SYNTHESIS AND TRANSFORMATION OF (N-SUBSTITUTED 2-METHYL-5-METHOXY-3-INDOLYL)SUCCINIC ACIDS

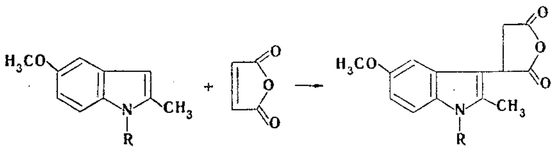
S. G. Agbalyan and G. V. Grigoryan

UDC 547.751.757.07

The reaction of N-substituted 2-methyl-5-methoxyindoles with maleic anhydride gave the corresponding (2-methyl-5-methoxy-3-indolyl)succinic anhydrides, which were hydrolyzed to acids and converted to monoamides by reaction with primary or secondary amines.

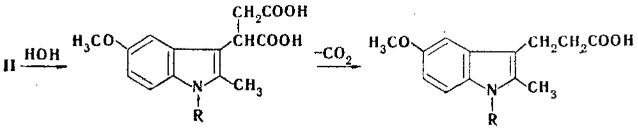
Indole reacts with maleic anhydride to give 2 : 1 or 3 : 1 adducts [1,2], depending on the conditions. The reaction of 2-methylindole and 2-ethoxyindole with maleic anhydride gives the corresponding 3-indolylsuccinic anhydrides [1,3].

We have studied the reaction of maleic anhydride with 5-methoxy-2-methylindoles (I), in which the joint effect of the 5-methoxy and 2-methyl groups substantially increases the nucleophilicity of the carbon atom in the 3 position of the indole ring [4].

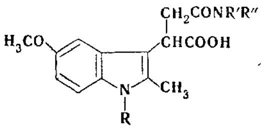

I II

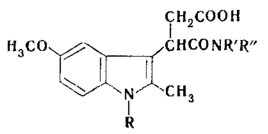
Compounds I condense with maleic anhydride when the reagents are heated on a water bath without a solvent to give 3-indolylsuccinic anhydrides II. The absorption bands characteristic for a substituted succinic anhydride (1685-1710, 1765-1790, and 1825-1845 cm^{-1}) are found in the IR spectra of II.

3-Indolylpropionic (IV) and 3-indolylsuccinic (III) acids are obtained when ahydrides II are heated with water. We were able to isolate only β-(1,2-dimethyl-5-methoxy-3-indolyl)succinic acid from the hydrolysis of (1,2-dimethyl-5-methoxy-3-indolyl)succinic anhydride. The same dicarboxylic acids (III) were obtained by fusing indoles I with maleic acid at 150°C.


III IV

One might have expected the formation of amides with structures V or VI in the reaction of anhydrides II with primary and secondary amines. Structure V, which is similar to that of the monoamide obtained by the reaction of phenylsuccinic anhydride with ammonia [5], is apparently the most probable structure.


V


VI

Institute of Organic Chemistry, Academy of Sciences of the Armenian SSR, Yerevan. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1525-1527, November, 1972. Original article submitted July 12, 1971.

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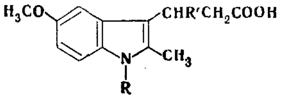
TABLE 1.



R	R′	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
H	COOH	180—182	$C_{14}H_{15}NO_5$	60,1	6,1	5,4	60,6	5,5	5,0	35
CH_3	COOH	190—194	$C_{15}H_{17}NO_5$	61,9	6,0	4,4	61,6	5,9	4,8	73
C_6H_5	COOH	170—174	$C_{20}H_{19}NO_5$	68,1	5,5	3,9	67,9	5,4	4,0	49
H	H	151—153	$C_{13}H_{15}NO_3$	66,8	6,6	6,2	66,9	6,4	6,0	52
C_6H_5	H	150—151	$C_{19}H_{19}NO_3$	73,6	6,1	4,6	74,0	6,1	4,5	22

TABLE 2. Amides (V) of β-Carboxy-β-(3-indolyl)propionic Acids

R	NR′R″	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
H	$N(C_2H_5)_2$	163—167	$C_{18}H_{24}N_2O_4$	64,9	7,0	8,3	65,0	7,3	8,4	71
H	$NHCH_2C_6H_5$	140—147	$C_{21}H_{22}N_2O_4$	68,3	6,3	7,7	68,8	6,0	7,6	42
CH_3	$NHCH_3$	140—143	$C_{16}H_{20}N_2O_4$	63,6	6,8	8,7	63,1	6,6	9,2	45
CH_3	$N(C_2H_5)_2$	142—143	$C_{19}H_{26}N_2O_4$	65,8	7,4	8,4	65,8	7,6	8,1	71
CH_3	NC_5H_{10}	126—129	$C_{20}H_{26}N_2O_4$	66,5	7,2	7,9	67,0	7,3	7,8	60
CH_3	$NHCH_2C_6H_5$	138	$C_{22}H_{24}N_2O_4$	69,6	6,6	7,9	69,4	6,4	7,8	43
C_6H_5	$NHCH_3$	146—150	$C_{21}H_{22}N_2O_4$	69,2	5,9	7,4	68,9	6,0	7,6	87
C_6H_5	$N(C_2H_5)_2$	140—145	$C_{24}H_{28}N_2O_4$	70,4	6,8	6,4	70,6	6,9	6,9	73
C_6H_5	$NHCH_2C_6H_5$	132—138	$C_{27}H_{26}N_2O_4$	73,0	5,6	6,0	73,3	5,9	6,3	50
C_6H_5	NC_5H_{10}	124—126	$C_{25}H_{28}N_2O_4$	71,5	6,6	6,6	71,4	6,7	6,6	72

