imidazole with acylating agents and of 2-mercaptonaphth[1,2-d]imidazole with 3-chloro-2,4-pentanedione.

In developing our research in [2-4], we have investigated the reaction of the previously synthesized 2-acylmethylthionaphth[1,2-d]imidazoles (I-IV) [1] with acylating agents. It was established that I-IV form 3-formyl(acetyl, propionyl)-2-acylmethylthionaphth[1,2-d]imidazoles (VI-XII, Table 1) when they are treated with acetic or propionic anhydrides, as well as with formic acid in the presence of acetic anhydride. When these compounds are heated with the appropriate acylating agents in the presence of sodium or potassium salts of carboxylic acids (also with the addition of phosphoric acid in the case of VIII), they are readily converted to 9-acyl(8-alkyl-9-acyl)naphth[1',2' : 4,5]imidazo[2,1-b]thiazoles (XIII-XX, Table 1). The latter were also obtained in one step under the conditions indicated above.

The acylation of I-IV could also proceed at the 3 position as well as the 1 position of the naphth[1,2-d]imidazole ring, which in the long run, after cyclization of the intermediate compounds, would lead to the formation of either XIII-XX or the corresponding naphth[2',1' : 4,5]imidazo[2,1-b]thiazole derivatives or mixtures of these isomers. In all cases, we isolated only one substance, the purity of which was confirmed by chromatography. The presence of acyl groups was confirmed by IR spectroscopy.

Considering that the reaction of 2-mercaptonaphth[1,2-d]imidazole with α-halo ketones proceeds unambiguously to form naphth[1',2' : 4,5]imidazo[2,1-b]thiazole derivatives [1], we accomplished the synthesis of 8-methyl-9-acetylnaphth[1',2' : 4,5]imidazo[2,1-b]thiazole (XV) [5] by the reaction of 2-mercaptonaphth[1,2-d]imidazole with 3-chloro-2,4-pentanedione. This compound proved to be identical to the corresponding sample obtained by the reaction of 2-acetonylthionaphth[1,2-d]imidazole (I) with acetic anhydride in the presence of sodium acetate and phosphoric acid or by cyclization, under similar conditions, of the N-acetyl derivative of I (VIII).



I-IV VI-XII XIII-XX

R=Alk, Ar; R¹=H, Alk

Thus it was simultaneously established that the intermediates also have 3-acyl-2-acylmethylthionaphth[1,2-d]imidazole structures (VI-XII).

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*See [1] for communication LXVII.

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TABLE 1. 3-Acyl-2-acylmethylthionaphth[1,2-d]imidazole (VI-XII) and 9-Acyl(8-alkyl-9-acyl)naphth[1',2' : 4,5]imidazo[2,1-b]thiazoles (XIII, XX)

