SYNTHESIS OF DIETHYLAMIDES OF α-DIETHYLAMINOCARBOXYLIC ACIDS USING α-TRICHLOROMETHYLCARBINOLS AND THEIR ACETATES UNDER PHASE-TRANSFER CATALYSIS CONDITIONS

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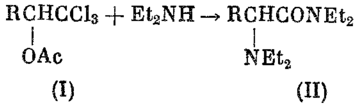
A synthesis has been reported for α-amino acids by the action of aromatic aldehydes with CCl_3 and CBr_3 anions in the presence of NH_2^- ions [1, 2], which may also be carried out in a phase-transfer catalytic system using saturated aqueous ammonium hydroxide [3].

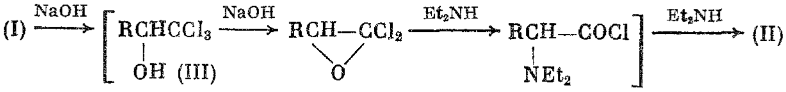
In the present work we showed that trichloromethylcarbinol acetates (Ia-c) [4] react with diethylamine in the presence of 50% aqueous NaOH and catalytic amounts of benzyltriethylammonium chloride (BTEAC) to form diethylamides of α-diethylamino acids (IIa-c) and not the expected α-diethylamino acids:



$$\underset{\text{(I)}}{\underset{\displaystyle OAc}{RCHCCl_3}} + Et_2NH \rightarrow \underset{\text{(II)}}{\underset{\displaystyle NEt_2}{RCHCONEt_2}}$$

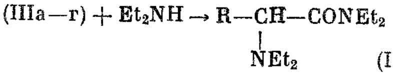
R = Me (a), R = Ph (b), R = MeCH=CH (c).

The reaction requires 4-6 h at 20°C. The yield of (IIa-c) is 30-80%. On the basis of previous results [1-3], the following scheme may be given for the formation of product (II):



$$\text{(I)} \xrightarrow{NaOH} \left[\underset{\displaystyle OH\ \text{(III)}}{RCHCCl_3} \xrightarrow{NaOH} \underset{\displaystyle O}{RCH{-}CCl_2} \xrightarrow{Et_2NH} \underset{\displaystyle NEt_2}{RCH{-}COCl} \right] \xrightarrow{Et_2NH} \text{(II)}$$

In order to confirm the first step of this scheme, the reactions of diethylamine were carried out directly with trichloromethylcarbinols (IIIa-c) under phase-transfer catalysis conditions, and the yields of products (IIa-c) were approximately the same. The analogous reaction was also carried out with trichloromethylcarbinol (IIId) obtained from citral with chloroform in the presence of 50% aqueous NaOH and BTEAC. However, even at 0°C, the reaction proceeds with significant tar formation and (IId) is obtained in only 17% yield.



$$\text{(IIIa—r)} + Et_2NH \rightarrow R{-}\underset{\displaystyle NEt_2}{CH}{-}CONEt_2 \qquad \text{(IIa—d)}$$

R = Me (a), R = Ph (b), R = MeCH=CH (c), R = $Me_2C{=}CHCH_2CH_2C(Me){=}CH$ (d)

The same products, (IIa) and (IIb), may be obtained starting from acylals of acetaldehyde (IVa) and benzaldehyde (IVb) and also from benzaldehyde itself (V). Thus, the reactions of (V) and acylals (IVa) and (IVb) with chloroform, diethylamine, and 50% aqueous NaOH in CH_2Cl_2 in the presence of catalytic amounts of BETEAC give diethylamides (IIa) and (IIb) in addition to carbinols (IIIa) and (IIIb). Crotonaldehyde acylal (IVc), R = MeCH=CH, gives a complex reaction under these conditions and gives a mixture of products containing $MeCH{=}CHCH\cdot(CCl_3)OAc$, $MeCH{=}CHCH(CCl_3)OH$, and (IIc), as indicated by gas–liquid chromatography.

The structures of the products were supported by PMR spectroscopy and elemental analysis and, in the case of (IId), by chemical ionization mass spectrometry (M^+, m/z 309, major fragment $[M - HCONEt_2]^+$, m/z 207). The course of these reactions and the purity of the products were monitored by gas–liquid chromatography.

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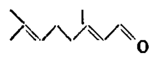
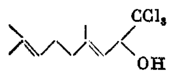
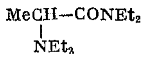
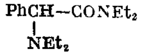
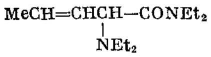
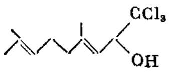
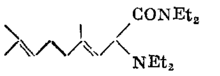
TABLE 1. Yields and Characteristics of the Products Obtained

