5. O. Reichel and A. Neubauer, Ann., No. 7/8, 1583 (1975).
6. G. Sipos, G. Schobel, and L. Balaspiri, J. Chem. Soc., (C), No. 9, 1154 (1970).

BISACYLATION OF THE ANHYDRIDE AND ESTERS OF 4-METHYL-1,2,3,4-TETRAHYDROPHTHALIC ACID

V. I. Dulenko, V. M. Golyak,
N. N. Alekseev, and N. F. Gorenko

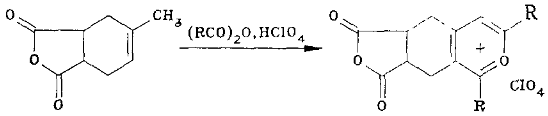
UDC 547.584'833.3'814

The bisacylation of the anhydride and esters of 4-methyl-1,2,3,4-tetrahydrophthalic acid by anhydrides of carboxylic acids in the presence of perchloric acid results in the formation of derivatives of 1,3-dialkyl-6, 7-dicarboxy-5,6,7,8-tetrahydro-2-benzopyrylium salts. Some reactions of the salts obtained, including their recyclization under the action of nucleophiles, have been studied. A convenient preparative method for the synthesis of 6,7-dicarboalkoxy-5,6,7,8-tetrahydroixoquinolines has been developed.

The increased interest in pyrylium salts in the past decade has resulted in the appearance of a large number of publications on their synthesis and reactions. The advances in this field have been reflected in several reviews, among which we should mention the most extensive [1-3].

In our opinion, one of the promising areas for the further development of the chemistry of pyrylium salts is the study which we began of the synthesis paths and the properties of functionally substituted pyrylium salts [4-7].

In order to further develop this work, as well as to synthesize new biologically active compounds, we studied the bisacylation of functionally substituted cyclic olefins, viz., the anhydride (I)* and esters (II) of 4-methyl-1,2,3,4-tetrahydrophthalic acid, which are functional derivatives of 1-methycyclohexene. The bisacylation of 1-methylcyclohexene itself was previously carried out by Praill and Whithear [9], who obtained 1,3-dimethyl-5,6,7,8-tetrahydro-2-benzopyrylium perchlorate with a 30% yield. We obtain pyrylium salts III with approximately the same yield by acylating I with carboxylic acid anhydrides in the presence of perchloric acid.



I

IIIa-c

III a $R=CH_3$, b $R=C_2H_5$, c $R=C_3H_7$

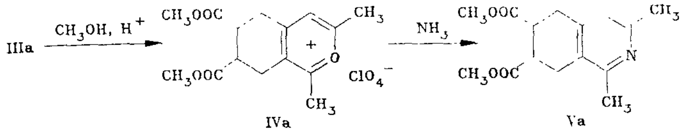
The structures of perchlorates III were confirmed by their IR spectra, which displayed the characteristic absorption bands of a cyclic anhydride (1860 and 1790 cm^{-1}) and a pyrylium cation (1640, 1550, 1510, and 1460 cm^{-1}). When compound IIIa is heated in methanol, it is converted into dimethyl ester IVa, which is converted under the action of ammonium into the corresponding derivative of 5,6,7,8-tetrahydroiaozuinoline (Va). The data from the PMR spectrum of compound Va [4] unequivocally prove the structures of salts III, whose PMR spectra could not be obtained due to their poor solubility.

---

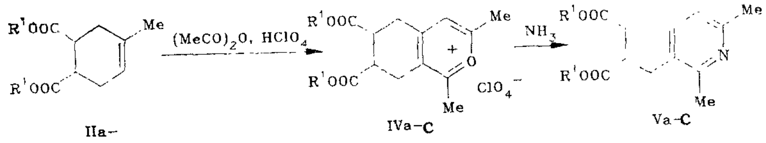
*For a preliminary report, see [4].

Institute of Physical Organic Chemistry and Carbon Chemistry, Academy of Sciences of the Ukrainian SSR, Donetsk 340114. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1318-1321, October, 1984. Original article submitted December 14, 1983; revision submitted March 12, 1984.

