INDOLES

I. A New Method for the Synthesis of 2-Substituted Tryptamines

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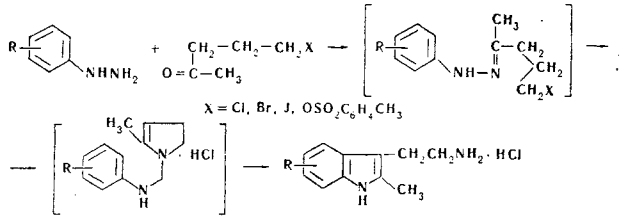
A new reaction has been found which occurs between arylhydrazine and a ketone possessing a halogen atom or a toluenesulfonyl group in the γ-position, when the mixture is boiled in an aqueous-alcoholic medium. High yields of 2-substituted tryptamines are formed.

Tryptamine derivatives play an extremely important role in biochemical processes. In recent years synthetic methods in this area have developed very rapidly [1, 2]. However, in the majority of cases the synthesis of tryptamines proceeds by first synthesizing the indole nucleus with the substituent group in the appropriate position and by then attaching the β-aminoethyl residue into position 3 by various methods.

It has been shown [3, 4] that when 5-chloro-2-pentanone reacts with arylhydrazines in an acid medium, 3-β-chlorethylindoles are formed according to the normal Fisher reaction. The latter were subsequently utilized by the authors for synthesizing certain tryptamines.

We discovered a new reaction by means of which 2-methyltryptamines may be obtained in a single stage in high yields from substituted arylhydrazines and compounds of the type, $CH_3COCH_2CH_2CH_2X$, where X = atoms of chlorine, bromine, iodine, or the p-toluene sulfonyl radical. The reaction product is a salt of tryptamine, which, when X is the tosyl group, is sparingly soluble and may be obtained in pure form. When ketone halides are used salts are formed which do not precipitate, and they must be converted into free bases which can then be purified by distillation, recrystallization, or sublimation. The reaction probably proceeds according to the following scheme:



Ketone halides of the above type can be readily obtained from technical grade acetopropyl alcohol (5-hydroxy-2-pentanone) treated with a concentrated solution of the appropriate hydrogen halide. The tosylation of acetopropyl alcohol to form the sulfonate ester proceeded in normal fashion by treating acetopropyl alcohol in pyridine at 0° with tosyl chloride. The product is unstable and decomposes on distillation (even under high vacuum). It cannot be stored. Best results at purification were obtained by passing the reaction product through a short column containing aluminum oxide. The purified product should be used immediately after it has been prepared. The iodides and bromides cannot be preserved, even in the dark at 0°. It is thus desirable to use chlorides in the reaction. The chloride can be preserved in the dark at 0° without change for approximately three months. Beyond this period it noticeably darkens but can be repurified by distillation.

EXPERIMENTAL

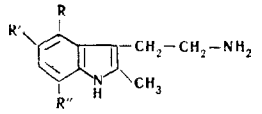
γ-Chloropropyl methyl ketone. A mixture of 102.1 g (1 mole) of freshly distilled acetopropyl alcohol in 350 ml (threefold excess) of concentrated hydrochloric acid was steam distilled. The chloride, isolated as an oil after dilution with distilled water, was twice extracted with ether, after which the ethereal layer was washed with water. The ether was removed by distillation under vacuum using a water-jet pump. The remaining oil was distilled under vacuum. A 79.6 g (70%) quantity of γ-chloropropyl methyl ketone was obtained, bp 73–74° (26 mm); n_D^{20} 1.4384; d_4^{20} 1.0342 [5].

γ-Bromopropyl methyl ketone. A 102.1 g quantity (1 mole) of acetopropyl alcohol was poured into saturated hydrobromic acid (400 ml) chilled to 0°. The reaction mixture was held at room temperature for 30 minutes. The darkened reaction mass was then poured into chilled water (sixfold volume of water) and mixed with ether. The ethereal solution was dried with calcium chloride. The ether was then removed by distillation at the lowest possible temperature, and the residue was distilled under vacuum. A 85.8 g (52%) quantity of γ-bromopropyl methyl ketone was obtained, bp 79–80° (20 mm) n_D^{20}, 1.4680; d_4^{20}, 1.3490 [6].

4-Pentanonyl p-toluenesulfonate. A 20 g quantity (0.105 mole) of p-toluene sulfonylchloride was added at 0° slowly in small portions to a solution prepared at 0° from 10.21 g (0.1 mole) of acetopropyl alcohol and 15.8 g (0.2 mole) of absolute pyridine. After the addition was completed the reaction mixture was stirred at 0° for 15 minutes and then at room temperature for two hours. The reaction mixture was then poured onto ice and the oil was separated and extracted with ether. The ethereal layer was washed with dilute hydrochloric acid, a weak solution of sodium bicarbonate, and water. The ether was removed by distillation under vacuum without heating. The residue was passed through a thin layer of aluminium oxide. A 12.5 g (48%) quantity of the sulfonate ester was obtained. On distillation it decomposes, n_D^{20} 1.5076; d_4^{20} 1.1718. Found, %: C 56.46, 56.40; H 6.24, 6.10. Calculated for $C_{12}H_{16}O_4S$, %: C 56.26; H 6.30.

