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TERTIARY AMINES AND QUATERNARY SALTS DERIVED FROM ALPHA-SUBSTITUTED STILBENES AND HETEROCYCLIC NITROGEN BASES

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N-bromosuccinimide and α-methylstilbenes, p-methyl-α-chlorostilbene, and p-methyltolan give bromomethyl derivatives, which react with piperidine to give tertiary amines. The latter and methyl iodide give quaternary salts.

With pyridine, γ-picoline, and quinoline, the p-bromomethyl-d-chlorostilbenes synthesized give quaternary bromides which are readily soluble in water and converted into perchlorates by $KClO_4$.

Bromomethylstilbenes unsubstituted at the double bond [1] are know to react with piperidine to give tertiary amines. As such amines are potentially interesting as physiologically active compounds, it was decided to extend the research to synthesizing amines of that type and preparing their quaternary salts. For that purpose alpha-substituted stilbenes with methyl groups in the benzene ring or at the double bond which had previously been prepared [2, 3] were utilized.

A number of tolans, α-chlorostilbenes, and α-methylstilbenes have been brominated, making use of the specific nature of N-bromosuccinimide as a brominating reagent [4, 5]. In that way the bromomethyltolans II and IV, and the bromomethylstilbenes I, II, and V-VIII (Table 1) were prepared. The oily bromomethylstilbene VII was used crude in subsequent preparations, as it decomposed when distilled under reduced pressure. Compounds I-VIII react smoothly with piperidine in ether or benzene solution. The free amines formed were not isolated, but converted into their hydrochlorides IXa-XVIa (Table 2).

Treatment of the hydrochlorides IXa-XIII with an aqueous solution of soda liberates the free bases IX-XIII (Table 2). In the cases of the hydrochlorides XIVa-XVIa, such treatment gives the amines XIV-XVI as thick oily compounds, which do not solidify, and decompose when distilled under reduced pressure.

Heating compounds IX and XI with powdered potassium hydroxide in dioxane leads to smooth dehydrochlorination and formation of the substituted tolans X and XII. These compounds were also synthesized from compounds II and IV by treatment with piperidine. This reverse synthesis simultaneously proves the structures of the tertiary amines IX and XI prepared.

The synthesized tertiary amines IX-XVI when heated for a short time in ether solution with methyl iodide give high yields of crystalline methiodides XVII-XXIV (Table 3).

The quaternary bromides XXV-XXX (Table 3), readily soluble in water, are prepared by heating the bromomethylstilbenes I, III, and V with pyridine, γ-picoline, and quinoline. Treatment of aqueous solutions of salts XXV-XXX with potassium perchlorate precipitates perchlorates XXXI-XXXIV, which are sparingly soluble, but crystallize well. Dibromide III and pyridine give a salt which deliquesces in air, and when an aqueous solution of this is treated with potassium perchlorate, perchlorate XXXV, which is stable and crystallizes well, is precipitated.

Experimental

p'-Bromomethyl-α-chlorostilbene (I). A mixture of 0.05 mole α-chloro-p'-methylstilbene, 0.05 mole N-bromosuccinimide, and 0.1 g benzoyl peroxide in 90 ml CCl_4 was refluxed for 6 hr, allowed to cool to room temperature, and the floating succinimide separated off. The filtrate was twice treated with 50 ml water, the organic layer separated, and dried over sodium sulfate. The solvent was distilled off under reduced pressure. In 24 hr the viscous oily material solidified. Recrystallization from petrol ether gave 10.6 g compound I.

Compounds II-VIII were prepared similarly to I, by brominating with N-bromosuccinimide, p-methyltolan, p,p'-dimethyl-α-chlorostilbene, p,p'-dimethyltolan, p-methyl-p'-nitro-α-chlorostilbene, p-ethyl-p'-nitro-α-chlorostilbene, α-methylstilbene, α-methyl-p-nitrostilbene respectively. Table 1 gives constants and analytical data.

N-[4-(α-chlorostyryl) benzyl piperidine hydrochloride (IXa). 3.07 g (0.01 mole) I and 1.7 g (0.02 mole) piperidine in 30 ml dry benzene were refluxed together on a water bath for 30 min. The contents of the small flask became a solid mass of crystals. After cooling the crystals were separated off, washed with dry ether, and a stream of dry hydrogen chloride passed into the ether-benzene solution. The crystals of hydrochloride which were precipitated were filtered off, washed with dry ether, and dried. Yield 2.66 g colorless crystals, purified by recrystallizing from isopropanol.