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were obtained with a UR-10 spectrophotometer.

3-Indolylsuccinic Anhydrides (II). A mixture of 0.01 mole of indole I [6-12] and 0.01 mole of maleic anhydride was heated on a water bath for 2 h. The reaction product was dissolved in methylene chloride and precipitated with petroleum ether. The resulting amorphous substances were sufficiently pure for analysis after reprecipitation (methylene chloride–petroleum ether). This method was used to obtain (2-methyl-5-methoxy-3-indolyl)succinic (38% yield, mp 146-147°. Found, %: C 64.6; H 4.7; N 5.4. $C_{14}H_{13}NO_4$. Calculated, %: C 64.8; H 5.0; N 5.4.) (1,2-dimethyl-5-methoxy-3-indolyl)succinic (86% yield, mp 148-150°. Found, %: C 65.7; H 5.9; N 5.1. $C_{15}H_{15}NO_4$. Calculated, %: C 65.9; H 5.5; N 5.1) and (2-methyl-5-methoxy-1-phenyl-3-indolyl) succinic anhydrides (61% yield, mp 94-98°. Found, %: C 72.0; H 5.5; N 4.2. $C_{20}H_{17}NO_4$. Calculated: C 71.6; H 5.1; N 4.2.)

Hydrolysis of Anhydrides II. A mixture of 0.01 mole of anhydride II and 5 ml of water was heated on a water bath for 2.5 h. The hot aqueous solution was decanted from the resulting resinous precipitate and cooled to precipitate the corresponding dicarboxylic acid (III, Table 1). IR spectra: C=O 1695-1710 cm^{-1}. The resinous precipitate of β-(3-indolyl)propionic acid (IV) was dissolved in alkali and precipitated with acetic acid (Table 1).

Reaction of Indoles I with Maleic Acid. A mixture of 0.01 mole of indole I and 0.01 mole of maleic acid was heated at 140-150° for 3.5 h. The reaction product was recrystallized from water and reprecipitated from methylene chloride solution by the addition of petroleum ether. The thus obtained dicarboxylic acids (III) did not depress the melting points of the acids obtained by hydrolysis of anhydrides II. The IR spectra of the acids obtained by both methods were identical.

Monoamides (V) of 3-Indolylsuccinic Acids. A mixture of 0.0038 mole of anhydride II and 0.012 mole of amine was heated on a water bath for 4 h. The reaction mixture was dissolved in alkali, and monoamides V were precipitated with hydrochloric acid (Table 2). Thin-layer chromatography on a loose layer of activity II Al_2O_3 with chloroform–methanol (85 : 15) demonstrated that only one substance is formed in the reaction.

LITERATURE CITED

1. O. Diels, K. Alder, and W. Lubbert, Ann., 490, 277 (1931).
2. R. M. Acheson, R. S. Feinberg, and A. R. Hands, J. Chem. Soc., 526 (1964).
3. H. Plieninger and D. Wild, Ber., 99, 3063 (1966).
4. J. B. Bell and H. G. Lindwall, J. Org. Chem., 13, 547 (1948).
5. C. Hahn and P. Walter, Ann., 353, 132 (1907).
6. A. N. Grinev, V. N. Ermakova, E. Vrotek, and A. P. Terent'ev, Zh. Obshch. Khim., 29, 2777 (1959).
7. A. N. Grinev, V. I. Shvedov, and A. P. Terent'ev, Zh. Obshch. Khim., 26, 1449 (1956).
8. A. N. Grinev, N. K. Kul'bovskaya, and A. P. Terent'ev, Zh. Obshch. Khim., 25, 1355 (1955).
9. A. N. Grinev, I. A. Zaitsev, V. I. Shvedov, and A. P. Terent'ev, Zh. Obshch. Khim., 28, 447 (1958).
10. C. D. Nenitzescu, Bull. Soc. Chim. Romania, 11, 37 (1929); Chem. Abstr., 24, 110 (1930).
11. A. N. Grinev, I. A. Zaitsev, N. K. Venevtseva, and A. P. Terent'ev, Zh. Obshch. Khim., 28, 1853 (1958).
12. A. N. Grinev, V. I. Shvedov, and E. K. Panisheva, Khim. Geterotsikl. Soedin., 1055 (1967).