THE PREPARATION OF 5-ALKYLTHIO, BRANCHED TRYPTAMINES

J. KENNETH HORNER, J. I. DEGRAW, AND W. A. SKINNER

Department of Pharmaceutical Chemistry, Life Sciences Research, Stanford Research Institute, Menlo Park, California

Received August 9, 1965

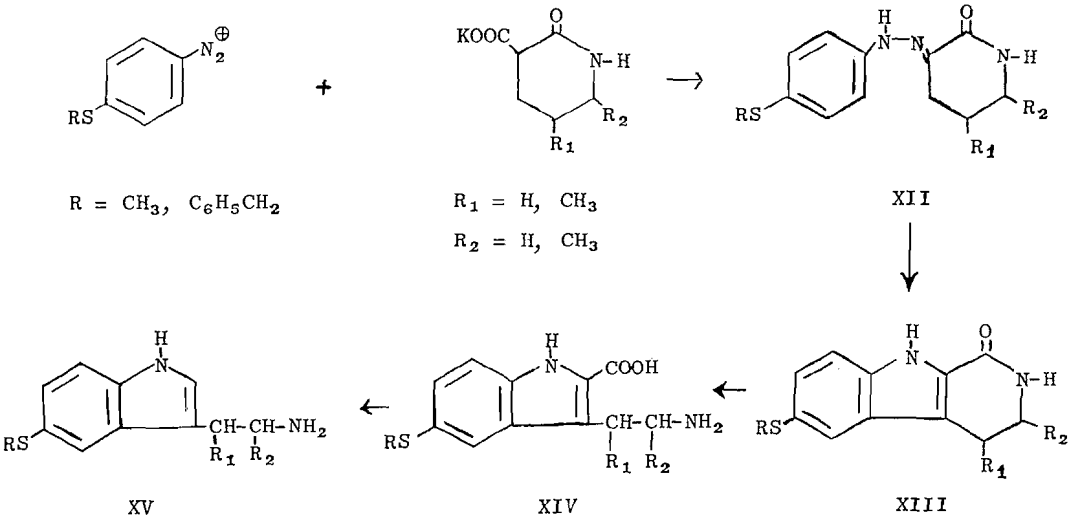
ABSTRACT

The Japp–Klingemann reaction has been employed to prepare six new tryptamines. Data on the intermediate phenylhydrazones, β-carbolines, and tryptamine carboxylic acids are presented. Syntheses of 5-methyl-, 6-methyl-, 5,5-dimethyl-, and 5,6-dimethyl-2-oxopiperidine-3-carboxylates are described.

Analogues of tryptamine have aroused considerable interest because of the implication of serotonin in the etiology of certain psychotic disorders. In a recent paper (1) we described the synthesis of the thiol analogue of serotonin. As an extension of this work we have now prepared some 5-alkylthio, branched-chain tryptamines.

The preparation of the various 5-alkylthiotryptamines was based on the piperidone procedure first introduced by Abramovitch and Shapiro (2). This route obviates the use of difficultly obtained indoles as starting materials and has been employed by several authors (1–5) for the synthesis of nuclear-substituted tryptamines. It was recently extended by Russian workers to include α-methyltryptamines (6, 7) and α,β-dimethyltryptamines (8). Abramovitch and Muchowski (9) further expanded the method to prepare β-methyltryptamines. An attempt by us to apply the method for the synthesis of 5-methylthio-β,β-dimethyltryptamine was unsuccessful when we were unable to hydrolyze the intermediate oxo-β-carboline (XIII-G; Table II). The general synthetic route is outlined in Reaction Scheme 1.

Utilizing the versatile Japp–Klingemann reaction, we prepared substituted 2,3-piperidione-3-(4′-alkylthio)phenylhydrazones (XII) from the various methyl-substituted



REACTION SCHEME 1.

3-carbethoxy-2-piperidones. The phenylhydrazones XII were cyclized in acid to the substituted 6-alkylthio-1,2,3,4-tetrahydro-1-oxo-β-carbolines (XIII). All β-carbolines underwent alkaline hydrolysis to the corresponding 3-aminoalkyl-5-alkylthio-2-indole carboxylic acid (XIV), except 4,4-dimethyl-6-methylthio-1,2,3,4-tetrahydro-1-oxo-β-carboline (XIII-G). With this compound, only starting material was isolated under a variety of alkaline hydrolytic conditions.

