SOME N-AMINOPROPYL AND N-AMINOPROPIONYL DERIVATIVES OF 3-SUBSTITUTED DIPHENYLAMINES

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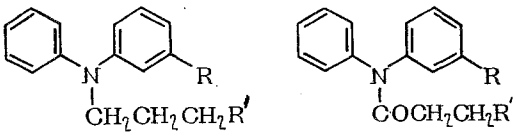
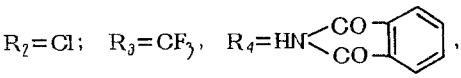
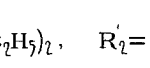
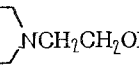
Many N-aminoalkyl derivatives of diphenylamine and substituted diphenylamines have biological activity [1-3]. In searching for pharmacologically active substances among diphenylamine derivatives, which are structurally similar to the corresponding phenothiazines, we have synthesized some N-aminopropyl and N-aminopropionyl derivatives of 3-substituted diphenylamines of the general formula:

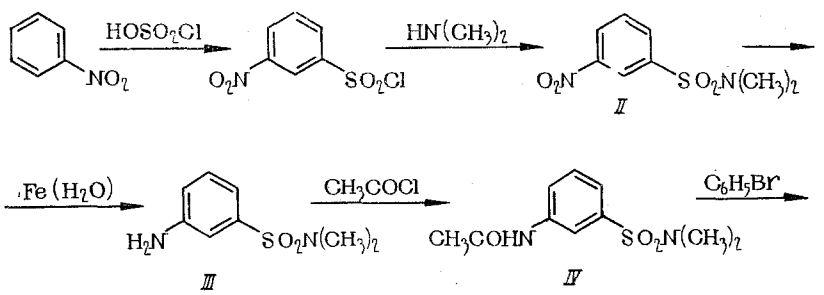


R: R_1=H; R_2=Cl; R_3=CF_3, R_4=  , R_5=$SO_2N(CH_3)_2$;

R′: R'_1=$N(C_2H_5)_2$, R'_2=  ; R'_3=, R'_4=

R'_5=  ; R'_6=

Commercially available products were used in the synthesis of the N-derivatives of 3-chloro and 3-trifluoromethyldiphenylamines. 3-Phthalimidodiphenylamine was obtained via the method described in [4]. We attempted to obtain 3-dimethylaminosulfonyldiphenylamine (I) by Ullman condensation of 3-dimethylaminosulfonylaniline (III) with o-chlorobenzoic acid and subsequence decarboxylation of 2-carboxy-3'-dimethylaminosulfonyldiphenylamine. However, the yield of (I) was low due to considerable resinification of the reaction products during decarboxylation. This compound was obtained in considerably better yield by reaction of N-acetyl-3-dimethylaminosulfonylaniline (IV) with bromobenzene according to the following scheme:



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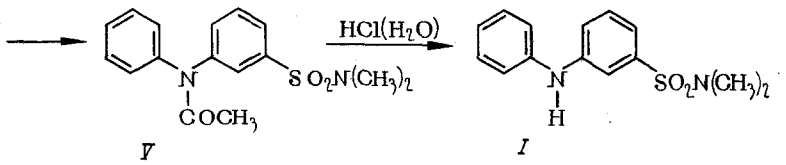


V I

3-Dimethylaminosulfonylnitrobenzene (II) was obtained by stirring a benzene solution of 3-nitrobenzenesulfonyl chloride, obtained according to [5], with an aqueous solution of dimethylamine. (II) was subsequently reduced with iron filings in aqueous medium in the presence of ammonium chloride to (III). After acetylation with acetyl chloride, the acetyl derivative (IV) was condensed with bromobenzene in the presence of copper bronze and potassium carbonate. The N-acetyl-3-dimethylaminosulfonyldiphenylamine (V) obtained was converted to (I) by saponification with an alcoholic solution of hydrochloric acid. Reaction of the 3-substituted diphenylamines with β-chloropropionyl chloride gave the corresponding N-(β-chloropropionyl)-diphenylamines. which on treatment with excess secondary amines furnish the N-aminoacyl derivatives of 3-substituted diphenylamines. The N-(γ-aminopropyl)-3-dimethylaminosulfonyldiphenylamines were obtained by reaction of (I) with γ-aminopropyl chlorides in toluene in the presence of sodium amide.

The hydrochlorides or oxalic acid salts of the compounds, presented in Table 1, were obtained for pharmacological testing.

The pure oxalate of N-(4-methyl-1-piperazinyl)-propionyl-3-dimethylaminosulfonyldiphenylamine was the most active compound with respect to increasing the coronary blood flow. However, the therapeutic application of this compound is limited by its toxicity. The remaining compounds had low activity.

