RESEARCH ON 4H-3,1-BENZOXAZINES.

10.* REACTIONS OF o-AMINOPHENYLDIPHENYLCARBINOL WITH HALOALKANOIC ACIDS

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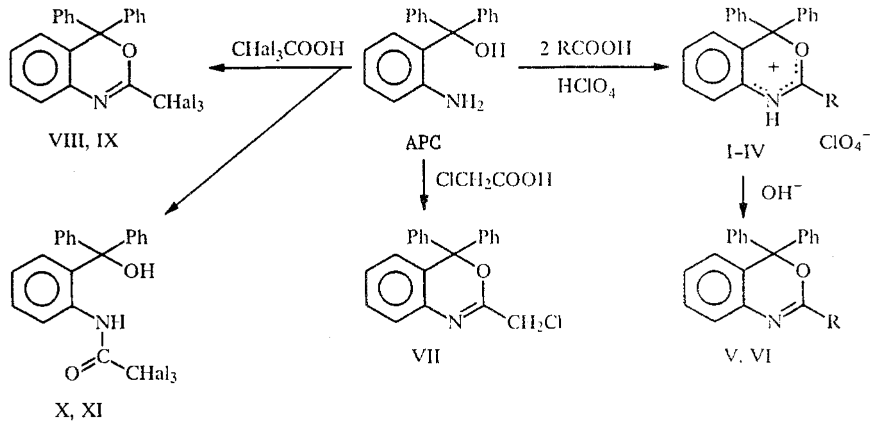
The conditions used to carry out the reaction of o-aminophenyldiphenylcarbinol with haloalkanoic acids and the structures of the resulting products are determined by the nature of the starting acid.

We have previously found a method for the synthesis of 4H-3,1-benzoxazines and their salts by the reaction of o-aminophenyldiphenylcarbinol (APC) with aliphatic, aromatic, and heteroaromatic carboxylic acids in the presence of 70% perchloric acid [1]. In order to obtain new compounds of the benzoxazine series with potential biological activity [2] it was logical to continue our study of this reaction with a number of other organic acids, particularly with halogen-containing acids. The new examples of the reaction of APC with various carboxylic acids described in this report are presented in the scheme (for a more nearly complete picture we have also indicated the previously described [1] reactions of APC with acetic and butyric acids).



I R = CH_3; II R = C_3H_7; III, V R = $CHBrCH_2CH_3$; IV, VI R = CH_2I; VIII, X Hal = Cl; IX, XI Hal = F

The reaction was carried out in refluxing chloroform using a twofold excess of the acylating agent [1]. For some of the reactions we used 70% $HClO_4$. The progress of the reactions was followed by means of TLC. The conditions and results of the reactions are presented in Table 1.

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*For communication 9 see [1].

†Deceased.

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TABLE 1. Conditions and Products of the Reaction of o-Aminophenyldiphenylcarbinol (APC) with Organic Acids

Starting acid	pKa*	[APC]: [$HClO_4$]	Reaction products
CH_3COOH	4,75	1 : 1	I**
$CH_3(CH_2)_2COOH$	4,80	1 : 1	II**
$C_2H_5CHBrCOOH$	—	1 : 1	III
ICH_2COOH	3,00	1 : 1	IV
$ClCH_2COOH$	2,87	1 : 0	VII
Cl_3CCOOH	0,70	1 : 0	VIII, X
F_3CCOOH	0,23	1 : 0	IX, XI

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*Literature data.

**The synthesis was previously described in [1].

TABLE 2. Characteristics of the Synthesized V-XI

Compound	Empirical formula	mp, °C	R_f	UV spec., (log ε)	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm	Yield, %
V	$C_{23}H_{20}BrNO$	170...171	0,78	278 (3,87)	1620 (C=N)	7,22 and 7,20 (10H, s.s, $(C_6H_5)_2$); 6,60 (4H, m, C_6H_4); 4,50 (1H, m, α-CH); 1,36 (5H, m β-CH_2, γ-CH_3)	80
VI	$C_{21}H_{16}INO$	133	0,65	—	1620 (C=N)	7,20 (10H, s, $(C_6H_5)_2$); 6,60 (4H, m, C_6H_4); 3,87 (2H, s, CH_2)	65
VII	$C_{21}H_{16}ClNO$	144	0,63	265 (3,77)	1620 (C=N)	7,18 and 7,15 (10H, s.s, $(C_6H_5)_2$); 6,58 (4H, m, C_6H_4); 4,08 (2H, s, CH_2)	75
VIII	$C_{21}H_{14}Cl_3NO$	150...151	0,70	282 (3,81)	1615 (C=N)	7,19 (10H, s, $(C_6H_5)_2$); 6,72 (4H, m, C_6H_4)	15
IX	$C_{21}H_{14}F_3NO$	149...150	0,83	264 (3,72)	1630 (C=N)	7,20 (10H, s, $(C_6H_5)_2$); 6,69 (4H, m, C_6H_4)	68
X	$C_{21}H_{16}Cl_3NO_2$	170...171	0,32	259 (4,09)	3440 (OH), 3200, 1680, 1560, 1290 (CONH)	7,20 (10H, s, $(C_6H_5)_2$); 6,60...8,02 (4H, m, C_6H_4); 3,67 (1H, br.s, OH); 10,60 (1H, br.s, NH)	70
XI	$C_{21}H_{16}F_3NO_2$	113...115	0,42	270 (3,71)	3450 (OH), 3290, 1680, 1560, 1310 (CONH)	7,22 (10H, s, $(C_6H_5)_2$); 6,64...8,10 (4H, m, C_6H_4); 2,05 (1H, br.s, OH); 10,2 (1H, br.s, NH)	5