Infrared, ultraviolet, and nuclear magnetic resonance spectra were obtained for 6-methylthio-1,2,3,4-tetrahydro-1-oxo-β-carboline and for the 3-methyl-, 4-methyl-, and 4,4-dimethyl-6-methylthio-1,2,3,4-tetrahydro-1-oxo-β-carbolines. In each case the spectra were inspected in an effort to find some difference in the 4,4-dimethyl compound which would account for its stability to basic hydrolysis. Enolization of the amide moiety of the lactam would confer alkaline stability upon the molecule, but infrared data failed to show any indication of C=N absorption in the critical 5.75–6.05 μ region in any of the β-carbolines. Ultraviolet spectra were unchanged when run in neutral and alkaline media, again indicating a lack of enolization. Nuclear magnetic resonance data on the four compounds, obtained on a 100 Mc instrument, showed the expected peaks and frequency shifts, except for those protons in the 5-positions. The 5-proton was found at 7.56 p.p.m. in both the non-methylated β-carboline and the 3-methyl β-carboline spectra. The 4-methyl spectrum showed a shift downfield of 0.11 p.p.m., and the 4,4-dimethyl a downfield shift of 0.22 p.p.m., for the 5-proton.

Menon and Simonson (10) reported that 4,4-dimethyl-2-piperidone was not hydrolyzed in base, while Kuhn and Jerchel (11) reported that 6-methyl-2-piperidone was opened under the same conditions. This retardation of ring-opening reactions by geminal substitution is well known, and Bordwell and co-workers (12) have theorized that the stabilizing effect is due to decreased ability of the departing atoms to move away from each other in the transition state. In our case nuclear magnetic resonance data have indicated interaction between the *gem*-dimethyls and the 5-proton. Molecular models suggest that there would also be rotational restriction between the *gem*-dimethyls and the carboxylate ion in the lyate species. These conditions would promote rapid reclosure to the lactam ring.

The 5-alkylthio, branched tryptamines (XV) were obtained in good yield by facile decarboxylation of the carboxylic acids (XIV) in a mixture of aqueous hydrochloric and acetic acids. Physical and analytical data for the compounds obtained by the above sequence are listed in Tables I–IV.

Except for ethyl 2-oxo-5,5-dimethylpiperidine-3-carboxylate (XI), the carbethoxypiperidones used in this work were prepared by modified versions of previously described procedures. These modifications along with references to the original methods are described in the Experimental section. The synthesis of ethyl 2-oxo-5,5-dimethylpiperidine-3-carboxylate (XI) was achieved by a three-step procedure starting with diethyl methylene malonate (13). The vinyl ester was allowed to react with 1-piperidino-2-methylpropene (14) to yield the formyl diester IX. The oxime X was prepared as described previously and hydrogenated over Raney nickel to yield piperidone XI, as shown in Reaction Scheme 2.

EXPERIMENTAL

Ethyl 2-Oxo-6-methylpiperidine-3-carboxylate (III)

A mixture of 1.2 g of ethyl 2-carbethoxy-4-acetylbutyrate (I) (15), 1.2 g of hydroxylamine hydrochloride, 6 ml of pyridine, and 6 ml of ethyl alcohol was refluxed for 3 h. The colorless solution was evaporated to dryness *in vacuo* and the residual syrup was partitioned between 15 ml of ether and 15 ml of water. The aqueous portion was extracted with another 15 ml of ether and the combined ether extracts were washed with 10 ml of water. The ether was dried and evaporated *in vacuo* to leave 0.98 g of syrup; λ_{max}^{film} 2.9–3.0 μ

TABLE I

2,3-Piperidione-*p*-alkylthiophenylhydrazones (XII)

XII	R	R_1	R_2	Yield (%)	Melting point* (°C)	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
A	CH_3	H	CH_3	76	215	59.3	6.51	16.0	59.1	6.58	16.0
B	$C_6H_5CH_2$	H	CH_3	27	225–227	67.2	6.24	12.4	67.0	6.18	12.3
C	CH_3	CH_3	H	47	222	59.3	6.51	16.0	59.2	6.57	15.8
D	$C_6H_5CH_2$	CH_3	H	58	215	67.2	6.24	12.4	67.1	6.23	12.4
E	CH_3	CH_3	CH_3	58	213	60.6	6.91	15.2	60.6	6.93	15.0
F	$C_6H_5CH_2$	CH_3	CH_3	92	215–217	68.0	6.56	11.9	67.8	6.58	12.1
G	CH_3	Di-CH_3	H	90	232	60.6	6.91	15.2	60.2	6.91	15.2

*All melting points are uncorrected and were taken on a Fisher–Johns melting block.