γ-Iodopropyl methyl ketone. A mixture of 10.21 g (0.1 mole) of acetopropyl alcohol was added to a fivefold volume of hydroiodic acid which had been freshly distilled over red phosphorus and was boiling continuously. The solution was left overnight. It was then poured onto ice and the separated oil extracted with ether. The ethereal solution was mixed with a solution of sodium sulfide in order to remove free iodine. On distillation 12.51 g (59%) of γ-iodopropyl methyl ketone were obtained, bp 102–103° (22 mm); n_D^{20} 1.5162; d_4^{20} 1.6507 [7].

2-Bromo-5-methoxyphenylhydrazine. A 32 g quantity (0.15 mole) of 3-amino-4-bromoanisole [1] was dissolved in 150 ml of concentrated hydrochloric acid on heating to 50–60°. The solution was cooled rapidly, and at 0° a solution of 10.5 g (0.152 mole) sodium nitrite in 35 ml of water was added. The blue solution of diazo compound was filtered rapidly through a glass filter. The filtrate was cooled at 1–5° and a cold solution of 105 g of $SnCl_2 \cdot 2H_2O$ in 90 ml



R	R′	R″	Yield %	Bp, °C (pressure, mm)	Mp, °C (after sublimation	R_f*	pK_a in 50% ethanol	Acid tartrate, mp, °C	Picrate				
									mp, °C	found, %		empirical formula	calculated, %	
										C	H		C	H
H	H	H	82**	203—208 (10)[8]	107	0.79	9.27	174—175	218—219	—	—	—	—	—
H	H	OCH_3	64	191—194 (0.5)	110—111	0.72	9.35	177—178	214—215	49.87	4.69	$C_{12}H_{16}N_2O \cdot C_6H_3N_3O_7$	49.88	4.41
H	H	CH_3	76	209—211 (7)	160—162	0.78	9.69	—	220—223	52.15	4.73	$C_{12}H_{16}N_2O \cdot C_6H_3N_3O_7$	51.79	4.58
OCH_3	H	Br	20	—	115—117	0.76	9.35	—	155—156	42.34	3.64	$C_{12}H_{15}BrN_2O \cdot C_6H_3N_3O_7$	42.20	3.54
H	OCH_3	H	65	210—214 (6)[9]	83—84	0.77	9.27	200—201	219—220	50.19	4.34	$C_{12}H_{16}N_2O \cdot C_6H_3N_3O_7$	49.88	4.41
H	CH_3	H	74	210—212 (8)	100—101	0.79	9.12	—	224—225	51.41	4.73	$C_{12}H_{16}N_2O \cdot C_6H_3N_3O_7$	51.79	4.58
H	$C_6H_5CH_2O$	H	82***		—	0.76	—	—	204—206	56.32	4.78	$C_{18}H_{20}N_2O \cdot C_6H_3N_3O$	56.57	4.55

*"Rapid" paper from the Volodarskii factory, system of pyridine-water-butanol (1:1:1)
**Yield for chloroketone and bromoketone—48%, for iodoketone—79%, and for tosylate—45%
***Isolated in the form of the hydrochloride with a mp of 102—103° (from alcohol)[9].

of concentrated hydrochloric acid was slowly added in drops with mixing at a rate such that the temperature did not exceed +5°. The temperature of the reaction mixture was held constant for two hours after which the precipitate was filtered by suction and decomposed with a 25% solution of sodium hydroxide. A 17.25 g quantity (53%) of 2-bromo-5-methoxyphenylhydrazine was obtained with a boiling point of 59° (from heptane). Found, %: N 13.41, 13.48. Calculated for $C_7H_9BrN_2O$, %: N 13.52. Hydrochloride, mp 189°.

General method of ring formation of arylhydrazines and γ-halogenpropyl methyl ketones. A solution of 0.1 mole of ketone halide in 20 ml of methanol was added to a boiling solution of 0.1 mole of substituted phenylhydrazine in a mixture of 280 ml methanol and 20 ml of water. The reaction mass was refluxed for 20 hours. The solvent was removed by distillation under vacuum using a water-jet pump, the residue was dissolved in 160 ml of hot 0.5% HCl, and the solution was filtered through 1 g of activated carbon. The filtrate was evaporated at 50° to a volume of approximately 40 ml and made alkaline with 20 ml of a 40% solution of sodium hydroxide. The separated tryptamine was extracted with hot benzene (80 ml), and the extracts were filtered and distilled under vacuum in a stream of nitrogen. The yields and constants of the tryptamines are presented in the table.

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