0009-3122/84/2010-1078$08.50

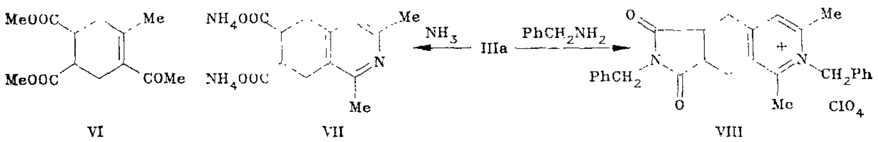


When esters IIa-c are acylated, the yield of perchlorates IVa-c improves considerably. The latter are low-melting compounds; therefore, they could not be isolated in the crystalline state, but under the action of ammonium they were converted into isoquinoline derivative to esters II.



II, IV, V a $R^1=CH_3$, b $R^1=C_2H_5$, c $R^1=C_3H_7$

The mechanism of bisacylation was previously discussed in [1, 5]. It includes the formation of a reactive β,γ-unsaturated ketone. We showed that the acetylation of IIa results in the parallel formation of α,β-unsaturated ketone VI, which can be recovered from the reaction mixture after the separation of perchlorate IVa. Its structure was confirmed by the IR and PMR spectra. Compound VI was also obtained following the neutralization of the ethereal filtrate obtained during the isolation of IIIa with a solution of sodium carbonate and its treatment with diazomethane.



In addition, we studied the recyclization of cation IIIa under the action of amines (ammonia and benzylamine). The reaction products were diammonium salt VII and pyridinium salt VIII, whose structures were proved by IR and PMR spectroscopy.

Thus, the introduction of the anhydride and esters of 4-methyl-1,2,3,4-tetrahydrophthalic acid into the bisacylation of olefins makes it possible to obtain new derivatives of 5,6,7,8-tetrahydro-isoquinoline after the intermediate formation of pyrylium salts. These derivatives may be of interest in the search for biologically active substances.

EXPERIMENTAL

The PMR spectra were obtained on a Tesla BS-487B spectrometer (80 MHz) in trifluoroacetic acid with TMS as a reference. The IR spectra were recorded on a UR-20 spectrometer in KBr tablets and in liquid petroleum.

Pure-grade cis-4-methyl-1,2,3,4-tetrahydrophthalic anhydride was used in the work. The dimethyl, diethyl, and dipropyl esters (IIa-c) were obtained by heating anhydride I with a tenfold excess of the alcohol in the presence of sulfuric acid. These properties correspond to the data in [10-12].

1,3-Dialkyl-6,7-anhydrodicarboxy-5,6,7,8-tetrahydro-2-benzopyrylium Perchlorates IIIa-c (Table 1). A suspension of 16.6 g (0.1 mole) of I in 0.7 mole of the carboxylic acid anhydride is gradually given an addition with stirring of 8 ml (0.1 mole) of 70% perchloric acid at a rate slow enough that the temperature of the reaction mixture does not rise above 90°C. After cooling to room temperature, 100-150 ml of ether are added. This results in the separation of perchlorate III in the form of a heavy oily layer, which quickly crystallizes. The precipitate is filtered, washing with ether, and crystallized from acetic acid or acetone.

Dimethyl 1,3-Dimethyl-5,6,7,8-tetrahydroisoquinoline-6,7-dicarboxylate (Va). A mixture of 3.3 g (0.01 mole) of perchlorate IIIa, 2 ml (0.04 mole) of concentrated sulfuric acid, and 50 ml of methanol is boiled for 10 h, cooled, and given an addition of a 25% aqueous solution of ammonia until the mixture displays a strong alkaline reaction. After 2 h, it is decanted