TABLE II

6-Alkylthio-1,2,3,4-tetrahydro-1-oxo-β-carbolines (XIII)

XIII	R	R_1	R_2	Method*	Yield (%)	Melting point (°C)	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
A	CH_3	H	CH_3	B	47	214	63.4	5.73	11.4	63.1	5.77	11.3
B	$C_6H_5CH_2$	H	CH_3	B	90	†	70.8	5.63	8.69	70.9	5.60	8.65
C	CH_3	CH_3	H	A	58	158	63.4	5.73	11.4	63.3	5.85	11.5
D	$C_6H_5CH_2$	CH_3	H	A	42	180	70.8	5.63	8.69	70.5	5.76	8.61
E	CH_3	CH_3	CH_3	A	‡	—	Noncrystalline					
F	$C_6H_5CH_2$	CH_3	CH_3	A	96	73–75	69.8§	7.12	7.08	69.7	7.13	7.25
G	CH_3	Di-CH_3	H	A	50	213	64.6	6.20	10.8	64.8	6.00	10.8

*Method A, hydrogen chloride and acetic acid; method B, 88–90% formic acid.
†Obtained as a noncrystalline glass by evaporative distillation, 210° at 0.3 mm.
‡Noncrystalline material was isolated and used in the next reaction without purification.
§Calculated as the isopropyl alcohol solvate.

TABLE III

5-Alkylthiotryptamine-2-carboxylic acids (XIV)

XIV	R	R_1	R_2	Yield (%)	Melting point (°C)	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
A	CH_3	H	CH_3	55	253 (decomp.)	59.2	5.65	10.6	59.2	5.70	10.8
B	$C_6H_5CH_2$	H	CH_3	50	—	Noncrystalline					
C	CH_3	CH_3	H	63	217–219	57.1*	6.28	10.2	56.9	5.92	9.98
D	$C_6H_5CH_2$	CH_3	H	95	207	65.4*	6.05	8.05	65.7	6.04	8.22
E	CH_3	CH_3	CH_3	42†	223–225	60.4	6.52	10.1	60.0	6.69	10.4
F	$C_6H_5CH_2$	CH_3	CH_3	94	200–202	67.8	6.26	7.91	67.4	6.43	7.97

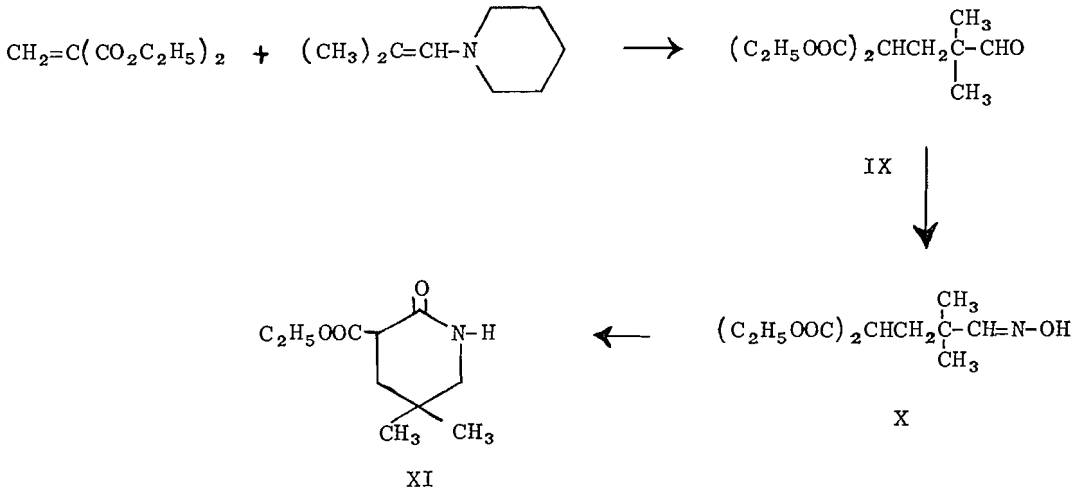
*Calculated as the hemihydrate.
†This yield includes the preparation of the noncrystalline β-carboline (XIII-E).