Table 1

Bromomethylstilbenes and Bromomethyltolans

Compound No.	Formula	Mp, °C	Molecular formula	Element	Found, %	Calculated, %	Yield, %
I	$C_6H_5C(Cl){=}CHC_6H_4CH_2Br$-*p*	77	$C_{15}H_{12}BrCl$	C	58.19; 58.34	58.53	70
				H	4.16; 4.11	3.90	
				Cl+Br	37.78; 37.34	37.56	
II	$C_6H_5C{\equiv}CC_6H_4CH_2Br$-*p*	90—91	$C_{15}H_{11}Br$	Br	29.72; 29.68	29.51	66
III	*p*-$BrCH_2C_6H_4C(Cl){=}CHC_6H_4CH_2Br$-*p*	120	$C_{16}H_{13}Br_2Cl$	C	48.25; 48.13	48.00	64
				H	3.16; 3.37	3.25	
				Cl+Br	48.65; 48.73	48.81	
IV	*p*-$BrCH_2C_6H_4C{\equiv}CC_6H_4CH_2Br$-*p*	138—140*	$C_{16}H_{12}Br_2$	Br	44.08; 44.14	43.95	50
V	*p*-$O_2NC_6H_4CH{=}C(Cl)C_6H_4CH_2Br$-*p*	122	$C_{15}H_{11}BrClNO_2$	N	4.26; 4.15	4.00	77
VI	*p*-$O_2NC_6H_4CH{=}C(Cl)C_6H_4CHBrCH_3$-*p*	92	$C_{16}H_{13}BrClNO_2$	N	3.65; 3.73	3.81	80
VII	$C_6H_5CH{=}C(C_6H_5)CH_2Br$	—	—	—	—	—	70**
VIII	*p*-$O_2NC_6H_4CH{=}C(C_6H_5)CH_2Br$	110	$C_{15}H_{12}BrNO_2$	N	4.34; 4.26	4.40	85

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* Decomposition

** Yield of crude substance

Table 2

Tertiary Amines and their Hydrochlorides

Compound No.	Formula*	Mp, °C	Molecular formula	Element	Found, %	Calculated, %	Yield, %
IX	$C_6H_5C(Cl)=CHC_6H_4CH_2NC_5H_{10}$	56	$C_{20}H_{22}ClN$	N	4.84; 4.56	4.50	95
				Cl	11.67; 11.75	11.95	
IXa	Hydrochloride of IX	202	$C_{20}H_{22}ClN \cdot HCl$	Cl	20.51; 20.41	20.40	87
X	$C_6H_5C\equiv CC_6H_4CH_2NC_5H_{10}$	47	$C_{20}H_{21}N$	N	4.86; 4.92	5.09	82
Xa	Hydrochloride of X	242**	$C_{20}H_{21}ClN \cdot HCl$	Cl	11.41; 11.62	11.39	78
XI	$C_5H_{10}NCH_2C_6H_4C(Cl)=CHC_6H_4CH_2NC_5H_{10}$	83	$C_{26}H_{33}ClN_2$	N	6.67; 6.72	6.86	90
				Cl	8.49; 8.55	8.70	
XIa	Hydrochloride of XI	310**	$C_{26}H_{35}Cl_3N_2$	Cl	22.03; 22.18	22.12	98
XII	$C_5H_{10}NCH_2C_6H_4C\equiv CC_6H_4CH_2NC_5H_{10}$	103	$C_{26}H_{32}N_2$	N	7.26; 7.33	7.52	88
XIIa	Hydrochloride of XII	325**	$C_{26}H_{33}ClN_2 \cdot HCl$	Cl	16.22; 16.12	15.95	85
XIII	p-$O_2NC_6H_4CH=C(Cl)C_6H_4CH_2NC_5H_{10}$	71	$C_{20}H_{21}ClN_2O_2$	N	7.76; 7.65	7.86	86
				Cl	9.75; 9.81	9.92	
XIIIa	Hydrochloride of XIII	211	$C_{20}H_{21}ClN_2O_2 \cdot HCl$	N	6.99; 7.25	7.12	95
XIVa	p-$O_2NC_6H_4CH=C(Cl)C_6H_4CH(CH_3)C_5H_{10} \cdot HCl$	234**	$C_{21}H_{23}ClN_2O_2 \cdot HCl$	Cl	17.28; 17.19	17.44	90
				N	6.64; 7.08	7.12	
XVa	$C_6H_5CH=C(C_6H_5)CH_2NC_5H_{10} \cdot HCl$	213	$C_{20}H_{23}N \cdot HCl$	Cl	11.45; 11.53	11.32	75
				N	4.29; 4.35	4.47	
XVIa	p-$O_2NC_6H_4CH=C(C_6H_5)CH_2NC_5H_{10} \cdot HCl$	228	$C_{20}H_{22}N_2O_2 \cdot HCl$	Cl	9.69; 9.75	9.93	70
				N	7.59; 7.62	7.81	