EXPERIMENTAL

3-Dimethylaminosulfonylnitrobenzene (II). A 30% aqueous solution of dimethylamine (45 g) was added dropwise with stirring to a solution of 22.1 g of 3-nitrobenzenesulfonyl chloride in 50 ml benzene, and the reaction mixture was stirred for 1.5 h. The crystals which precipitated on cooling were filtered, washed with water, and dried to give 20.6 g of (II) with mp 120-121° after recrystallization from ethanol. Found, %: N 12.24, 12.33; S 14.12, 14.32. $C_8H_{10}N_2O_4S$. Calculated, %: N 12.16; S 13.95.

3-Dimethylaminosulfonylaniline (III). (II) (57.5 g) and 84 g of iron filings were added in small portions during 2 h to a refluxing solution of 4 g of ammonium chloride in 500 ml water with stirring. The mixture was then refluxed for 3 hours, filtered, and the product extracted with several portions of hot water to give 45.5 g of (III). After recrystallization from abs. ethanol (III) had mp 154-156°. Found, %: N 14.05, 14.13. $C_8H_{12}N_2O_2S$. Calculated, %: N 13.99.

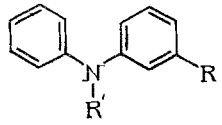
N-acetyl-3-dimethylaminosulfonylaniline (IV). A mixture of 18.6 g of (III), 20 g of acetyl chloride, and 25 ml of chloroform was refluxed for 4 h. The resulting crystals were filtered, washed with acetic acid, and dried to give 19 g of (IV). After recrystallization from aqueous ethanol, the product had mp 168.5-169.5°. Found, %: N 11.25, 11.20. $C_{10}H_4N_2O_3S$. Calculated %: N 11.56.

N-Acetyl-3-dimethylaminosulfonyldiphenylamine (V). A mixture of 21.2 g of (IV), 40 g of bromobenzene, 13.5 g of potassium carbonate and ca. 0.5 g of copper bronze was heated in an oil bath for 28 h. The bromobenzene was distilled off, and the residue was filtered and recrystallized from abs. alcohol to give 16.9 g of (V). After repeated recrystallizations the product had mp 157-158°. Found, %: N 8.92; S 9.97, 9.99. $C_{16}H_{18}N_2O_3S$. Calculated, %: N 8.80; S 10.07.

3-Dimethylaminosulfonyldiphenylamine (I). A mixture of 16.9 g (V), 20 ml of alcohol, and 20 ml of conc. hydrochloric acid was refluxed for 5 h. The precipitate was filtered, dried, and crystallized from 80% alcohol to give 9 g of (I) mp 124-126°. Found, %: N 10.53; S 11.33. $C_{14}H_{16}O_2N_2S$. Calculated, %: N 10.14; S 11.59.

N-(β-chloropropionyl)-3-dimethylaminosulfonyldiphenylamine. To 8.3 g of (I), moistened with chloroform, was gradually added 5.7 g of β-chloropropionyl chloride and the mixture was refluxed for 3 h. After cooling, the resulting crystals were filtered and washed with a small amount of chloroform to give 9.5 g of product. After recrystallization from abs. alcohol a product with mp 176-177° was obtained. Found, %: Cl 9.69, 9.52; N 7.33, 7.29; S 8.70, 8.76. $C_{17}H_{19}O_3N_2ClS$. Calculated, %: Cl 9.67; N 7.63; S 8.74.

TABLE 1



R	R′	Isolated salt	Mp (in deg)	Found (in %).			Empirical formula	Calculated (in %)		
				N	S	Cl		N	S	Cl
R_1	$COCH_2CH_2$ (R_1^1)	Hydrochloride	130—1 (ethyl acetate)	8,25, 8,35		10,66, 10,71	$C_{19}H_{25}N_2OCl$	8,41		10,65
R_2	$COCH_2CH_2$ (R_1^1)	»	143—4 (acetone)	7,85, 7,73		9,68, 9,75,	$C_{19}H_{24}N_2OCl_2$	7,63		9,65
R_3	$COCH_2CH_2$ (R_1^1)	»	115—7 (ethyl acetate)	6,81, 6,70		8,92, 8,93	$C_{20}H_{24}N_2OF_3Cl$	6,99		8,86
R_4	$COCH_2CH_2$ (R_1^1)	»	153—4 (isopropyl alcohol)	8,54, 8,63		7,23, 7,25	$C_{27}H_{28}N_3O_3Cl$	8,79		7,42
R_5	$COCH_2CH_2$ (R_1^1)	»	129—30 (abs. ethanol)		7,41, 7,35	8,04, 8,03	$C_{21}H_{30}N_3O_3ClS$			8,06
R_5	$COCH_2CH_2$ (R_2^1)	Oxalate	177—8* (isopropyl alcohol)	8,22, 8,05			$C_{23}H_{29}N_3O_8S$	8,28	7,29	
R_5	$COCH_2CH_2$ (R_2^1)	Dioxalate	213* (water)	9,04, 8,90	6,18, 6,04		$C_{26}H_{34}N_4O_{11}S$	9,18	6,31	
R_5	$COCH_2CH_2$ (R_3^1)	»	184* (aq. alcohol)	8,65, 8,54	5,41, 5,40		$C_{27}H_{36}N_4O_{12}S$	8,75	5,25	
R_5	$CH_2CH_2CH_2$ (R_3^1)	Oxalate	120—2* (isopropyl alcohol)		5,22, 5,23		$C_{25}H_{37}N_3O_6S$		5,01	
R_5	$CH_2CH_2CH_2$ (R_5^1)	Hydrochloride	188—90* (abs. ethanol)		6,37, 6,38 7,22, 7,06	7,92, 7,89	$C_{21}H_{30}N_3O_3ClS$		6,31 7,39	
	$CH_2CH_2CH_2$ (R_6^1)	Dioxalate	205—6* (ethanol)	9,32, 9,35	5,10, 5,06		$C_{26}H_{36}N_4O_{10}S$	9,40	5,36	8,20