TABLE IV

5-Alkylthio, methyl-substituted tryptamines (XV)

XV	R	R_1	R_2	Yield* (%)		Melting or boiling point (°C)	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
A	CH_3	H	CH_3	75	Free base	108	65.4	7.32	12.7	64.9	7.22	12.5
B	$C_6H_5CH_2$	H	CH_3	46	Picrate†	200	54.9	4.41	13.3	54.9	4.57	13.2
C	CH_3	CH_3	H	79	HCl	212–215	56.1	6.67	10.9	56.0	6.65	11.1
D	$C_6H_5CH_2$	CH_3	H	69	HCl	210	64.9	6.36	8.42	64.7	6.23	8.15
E	CH_3	CH_3	CH_3	68	Picrate	202–205	49.2	4.57	15.1	49.4	4.67	15.1
F	$C_6H_5CH_2$	CH_3	CH_3	72	Free base	170 at 0.3	73.5	7.14	9.03	73.8	7.20	8.99

*Yields calculated for free bases.
†XV-B hydrochloride, m.p. 219°.



REACTION SCHEME 2.

(NH, OH), 5.7–5.8 μ (ester C=O), 6.0 μ (C=N). The material was not purified further and was used directly in the next reaction.

A mixture of 185.7 g of ethyl 2-carbethoxy-4-acetylbutyrate ketoxime (II), 6 teaspoonfuls of W-2 Raney nickel, and 150 ml of ethyl alcohol was shaken under 3 atmospheres of hydrogen at 80°. The absorption of gas was complete after 98 h. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo* to leave 117 g (84%) of off-white crystals. A portion was recrystallized from cyclohexane to yield an analytical sample, m.p. 71–73° (lit. m.p. 73° (7)). A more direct method (16) for the preparation of III has recently appeared.

Ethyl 2-Carbethoxy-4-acetylvalerate (IV)

To a solution of 0.2 g of sodium in 135 ml (0.84 mole) of diethyl malonate was added 18.0 g (0.21 mole) of methyl isopropenyl ketone over 15 min. The temperature rose to 45° and was maintained there by an external cold water bath. The mixture was stirred for 20 min, neutralized with acetic acid, and distilled *in vacuo* through a short Vigreux column. Excess diethyl malonate (95 g) was collected at 60–100° and 1.2 mm, and 39.7 g (76%) of product was collected at 122–132° and 1.2 mm. Redistillation of the latter fraction gave 32.2 g (62%), b.p. 116–122° at 1.0 mm.

In larger runs, the methyl isopropenyl ketone was distilled from a 50% monomer solution (K & K Chemical Co.) directly into the sodiomalonate solution. Yields of 70–75% were obtained by this procedure.

The analytical sample boiled at 124–125° and 1.7 mm.

Anal. Calcd. for $C_{12}H_{20}O_5$: C, 59.0; H, 8.25. Found: C, 59.1; H, 8.24.

Ethyl 2-Oxo-5,6-dimethylpiperidine-3-carboxylate (VI)

Ethyl 2-carbethoxy-4-acetylvalerate ketoxime (V) was prepared from the keto ester IV by the same procedure used to prepare oxime II.

A mixture of 126.8 g of oxime V, 2.5 teaspoonfuls of W-2 Raney nickel, and 150 ml of ethyl alcohol was shaken with hydrogen at 4 atmospheres and 100° for 66 h, thereby consuming 91% of the theoretical amount of gas. The catalyst was removed, and the solvent was evaporated to leave 96.3 g (99%) of the piperidone VI; λ_{max}^{film} 3.10 μ (NH), 5.75 μ (ester C=O), 5.99 μ (lactam C=O), *no* 10.69 μ band as seen in oxime V. The analytical sample was prepared by dissolving the oil in benzene and filtering the solution to separate a small amount of free acid. The benzene was concentrated and the residue was heated at 100° under reduced pressure. The residual oil did not crystallize. Reference 8 listed m.p. 67–68°.