Compound	R	R′	Mp (dec.), °C	ν_{CO}, cm^{-1}	Empirical formula	Found, %				Calculated, %				Yield, %
						C	H	N	S	C	H	N	S	
VI	H	C_6H_4Br-*p*	123—124	1665, 1680	$C_{20}H_{13}BrN_2O_2S$*	56,3	2,6	7,0	7,9	56,5	2,6	6,6	7,5	85
VII	H	$C_6H_4NO_2$-*p*	146—148	1680	$C_{20}H_{13}N_3O_4S$	61,7	3,6	10,7	8,3	61,4	3,3	10,7	8,2	96
VIII	CH_3	CH_3	182—183	1710	$C_{15}H_{14}N_2O_2S$	64,3	5,0	9,6	10,6	64,4	4,7	9,4	10,5	97
IX	CH_3	C_6H_5	172—173	—	$C_{21}H_{16}N_2O_2S$	70,0	4,4	7,8	8,9	70,0	4,5	7,8	8,9	97
X	CH_3	C_6H_4Br-*p*	170—171	1675, 1690	$C_{21}H_{15}BrN_2O_2S$*	57,1	3,5	6,4	7,3	57,4	3,4	6,4	7,3	96
XI	CH_3	$C_6H_4NO_2$-*p*	233—234	1740	$C_{21}H_{15}N_3O_4S$	62,7	3,6	10,6	8,0	62,2	3,7	10,4	7,9	99
XII	C_2H_5	C_6H_4Br-*p*	149—150	1680, 1710	$C_{22}H_{17}BrN_2O_2S$*	58,1	3,8	6,6	7,1	58,3	3,8	6,2	7,1	98
XIII	H	C_6H_5	168—170		$C_{20}H_{12}N_2OS$	72,3	4,1	8,6	10,2	73,1	3,7	8,5	9,8	97
XIV	H	$C_6H_4NO_2$-*p*	258—259		$C_{20}H_{11}N_3O_3S$	64,8	2,9	11,7	8,6	64,3	2,7	11,3	8,6	83
XV	CH_3	CH_3	246—248		$C_{16}H_{12}N_2OS$	71,2	4,8	11,4	13,0	71,4	4,8	11,1	12,7	82
XVI	CH_3	C_6H_5	192—194		$C_{21}H_{14}N_2OS$	73,1	4,1	7,8	9,7	73,6	4,1	8,2	9,4	67
XVII	CH_3	C_6H_4Br-*p*	250—251	1680	$C_{21}H_{12}BrN_2OS$*	59,8	3,3	6,3	7,9	59,9	3,1	6,6	7,6	80
XVIII	CH_3	$C_6H_4NO_2$-*p*	243—244	1680	$C_{21}H_{13}N_3O_3S$	65,7	3,7	11,0	8,0	65,1	3,4	16,8	8,3	87
XIX	C_2H_5	C_6H_5	190—192	1675	$C_{22}H_{16}N_2OS$	73,9	4,4	8,2	8,6	74,1	4,5	7,9	9,0	87
XX	C_2H_5	C_6H_4Br-*p*	178—180		$C_{22}H_{15}BrN_2OS$	—	—	6,7	7,7	—	—	6,4	7,3	80

*The compositions of VI, X, XII, and XVII were also confirmed by the determination of the bromine content.

EXPERIMENTAL

The starting 2-acetonyl(phenacyl, p-bromophenacyl, p-nitrophenacyl)thionaphth[1,2-d]imidazoles (I-IV) were previously described in [1].

2-(α-Acetylacetonylthio)naphth[1,2-d]imidazole (V). This compound was obtained in 94% yield by the reaction of 2-mercaptonaphth[1,2-d]imidazole [6] with 3-chloro-2,4-pentanedione by the method in [1] and had mp 165-166° (dec., from aqueous acetone). Found: C 64.4; H 4.8; N 9.2; S 10.9%. $C_{16}H_{14}N_2O_2S$. Calculated: C 64.4; H 4.7; N 9.4; S 10.7%.

3-Acyl-2-acylmethylthionaphth[1,2-d]imidazoles (VI-XII, Table 1). A solution of 0.005 mole of III or IV in 30 ml of a previously prepared mixture of 85% HCOOH and $(CH_3CO)_2O$ (1 : 2) was allowed to stand for 24 h (to prepare VII) or was refluxed for 1 h (VI). The mixture was poured into water, and the precipitate was removed by filtration and washed with water.

B) A solution of 0.005 mole of I-IV in 20 ml of $(CH_3CO)_2O$ was heated for 30 min at 95-97° (to obtain VIII and IX) or was refluxed for 5 min (X and XI). The mixture was cooled and worked up as in experiment A. Compound XII was obtained in the same way as X by refluxing III with propionic anhydride.

Compounds VI-XII are colorless (VIII, IX, and XII), yellow (VII, X, and XI), or slightly yellowish (VI) crystalline substances that are readily hydrolyzed to the starting I-IV on heating in water, especially in the presence of acids or alkalis. The compounds were purified for analysis by crystallization from ethanol (VI and VIII), dioxane (VII and XI), or aqueous dioxane (IX, X, and XII). Only one spot was detected during chromatography of VII and XI on Al_2O_3: VII, R_f 0.66 [$CHCl_3$–CCl_4–dichloroethane (2.5 : 1 : 1)], 0.72 [dichloroethane–ethanol (2.5 : 1)]; XI, R_f 0.81 [dichloroethane–ethanol (2.5 : 1)], 0.85 [$CHCl_3$–CCl_4–dichloroethane (2.5 : 1 : 1)].