*Substance melts with decomposition.

N-(β-chloropropionyl)-diphenylamine. β-chloropropionylchloride (12.9 g) was added to a toluene solution of 16.9 g of diphenylamine and the mixture was refluxed for 3 h. The toluene and excess β-chloropropionyl chloride were then distilled off to give 21 g of a substance which, after crystallization from alcohol, had mp 94-95°. Found, %: Cl 13.75, 13.69. $C_{15}H_{14}ClNO$. Calculated, %: Cl 13.65.

N-(β-chloropropionyl)-3-phthalimidodiphenylamine was obtained under the conditions described above. From 3.12 g of 3-phthalimidodiphenylamine and 1.51 g of β-chloropropionyl chloride were obtained 3.6 g of a crystalline substance mp 182° (decomposition, from alcohol). Found %: Cl 8.58, 8.55; N 7.29, 7.33. $C_{23}H_{17}ClN_2O_3$. Calculated %: Cl 8.76; N 6.92.

N-(β-piperidylpropionyl)-3-dimethylaminosulfonyldiphenylamine. A mixture of 4.8 g of N-(β-chloropropionyl)-3-dimethylaminosulfonyldiphenylamine, 3 g of piperidine, and 100 ml of dry benzene was refluxed for 3 h. The piperidine hydrochloride which precipitated on cooling was filtered, and the filtrate was shaken twice with 20% hydrochloric acid, and the acid layer was neutralized with base. The precipitate, after standing in the cold, was filtered, washed with water, and dried to give 4.8 g of a product with mp 105-106°. After two recrystallizations from abs. alcohol the product had mp 107.5-108.5°. Found %: N 9.98, 9.90; S 7.75, 7.88. $C_{22}H_{29}O_3N_3S$. Calculated %: N 10.12; S 7.71. The oxalate was obtained by introduction of a calculated amount of oxalic acid into a saturated solution of N-(β-piperidylpropionyl)-3-dimethylaminosulfonyldiphenylamine in abs. alcohol. The resulting precipitate was filtered, washed, and recrystallized from abs. alcohol to give a product with mp 150-151° (decomposition). Found %: N 8.09, 8.02; S 6.33, 6.40. $C_{24}H_{31}O_7N_3S$. Calculated %: N 8.31; S 6.33.

The other N-(β-aminopropionyl)-derivatives of diphenylamines listed in Table 1 were similarly obtained (in benzene or toluene).

1-chloro-3-piperidinopropane. A solution of 7.9 g of 1-bromo-3-chloropropane and 8.5 g of piperidine in 50 ml of toluene was heated for 3 h. The precipitate of piperidine hydrobromide was filtered, and the toluene solution was used to prepare N-(γ-piperidinopropyl)-3-dimethylaminosulfonyldiphenylamine.

N-(γ-piperidinylpropyl)-3-dimethylaminosulfonyldiphenylamine. A mixture of 6.9 g of 3-dimethylaminosulfonyldiphenylamine, 1.2 g of sodium amide, and 100 ml of toluene was refluxed under stirring for 2 h. A calculated amount of a toluene solution of 1-chloro-3-piperidinopropane was then added without cessation of heating and stirring, and the mixture was heated for 5 h. After cooling and filtering, the toluene solution was shaken with hydrochloric acid. The viscous dark resin which precipitated in the aq. layer, quickly crystallized. The crystals were filtered, washed with a small amount of cold water, and dried. After three recrystallization from isopropyl alcohol, N-(γ-piperidinylpropyl)-3-dimethylaminosulfonyldiphenylamine hydrochloride was isolated as grey crystals with mp 198-200° (decomposition). Found %: Ce 7.86, 7.88; N 9.64, 9.72; S 7.25, 7.10. $C_{22}H_{31}NO_2S \cdot HCl$. Calculated %: Ce 8.11; N 9.60; S 7.31.

The salts of N-(γ-aminopropyl)-3-dimethylaminosulfonyldiphenylamine listed in Table 1 were obtained in a similar manner.

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