It is apparent from Table 1 that an equimolar amount of $HClO_4$ is necessary for the formation of benzoxazine structures in the reaction of APC with alkanoic and haloalkanoic acids, the pK_a of which ≥ 3.00. Perchloric acid (in the case of the formation of perchlorates I-IV) is simultaneously the catalyst and the reagent. The necessity of using $HClO_4$ is eliminated with an increase in the strength of the acid, since it prevents realization of the reaction. For example, haloacetic acids — $ClCH_2COOH$, CCl_3COOH, and CF_3COOH — react only when $HClO_4$ is absent. Consequently, in the series of investigated acids their acylating abilities correspond to their acidities, in agreement with the literature data [2].

A mixture of the corresponding benzoxazine (VIII or IX) and amide (X or XI) is formed in each case in the reaction of APC with CCl_3COOH or CF_3COOH; this was not observed in the reaction of APC with the other acids. The same results were also obtained under conditions that exclude opening of the heteroring via hydrolysis (refluxing of the reaction mixture with removal of the water). The formation of amides in these cases can be explained by the difficulty involved in the formation of a heteroring as a consequence of steric hindrance — the presence of bulky trichloro(fluoro)methyl substituents attached to the carbonyl carbon atom.

All of the compounds obtained are colorless crystalline substances. Their structures were confirmed by spectral methods (Table 2) and the results of elementary analysis, while the structures of salts III and IV were also confirmed by obtaining the corresponding bases — 2-(1-bromo-1-propyl)-4,4-diphenyl-4H-3,1-benzoxazine (V) and 2-iodomethyl-4,4-diphenyl-4H-3,1-benzoxazine (VI) — after their treatment with ammonium hydroxide.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a Specord IR-75 spectrometer. The PMR spectra of solutions in $CDCl_3$ were obtained with a Tesla BS-467 spectrometer (60 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The electronic spectra of solutions in ethanol were recorded with a Specord UV-vis spectrophotometer. Thin-layer chromatography was carried out on Silufol UV-254 plates in benzene—ether (9:1) with development by iodine vapors.

The results of elemental analysis of the synthesized compounds were in agreement with the calculated values.

2-(α-Bromopropyl)-4,4-diphenyl-4H-3,1-benzoxazinium Perchlorate (III, $C_{23}H_{21}ClBrNO_5$). A 0.31-g (0.0031 mole) sample of 70% $HClO_4$ was added dropwise with refluxing in the course of 30 min to a mixture of 0.86 g (0.0031 mole) of APC and 1.03 g (0.0062 mole) of α-bromobutyric acid in 10 ml of chloroform, after which the mixture was refluxed for another 2 h. It was then cooled, and product III was precipitated by the addition of absolute ether. The yield of the product, which had mp 215°C, was 1.19 g (76%). IR spectrum: 3030, 1600, 1580 ($C{=}CH_{ar}$); 2750, 1630 (O—C^+—N); 1120, 1050 cm^{-1} (ClO_4^-).

2-Iodomethyl-4,4-diphenyl-4H-3,1-benzoxazinium Perchlorate (IV, $C_{21}H_{17}ClINO_5$) was synthesized similarly. The yield of the product, which had mp 120°C (dec.), was 0.74 g (45%). IR spectrum: 3030, 1610, 1590 ($C{=}CH_{ar}$); 2730, 1660 (O—C^+—N); 1120, 1080 cm^{-1} (ClO_4^-).

2-Chloromethyl-4,4-diphenyl-4H-3,1-benzoxazine (VII). A mixture of 1.37 g (0.005 mole) of APC, 0.94 g (0.01 mole) of monochloroacetic acid, and 12 ml of chloroform was refluxed for 3 h, after which the solvent was removed by distillation, and the residue was recrystallized from alcohol.

A mixture of benzoxazine VIII and amide X or a mixture of benzoxazine IX and amide XI, respectively, was similarly obtained from APC and trichloroacetic acid or trifluoroacetic acid and was separated with a column packed with silica gel (L 40/100) in benzene—ether (4:1).

REFERENCES

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