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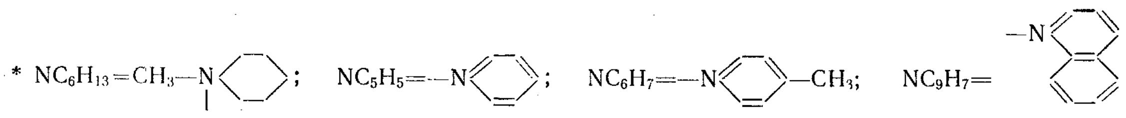
* NC_5H_{10} -1-piperidyl

** Decomposition

Table 3

Quaternary Salts

Compound No.	Formula*	Mp, °C	Molecular formula	Element	Found, %	Calculated, %	Yield, %
XVII	$[C_6H_5C(Cl)=CHC_6H_4CH_2NC_6H_{13}]+y-$	205	$C_{21}H_{25}ClyN$	N	2.98; 2.99	3.06	96
XVIII	$[C_6H_5C\equiv CC_6H_4CH_2NC_6H_{13}]+y-$	187	$C_{21}H_{24}yN$	N	3.39; 3.29	3.35	75
XIX	$[C_6H_{13}NCH_2C_6H_4C(Cl)\equiv CHC_6H_4CH_2NC_6H_{13}]++2y-$	258 (decomp.)	$C_{28}H_{39}Cly_2N_2$	N	4.25; 4.32	4.13	90
XX	$[C_6H_{13}NCH_2C_6H_4C--CC_6H_4CH_2NC_6H_{13}]++2y-$	211	$C_{28}H_{38}y_2N_2$	N	4.57; 4.46	4.36	78
XXI	$[p\text{-}O_2NC_6H_4CH=C(Cl)C_6H_4CH_2NC_6H_{13}]+y-$	225	$C_{21}H_{24}ClyN_2O_2$	N	5.80; 5.73	5.62	71
XXII	$[p\text{-}O_2NC_6H_4CH=C(Cl)C_6H_4CH(CH_3)NC_6H_{13}]+y-$	221	$C_{22}H_{26}ClyN_2O_2$	N	5.38; 5.29	5.47	74
XXIII	$[C_6H_5CH=C(C_6H_5)CH_2NC_6H_{13}]+y-$	199	$C_{21}H_{26}yN$	N	3.43; 3.37	3.34	80
XXIV	$[p\text{-}O_2NC_6H_4CH=C(C_6H_5)CH_2NC_6H_{13}]+y-$	176	$C_{21}H_{25}yN_2O_2$	N	5.95; 5.89	6.03	79
XXV	$[C_6H_5C(Cl)=CHC_6H_4CH_2NC_5H_5]+Br-$	195	$C_{20}H_{17}BrClN$	N	3.62; 3.75	3.60	75
XXVI	$[C_6H_5C(Cl)=CHC_6H_4CH_2NC_6H_7]+Br-$	188	$C_{21}H_{19}BrClN$	N	3.30; 3.25	3.49	65
XXVII	$[C_6H_5C(Cl)=CHC_6H_4CH_2NC_9H_7]+Br-$	191	$C_{24}H_{19}BrClN$	N	3.13; 3.05	3.20	48
XXVIII	$[p\text{-}O_2NC_6H_4CH=C(Cl)C_6H_4CH_2NC_5H_5]+Br-$	244	$C_{20}H_{16}BrClN_2O_2$	N	6.74; 6.54	6.48	85
XXIX	$[p\text{-}O_2NC_6H_4CH=C(Cl)C_6H_4CH_2NC_6H_7]+Br-$	197	$C_{21}H_{18}BrClN_2O_2$	N	6.14; 6.34	6.27	84
XXX	$[p\text{-}O_2NC_6H_4CH=C(Cl)C_6H_4CH_2NC_9H_7]+Br-$	234	$C_{24}H_{18}BrClN_2O_2$	N	5.57; 5.72	5.81	64
XXXI	$[C_6H_5C(Cl)=CHC_6H_4CH_2NC_5H_5]+ClO_4-$	165	$C_{20}H_{17}Cl_2NO_4$	Cl	17.22; 17.38	17.44	78
XXXII	$[p\text{-}O_2NC_6H_4CH=C(Cl)C_6H_4CH_2NC_5H_5]+ClO_4-$	205	$C_{20}H_{18}Cl_2N_2O_6$	Cl	15.92; 15.95	15.74	72
XXXIII	$[p\text{-}O_2NC_6H_4CH=C(Cl)C_6H_4CH_2NC_6H_7]+ClO_4-$	145	$C_{21}H_{19}Cl_2N_2O_6$	Cl	15.42; 15.45	15.27	76
XXXIV	$[p\text{-}O_2NC_6H_4CH=C(Cl)C_6H_4CH_2NC_9H_7]+ClO_4-$	225	$C_{24}H_{18}Cl_2N_2O_6$	Cl	14.19; 14.32	14.17	56
XXXV	$[C_5H_5NCH_2C_6H_4C(Cl)=CHC_6H_4CH_2NC_5H_5]{+}{+}2ClO_4-$	212	$C_{26}H_{23}Cl_3N_2O_8$	Cl	17.94; 17.97	17.82	73