9-Acyl- and 8-Alkyl-9-acylnaphth[1',2' : 4,5]imidazo[2,1-b]thiazoles (XIII-XX, Table 1). A) An equal by weight amount of HCOONa • $2H_2O$ and 20 ml of a mixture (1 : 2) of HCOOH and $(CH_3CO)_2O$ were added to 0.005 mole of II, IV, or VII, and the resulting solution was refluxed for 2 h and cooled. It was then poured into water, and the precipitate (XIII, XIV) was removed by filtration and washed with water.

B) A mixture of 0.005 mole of II-IV or XII, an equal amount of anhydrous CH_3COONa or C_2H_5COOK, and 20 ml of $(CH_3CO)_2O$ or $(C_2H_5CO)_2O$ was refluxed and worked up as in experiment A to give XVI-XX.

C) A mixture of 1.5 g of I or VIII, 1.5 g of CH_3COONa, and 20 ml of a previously prepared mixture (1 : 1) of $(CH_3CO)_2O$ and 85% H_3PO_4 was refluxed and worked up as in experiment A to give 82-92% of XV.

D) A solution of 2 g (0.01 mole) of 2-mercaptonaphth[1,2-d]imidazole and 1.3 g (0.01 mole) of 3-chloro-2,4-pentanedione in 30 ml of ethanol was refluxed for 4 h, cooled, and neutralized with ammonium hydroxide. The precipitate was removed by filtration and washed with water to give 2 g (71%) of XV.

E) A solution of 1.5 g of V in 20 ml of ethanol and 3 ml of concentrated HCl was refluxed and worked up as in experiment D to give 1 g (75%) of XV.

No melting point depressions were observed for mixtures of XIV, XV, and XX obtained by the various methods. Compounds XIII-XX were cream-colored (XV, XVI) or yellow (XIII, XIV, XVII-XX) substances that gave qualitative reactions for a carbonyl group. The compounds were purified for analysis by crystallization from butyl alcohol (XV) or aqueous dioxane (XIII, XIV, XVI-XX). One spot was obtained when XIII and XV were chromatographed on Al_2O_3: XIII, R_f 0.93 [dioxane–dichloroethane (2.5 : 1)], 0.87 [ethanol–dichloroethane (2.5 : 1)], 0.92 [$CHCl_3$–CCl_4–dichloroethane (2.5 : 1 : 1)]; XV, R_f 0.91 [dioxane–dichloroethane (2.5 : 1)], 0.90 [$CHCl_3$–CCl_4–dichloroethane (2.5 : 1 : 1)].

The IR spectra of mineral oil suspensions were recorded with a UR-10 spectrometer. We thank Yu. N. Sheinker and his co-workers for recording the IR spectra.

LITERATURE CITED

1. E. G. Knysh, A. N. Krasovskii, and P. M. Kochergin, Khim. Geterotsikl. Soedin., 25 (1972).
2. P. M. Kochergin, Zh. Obshch. Khim., 26, 2916 (1956).
3. I. A. Mazur, P. M. Kochergin, and V. G. Tromsa, Khim. Geterotsikl. Soedin., 389 (1971).
4. A. N. Krasovskii, P. M. Kochergin, and T. E. Kozlovskaya, Khim. Geterotsikl. Soedin., 393 (1971).
5. P. M. Kochergin, A. N. Krasovskii, and E. G. Knysh, USSR Author's Certificate No. 232,976; Byull. Izobr., No. 2, 30 (1969).
6. I. G. Farbenindustrie, German Patent No. 557,138; Chem. Abstr., 27, 1233 (1933).