Starting compound	Product obtained	Yield, %	mp, bp °C (p, mm Hg)	n_D^{20}	Found/Calculated, %				PMR spectrum, (δ, ppm, J, Hz)
					C	H	Cl	N	
	 (IIId)	44	100–106 (0,3)	1,5095	49,28 / 48,62	6,63 / 6,26	38,65 / 39,22		1,6 s, 1,67 s (6H, $Me_2C=$), 1,8 s (3H, CH_3), 2,1–2,18 m (4H, $2CH_2$), 2,97 s (1H, OH), 4,69 d (1H, $C\underline{H}(OH)CCl_3$, J=8), 4,92–5,20 m (1H, CH=), 5,33 d (1H, $=C\underline{H}CH(OH)CCl_3$, J=8)
$MeCH(OAc)_2$ (IVa)	 $\underset{NEt_2}{MeCH}{-}CONEt_2$ (IIa)	80	126–127 (30)	1,4558	65,88 / 65,95	11,87 / 12,07		13,67 / 13,98	0,82–1,24 m (15H, $5CH_3$), 2,08–2,68m (4H, $2CH_2$ amine), 2,89–3,37m (4H, $2CH_2$ amide), 3,52 k (1H, CH, J=6)
$MeCH(CCl_3)OAc$ (Ia)		85							
$MeCH(CCl_3)OH$ (IIIa)		79							
PhCHO (V)	 $\underset{NEt_2}{PhCH}{-}CONEt_2$ (IIb)	47	119–120 (0,5)	1,5180	73,13 / 73,24	9,92 / 10,00		10,43 / 10,68	0,78–1,0 m (12H, $4CH_3$), 2,4–2,7 m (4H, $2CH_2$ amine), 2,9–3.4 m(4H, $2CH_2$ amide), 4,44 s (1H, CH), 7,00–7,2 m (5H, Ph)
$PhCH(OAc)_2$ (IVb)		45							
$PhCH(CCl_3)OAc$ (Ib)		40							
$PhCH(CCl_3)OH$ (IIIb)		48							
$MeCH{=}CHCH(CCl_3)OAc$ (Ic)	 $MeCH{=}\underset{NEt_2}{CHCH}{-}CONEt_2$ (IIc)	30	100–102 (1,0)	1,4715	68,70 / 68,98	11,34 / 11,57		12,01 / 12,33	0,83–1,2 m (12H, $4CH_3$), 1,67 d (3H, CH_3), J=6), 2,1–2,5 m (4H, $2CH_2$ amine), 2,9–3,6 m (4H, $2CH_2$ amide), 3,7 d (1H, CH, J=9), 5,3–5,7 m (2H, CH=CH)
$MeCH{=}CHCH(CCl_3)OH$ (IIIc)		30							
 (IIId)	 (IId)	17	125–140 (0,4)	1,4907					0,85–1,27 m (12H, $4CH_3$), 1,57–1,77 m (9H, $3CH_3$), 2,0–2,18 m (4H, $2CH_2$), 2,30–2,84 m (4H, $2CH_2$ amine), 3,07–3,75 m (4H, $2CH_2$ amide), 4,11 d (1H, $CH(NEt_2)$, J=9), 4,9–5,16 m (1H, CH=), 5,33 d (1H, $=C\underline{H}-CHCO$), J=9)

EXPERIMENTAL

The gas–liquid chromatographic analysis was carried out on LKhM-8 and MD-5 chromatographs with flame-ionization detection, nitrogen as the carrier gas, and a 1.4 × 0.003 m glass column packed with 5% SE-30 on Chromaton N-AW-DMCS. The PMR spectra were taken on a Tesla BS-497 spectrometer at 100 MHz in CCl_4 with TMS as the internal standard.

Preparation of (IIId). Samples of 0.05 mole citral and 5 ml 50% aqueous NaOH were added dropwise simultaneously with vigorous stirring to a mixture of 0.1 mole $CHCl_3$ and 0.05 mmole BETEAC in 20 ml CH_2Cl_2 cooled to 0°C. The mixture was stirred at this temperature for 1 h, poured into water, and extracted with methylene chloride. The extract was washed with water and dried over $MgSO_4$. The solvent was evaporated, and the residue was distilled. The yield and characteristics of the product are given in Table 1.

Reactions with (Ia-c) and (IIIa-c). A sample of 10 ml 50% aqueous NaOH was added with vigorous stirring to a mixture of 0.05 mole carbinol (III) or acetate (I), 0.1 mole Et_2NH, and 0.05 mmole BETEAC in 20 ml CH_2Cl_2 at $\sim$20°C. Spontaneous warming to 30-40°C was observed. The reaction mixture was stirred at this temperature for 6-7 h and then diluted with water. The organic layer was separated, washed with water, and dried over $MgSO_4$. The solvent was evaporated, and the residue was distilled. The yields and characteristics of products (IIa-c) are given in Table 1.

Reaction with (IIId). A sample of 10 ml 50% aqueous NaOH was added with vigorous stirring and cooling to 0-5°C to a mixture of 0.05 mole (IIId), 0.15 mole Et_2NH, and 0.05 mmole BTEAC in 20 ml CH_2Cl_2. The reaction mixture was stirred at this temperature for 0.5 h and then at about 20°C for 3 h. The reaction mixture was worked up as described above. The yields and characteristics of (IId) are given in Table 1.

The reactions with (IVa), (IVb), and (V) were carried out as in the case of (Ia-c) and (IIIa-c) but in the presence of 0.1 mole $CHCl_3$.

CONCLUSIONS

Trichloromethylcarbinols and their acetates react with diethylamine under phase-transfer catalysis conditions to give diethylamides of α-diethylaminocarboxylic acids. The same products are formed in the reaction of aldehyde acylals with chloroform and diethylamine in the 50% aqueous NaOH–BTEAC phase-transfer catalytic system.

LITERATURE CITED

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4. G. V. Kryshtal', V. S. Bogdanov, L. A. Yanovskaya, Yu. P. Volkov, and E. N. Trusova, Izv. Akad. Nauk SSSR, Ser. Khim., 2820 (1981).