* NC_6H_{13}=CH_3—N ; NC_5H_5=—N ; NC_6H_7=—N —CH_3; NC_9H_7= —N

Hydrochlorides Xa-XIVa were prepared from compounds II-VI respectively, similarly to the hydrochloride IXa. Amine hydrochlorides XVa-XVIa were prepared from compounds VII, VIII, in dry ether. Table 2 gives constants and analytical data for hydrochlorides IXa-XVIa.

N-[4-(α-chlorostyryl) benzyl] piperidine (IX). A solution of 2 g (5.8 mmole) hydrochloride IXa in 70 ml water was treated with a saturated sodium carbonate solution until alkaline to litmus. After 24 hr the oil formed solidified. Recrystallization from aqueous methanol (1 : 5) gave 1.7 g compound IX. Amines X-XIII were prepared similarly (see Table 2).

4-[N-piperidylmethyl)tolan (X). 1.6 g (5.3 mmole) compound IX and 1.3 g (23 mmole) powdered potassium hydroxide, and 15 ml dioxane were refluxed for 8 hr, cooled, 50 ml water added, when an oily layer separated, which solidified in 10 hr. After washing with water, and recrystallizing from aqueous methanol, 1.2 g X was obtained. An 80% yield of XII was similarly prepared from compound XI.

N-[4-(α-chlorostyryl) benzyl] piperidine methiodide (XVII). 0.01 mole amine IX, 0.015 mole methyl iodide, and 20 ml ether-acetone (1 : 1) were refluxed for 30 min. The crystalline precipitate formed was washed with dry ether and recrystallized from methanol-ether (5 : 1). Methiodides XVIII-XXI were prepared similarly.

To prepare the quaternary salts XXII-XXIV hydrochlorides XIVa-XVIa were made alkaline with aqueous soda, and the oily amine liberated, without further purification, dissolved in the ether-acetone mixture, and methyl iodide added to the solution.

[4-(α-chlorostyryl) benzyl] pyridinium bromide (XXV). 0.01 mole compound I, 2 g dry pyridine, and 10 ml benzene were refluxed together for 1 hr. The resultant crystalline product was cooled, filtered off, and washed with ether. Yield 3.5 g colorless crystals of compound XXV. Similarly compounds I and V gave, with the appropriate bases, bromides XXVI-XXX.

[4-(α-chlorostyryl) benzyl] pyridinium perchlorate (XXXI). To 1.75 g (4.5 mmole) compound XXV in 50 m water was added 15 ml of a saturated solution of $KC10_4$, the precipitate formed filtered off, and recrystallized from ethanol. Yield 1.42 g colorless crystals of XXXI. Perchlorates XXXII-XXXIV were similarly prepared from compounds XXXII-XXXIV (Table 3).

Perchlorate XXXV. 4 g pyridine was added to a solution of 0.01 mole bromide III in 20 ml benzene. After heating, the precipitate which formed was separated off, dissolved in 50 ml water, and 15 ml saturated $KC10_4$ solution added, when a precipitate immediately formed, and was recrystallized from alcohol.

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