TABLE 1. Characteristics of Compounds IIIa-c and Va-c

Compound	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	Cl (N)		C	H	Cl (N)	
IIIa	280	47,3	4,0	10,9	$C_{13}H_{13}ClO_8$	46,9	3,9	10,6	25
IIIb	185—186	50,4	4,9	10,0	$C_{15}H_{17}ClO_8$	49,9	4,7	9,8	23
IIIc	184—185	51,9	5,7	9,4	$C_{17}H_{21}ClO_8$	52,5	5,4	9,1	22
Va	202—204 (5)	64,8	6,7	(5,1)	$C_{15}H_{19}NO_4$	64,9	6,8	(5,0)	57
Vb	237—238 (5)	66,9	7,6	(4,4)	$C_{17}H_{23}NO_4$	66,8	7,5	(4,5)	50
Vc	260—265 (5)	68,1	8,2	(4,1)	$C_{19}H_{27}NO_4$	68,3	8,1	(4,2)	45

---

*The bp, °C (pressure, mm) is given for compounds Va-c.

into an equal volume of water and extracted with ether, and the ethereal solution is washed with water and dried. The solvent is evaporated, and the residue is crystallized by triturating it with hexene. The yield was 1.1 g (40%), and the mp was 109-110°C (from heptane). PMR spectrum: 2.34 (3H, s) and 2.36 (3H, s) (1-CH_3 and 3-CH_3), 3.00 (6H, m, 6,8-CH_2, 6,7-CH), 3.58 (3H, s) and 3.62 (3H, s) (6-$COOCH_3$ and 7-$COOCH_3$), 6.58 ppm (1H, s, 4-h). Found: C, 64.7; H, 6.7; N, 5.1%. Calculated for $C_{15}H_{19}NO_4$: C, 64.9; H, 6.8; 5.0%. Picrate, mp 130-131°C (from ethanol). Found: N, 11.1%. Calculated for $C_{21}H_{22}N_4O_{11}$: N, 11.1%.

Esters of 1,3-Dimethyl-5,6,7,8-tetrahydroisoquinoline-6,7-dicarboxylic Acid (Va-c, Table 1). A solution of 0.1 mole of ester IIa-c in 60 ml (0.57 mole) of acetic anhydride is given an addition of 8 ml (0.1 mole) of 70% perchloric acid with stirring, the temperature of the reaction mixture not being allowed to rise above 80°C. After cooling, 100 ml of ether are added. The lower oily layer formed separated by decantation, diluted with 100 ml of the alcohol, and mixed with 20 ml of a 25% aqueous solution of ammonia. After 2 h, the mixture is diluted with 200 ml of water and extracted by ether (two 100-ml portions). The ether is distilled off, the residue is vacuum-distilled, and compounds Va-c are obtained.

Dimethyl 4-Methyl-5-acetyl-1,2,3,4-tetrahydrophthalate (VI). A. The ethereal solution separated by decantation from the preceding experiment (the acetylation of IIa) is neutralized by an aqueous solution of sodium carbonate until the evolution of CO_2 ceases, the ethereal layer is separated, washed with water, and dried over $CaCl_2$. The solvent is distilled off, and the residue is vacuum-distilled. This yields 7.6 g of VI, bp 185-190°C (3 mm Hg). IR spectrum: 1735 $(COOCH)_3$, 1690 (C=C), 1630 cm^{-1} (C=C). PMR spectrum (CCl_4): 1.78 (3H, s, 4-CH_3). 2.10 (3H, s, $COCH_3$), 2.42-2.87 (6H, m, 1,2-CH, 3.6-CH_2), 3.57 ppm (6H, s, 1,2-$COOCH_3$). Found: C, 61.6; H, 7.1%. Calculated for $C_{13}H_{18}O_5$: C, 61.4; H, 7.0%.

B. The ethereal filtrated obtained after the isolation of IIIa (see the synthesis of IIIa-c) is treated with an aqueous solution of sodium carbonate until the acids in the ethereal solution are completely neutralized. The aqueous layer is separated, free of neutral organic impurities by extraction with ether (two 50-ml portions), and acidified by hydrochloric acid to pH 1-2. The acidified aqueous solution is extracted by ether, and the ether is dried over $CaCl_2$ and evaporated. The crystalline residue is dissolved in 50 ml of methanol, and the solution obtained is given an addition of an ethereal solution of diazomethane in small portions until the evolution of nitrogen ceases. The solution is diluted with 100 ml of water, the organic products are extracted by 100 ml of ether, and the ethereal extract is washed with a solution of sodium carbonate and water and dried over $CaCl_2$. After evaporation of the ether, the residue is vacuum-distilled. This yields 9.7 g (46%) of keto ester VI, which is identical, according to its IR spectrum, to the compound described in method A.