Anal. Calcd. for $C_{10}H_{17}NO_3$: C, 60.3; H, 8.60; N, 7.03. Found: C, 60.0; H, 8.53; N, 7.10.

Ethyl 2-Oxo-5-methylpiperidine-3-carboxylate (VIII)

This compound was prepared essentially by the method of Abramovitch and Muchowski (9). The procedure involved the Michael addition of diethyl malonate and methacrylonitrile. The resulting ethyl 2-carbethoxy-4-cyanovalerate (VII) was hydrogenated to yield the piperidone VIII. We were able to effect this reduction over platinum oxide at low pressure, while the above authors utilized Raney nickel at high pressure.

Ethyl 2-Carbethoxy-4-formylisovalerate (IX)

To 88.0 g (0.63 mole) of 1-piperidino-2-methylpropene (14) was rapidly added 110.0 g (0.63 mole) of

diethyl methylene malonate (13). The resulting warm solution was cooled to room temperature and allowed to stand for 1 h. Ice water (100 ml) was added, and the mixture was adjusted to pH 3–4 with 6 *N* hydrochloric acid and stirred for 15 min. The acidic mixture was extracted with two 250 ml portions of ether. The ether was washed twice with 250 ml portions of water, and then with 100 ml of saturated sodium bicarbonate. The ethereal solution was dried and evaporated *in vacuo* to leave 110 g of a colorless syrup, which was distilled at 114–120° and 1.3 mm to give 71.5 g (46%). An analytical sample had b.p. 95–96° at 1.0 mm; λ_{max}^{film} 3.60 μ, 3.70 μ (aldehyde, C—H), 5.7–5.8 μ (ester, aldehyde C=O).

Anal. Calcd. for $C_{12}H_{20}O_5$: C, 59.0; H, 8.25. Found: C, 58.8; H, 8.39.

Ethyl 2-Oxo-5,5-dimethylpiperidine-3-carboxylate (XI)

Ethyl 2-carboxy-4-formylisovalerate aldoxime (X) was prepared from the formyl ester IX by the same procedure used to prepare the oxime II.

A mixture of 59.0 g of the oxime X, 5 teaspoonfuls of W-2 Raney nickel, and 150 ml of ethyl alcohol was shaken for 48 h under 3 atmospheres of hydrogen at 60°. The catalyst was removed and the solvent evaporated to leave 46.7 g (98%) of a syrup which crystallized after 2 weeks. A portion was triturated with cyclohexane to yield white crystals, m.p. 44–47°.

Anal. Calcd. for $C_{10}H_{17}NO_3$: C, 60.3; H, 8.60; N, 7.03. Found: C, 60.0; H, 8.55; N, 7.00.

2,3-Piperidione-p-alkylthiophenylhydrazones (XII)

All phenylhydrazones (XII-A–XII-G) listed in Table I were prepared by the same general procedure, which is described here for the preparation of 6-methyl-2,3-piperidione-3-(4′-methylthio)phenylhydrazone (XII-A).

Ethyl 2-oxo-6-methylpiperidine-3-carboxylate (III) (9.7 g, 0.05 mole) was dissolved in 25 ml of warm ethyl alcohol, cooled to 0°, and diluted with a solution of 3.5 g (0.05 mole) of potassium hydroxide in 75 ml of water. This clear solution was chilled overnight and diluted with 200 g of a mixture of cracked ice and water. The cold solution was stirred while a suspension of 4-methylthiobenzene diazonium chloride was added in one portion followed by the immediate addition of 6 g of sodium acetate. The diazonium salt was prepared from 0.05 mole of 4-methylthioaniline in 30 ml of 4 *N* hydrochloric acid and 0.05 mole of sodium nitrite. In the formation of this diazonium salt it was necessary to stir the reactants for 1–2 h at 0° to ensure complete reaction. The mixture was stirred at 0° for 6 h, and the tan solid was collected by filtration and washed well with water. The crude material was washed with ether, and then with cold ethyl alcohol, and was sufficiently pure for further reactions.

An analytical sample, m.p. 215°, was prepared by recrystallizations from 2-methoxyethanol and then from dilute ethyl alcohol.

All crystalline phenylhydrazones XII had infrared absorption spectra with these approximate values; λ_{max}^{Nujol} 3.10 μ, 3.15 μ (NH), 6.00 μ (amide C=O), 6.23 μ (aryl), 6.44 μ (amide II). The three benzyl-substituted hydrazones (XII-B, XII-D, and XII-F) showed 1,4-disubstituted benzene absorption near 12.1 μ.

5-Alkylthio-1,2,3,4-tetrahydro-1-oxo-β-carbolines (XIII)

The phenylhydrazones XII were cyclized to the β-carbolines (XIII-A–XIII-G) listed in Table II by a general method with either hydrogen chloride and glacial acetic acid or 88–90% formic acid. The preparation of 3-methyl-6-methylthio-1,2,3,4-tetrahydro-1-oxo-β-carboline (XIII-A) is described below. The acetic acid modification follows.

A solution of 9.5 g (0.035 mole) of 6-methyl-2,3-piperidione-3-(4′-methylthio)phenylhydrazone (XII-A) in 80 ml of 88–90% formic acid was refluxed for 1 h, cooled to 25°, and concentrated *in vacuo*. The residue was washed with ice and water, then separated, and triturated with ethyl alcohol to give a tan solid. This solid was collected and used in the next reaction without further purification. An analytical sample, m.p. 214°, was prepared by recrystallizations from butyl chloride – ethyl alcohol mixtures and finally from isopropyl alcohol.

In the preparation of the six β-carbolines XIII-C–XIII-G the phenyl hydrazones XII-C–XII-G were dissolved in glacial acetic acid either at 25° or by slight warming, and then hydrogen chloride was passed into the solutions for 15 min. To obtain maximum yields and to avoid decomposition, the resulting suspensions were heated for varying periods of time and at different temperatures: C, 15 min on a steam bath; D, 15 min at reflux; E, 10 min on a steam bath and 40 min at reflux; F, 1 min at reflux and 40 min at 25°; G, 15 min at reflux. These acetic acid solutions were then cooled, concentrated to approximately one-third volume under reduced pressure, and diluted with ice water. The aqueous portion was decanted and the gums were crystallized from hot isopropyl alcohol.

The β-carbolines XIII showed comparable infrared absorption spectra; λ_{max}^{Nujol} 2.90 μ, 3.07 μ (NH), 5.97 μ (amide C=O). Ultraviolet spectra: λ_{max}^{EtOH} XIII-A, 231 mμ (ϵ = 14 000); XIII-C, 248 mμ (ϵ = 16 000); XIII-G, 233 mμ (ϵ = 16 000). Nuclear magnetic resonance spectra were run in deuterated chloroform. Locations of the peaks for the 5-proton were: XIII-A, 7.56 p.p.m.; XIII-C, 7.67 p.p.m.; XIII-G, 7.78 p.p.m.

5-Alkylthiotryptamine-2-carboxylic Acids (XIV)

The tryptamine carboxylic acids XIV-A–XIV-F listed in Table III were prepared by the following

general procedure, which is described for the preparation of 3-(2′-aminopropyl)-5-methylthio-2-indole carboxylic acid (XIV-A). One β-carboline XIII-G did not yield an amino acid under these alkaline hydrolytic conditions.

A solution of 3.8 g (15 mmoles) of 3-methyl-6-methylthio-1,2,3,4-tetrahydro-1-oxo-β-carboline (XIII-A) in 75 ml of ethyl alcohol was mixed with a solution of 12 g (0.18 mole) of potassium hydroxide in 20 ml of water and heated under reflux for 12 h. The solution was cooled, concentrated to half volume *in vacuo*, and diluted with water. The alkaline aqueous solution was passed through filter aid and charcoal, and then adjusted to pH 5 with acetic acid. The resulting solid was isolated by filtration and was of sufficient purity for use in further reactions. An analytical sample, m.p. 253° (decomp.), was prepared by recrystallizations from dilute ethyl alcohol.

The solid tryptamine carboxylic acids XIV showed similar infrared absorption spectra; λ_{max}^{Nujol} 2.94 μ (NH), 3.10 μ (NH, OH), 5.90 μ (acid C=O), 6.20 μ (aryl).