Diammonium 1,3-Dimethyl-5,6,7,8-tetrahydroisoquinoline-6,7-dicarboxylate (VII). A suspension of 3.32 g (0.01 mole) of perchlorate IIIa in 50 ml of dry ethanol is saturated with gaseous ammonia over the course of 30 min. The precipitate formed is filtered and washed with ether. The yield is 2 g (72%), and the mp 175-177°C (decomposition). IR spectrum: 1660, 1400 cm^{-1} ($COONH_4$). Found: C, 54.8; H, 7.1; N, 14.9%. Calculated for $C_{13}H_{21}N_3O_4$: C, 55.1; H, 7.4; N, 14.8%.

N-Benzyl-1,3-dimethyl-2-benzyl-5,6,7,8-tetrahydroisoquinoline-6,7-dicarboximide Perchlorate (VIII). A mixture of 3.32 g (0.01 mole) of IIIa, 2.2 ml (0.02 mole) of benzylamine, and 50 ml of dioxane is boiled for 4 h. The mixture is cooled, and 150 ml of ether are added. The precipitate formed is filtered and washed with ether. The yield is 4.8 g (96%), and the mp 167-169°C (from propanol). PMR spectrum: 2.73 (6H, s, 1,3-CH_3), 3.43 (4H, s, 5, 8-CH_2), 3.83 (2H, m, 6.7-CH), 4.66 (2H, s, N—CH_2), 5.70 (2H, s, 2-CH_2), 7.40 (10H, m, 2- and N—Ph), 7.61 (1H, s, 4-H). Found: C, 63.2; H, 5.3; N, 5.7; Cl, 6.7%. Calculated for $C_{27}H_{27}ClN_2O_6$: C, 63.4; H, 5.2; N, 5.4; Cl, 6.9%.

LITERATURE CITED

1. A. T. Balaban, W. S. Schroth, and I. Fischer, Adv. Heterocycl. Chem., 12, 241 (1969).
2. A. T. Balaban, G. N. Dorofeenko, A. Dinculescu, I. Fischer, V. V. Mezheritskii, and A. V. Koblik, Adv. Heterocycl. Chem., Suppl. 2 (1982).
3. G. N. Dorofeenko, E. I. Sadekova, and E. V. Kuznetsov, Preparative Chemistry of Pyrylium Salts [in Russian], Izd. Rostovsk. Univ., Rostov-on-Don (1972).
4. V. I. Dulenko, N. N. Alekseev, and V. M. Golyak, Khim. Geterotsikl. Soedin., No. 10, 1424 (1975).
5. V. I. Dulenko, V. M. Golyak, N. N. Alekseev, and V. I. Gubar', Khim. Geterotsikl. Soedin., No. 7, 904 (1983).
6. V. I. Dulenko, N. N. Alekseev, V. M. Golyak, and L. V. Dulenko, Khim. Geterotsikl. Soedin., No. 8, kk35 (1977).
7. V. I. Dulenko and V. M. Golyak, Zh. Org. Khim., 16, 1109 (1980).
8. A. T. Balaban and C. D. Nenitzescu, Ann. Chem., 625, 74 (1959).
9. P. F. G. Praill and A. L. Whithear, J. Chem. Soc., 3573 (1961).
10. A. A. Petrov and N. P. Sopov, in: Collected Papers on General Chemistry [in Russian], Vol. 2, Izd. Akad. Nauk SSSR, Moscow—Leningrad (1953), p. 853.
11. W. J. Bailey, I. Rosenberg, and L. I. Young, J. Am. Chem. Soc., 76, 2251 (1954).
12. L. A. Mukhamedova, M. I. Kudryavtseva, M. Kh. Baiburova, T. M. Malyshko, and G. V. Lentyagin, Neftekhimiya, 2, 372 (1962).