5-Alkylthio, Branched Tryptamines (XV)

The acidic decarboxylations of the tryptamine carboxylic acids XIV-A–XIV-F to the corresponding tryptamines XV-A–XV-F were run as described below in the preparation of 3-(2′-aminopropyl)-5-methylthioindole (XV-A). The substituted tryptamines are listed in Table IV.

A solution of 2.0 g (7.6 mmoles) of 3-(2′-aminopropyl)-5-methylthio-2-indole carboxylic acid (XIV-A) in 30 ml of acetic acid and 40 ml of 2 *N* hydrochloric acid was heated under reflux for 15 h. The clear solution was concentrated to near dryness and diluted with water. The acidic solution was passed through filter aid and charcoal, and adjusted to pH 10. The separated oil was extracted with ether; the ethereal solution was dried and concentrated to yield the free crystalline tryptamine XIV-A. Recrystallization from dilute ethyl alcohol gave an analytical sample, m.p. 108°.

The remaining tryptamines XV-B–XV-F were oils. For analytical purposes they were either converted into the picrate salts and recrystallized from 2-methoxyethanol–water (XV-B, XV-E), or converted into the hydrochloride salts in 6 *N* hydrochloric acid and recrystallized from dilute hydrochloric acid (XV-C, XV-D). One tryptamine (XV-F) was evaporatively distilled in a short-path tube for analysis.

All of the tryptamines that were prepared showed closely related infrared absorption spectra; λ_{max}^{Nujol} 3.00 μ (indole NH), 6.20 μ, 6.25 μ (NH_2, aryl). The benzyl derivatives had monosubstituted benzene absorption at 12.9 μ and 14.2 μ.

REFERENCES

1. J. K. Horner and W. A. Skinner. Can. J. Chem. **42**, 2904 (1964).
2. R. A. Abramovitch and D. Shapiro. J. Chem. Soc. 4589 (1956).
3. E. Adlerova *et al.* Collection Czech. Chem. Commun. **25**, 784 (1960).
4. A. Allais. Fr. Patent No. 1,186,258 (August 19, 1959); Chem. Abstr. **55**, 23562 (1961).
5. M. von Strandtmann, M. P. Cohen, and J. Shavel, Jr. J. Med. Chem. **6**, 719 (1963).
6. A. G. Terzyan, R. R. Safrazbekyan, R. S. Sukasyan, and G. T. Tatevosyan. Izv. Akad. Nauk Arm. SSR Khim. Nauki, **14**, 261 (1961); Chem. Abstr. **57**, 8531 (1962); Experientia, **17**, 493 (1961).
7. N. N. Suvorov, M. N. Preobrazhenskaya, and N. V. Uvarova. Zh. Obshch. Khim. **32**, 1567 (1962); Chem. Abstr. **58**, 4499 (1963); Zh. Obshch. Khim. **33**, 3738 (1963); Chem. Abstr. **60**, 7975 (1964).
8. A. V. Mkhitaryan, A. A. Kogodovskaya, A. G. Terzyan, and G. T. Tatevosyan. Izv. Akad. Nauk Arm. SSR Khim. Nauki, **15**, 379 (1962); Chem. Abstr. **59**, 2753 (1963).
9. R. A. Abramovitch and J. M. Muchowski. Can. J. Chem. **38**, 554 (1960).
10. K. N. Menon and J. L. Simonson. J. Chem. Soc. 304 (1929).
11. R. Kuhn and D. Jerchel. Chem. Ber. **76**, 413 (1943).
12. F. G. Bordwell, C. E. Osborne, and R. D. Chapman. J. Am. Chem. Soc. **81**, 2698 (1959).
13. A. Sakurai, H. Midoridawa, and S. Aoyama. J. Sci. Res. Inst. Tokyo, **52**, 112 (1958).
14. E. Benzing. Angew. Chem. **71**, 521 (1959).
15. F. Korte and H. Machleidt. Chem. Ber. **90**, 2143 (1957). N. C. Ross and R. Levine. J. Org. Chem. **29**, 2346 (1964).
16. J. Shavel, Jr., M. von Strandtmann, and M. P. Cohen. U.S. Patent No. 3,182,071 (May 4, 1965).