# 75. *Pyrazine Derivatives. Part II. A Synthesis of a Racemic 2-Hydroxy-3 : 6-di-sec.-Butylpyrazine and its Relationship to Deoxyaspergillic Acid.*

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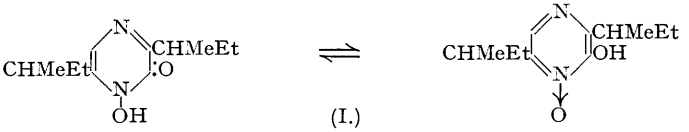
A synthesis of a racemic 2-*hydroxy*-3 : 6-*di*-sec.-*butylpyrazine*, m. p. 122—124° (IX), is described using the route adumbrated by (II)—(IX). The synthesis was undertaken as a preliminary step towards the synthesis of the antibacterial compound, aspergillic acid, isolated from culture filtrates of *Aspergillus flavus* by White and Hill. With the object of obtaining the *d*- and *l*-forms corresponding to the racemate, m. p. 122—124°, attempts were made to resolve 2-*amino*-3 : 6-*di*-sec.-*butylpyrazine* (VIII), the penultimate product of the synthesis. Although the base (VIII) gave a crystalline d-*camphorsulphonate* and a crystalline d-*bromocamphor-π-sulphonate*, fractional crystallisation of these salts did not lead to a resolution. The base (VIII) was also converted into 2-*phthalamido*-3 : 6-*di*-sec.-*butylpyrazine* (X) which gave a crystalline brucine *salt*; fractionation of this salt likewise failed to effect a resolution.

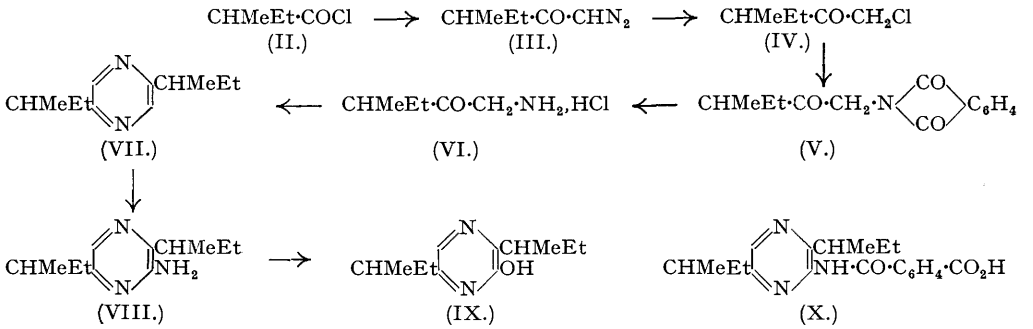
A comparison of the racemic 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine with deoxyaspergillic acid, $[\alpha]_D$ + 10°, obtained by partial reduction of aspergillic acid by Dutcher and Wintersteiner, is complicated by optical relationships. The ultra-violet absorption spectra of the two compounds are very similar and provide some evidence that deoxyaspergillic acid is a hydroxypyrazine derivative.

A mould tentatively identified as *Aspergillus flavus* was shown by White (*Science*, 1940, **92**, 127) to grow readily on a medium containing tryptone, yielding filtrates which are bactericidal for some Gram-negative as well as Gram-positive bacteria. White and Hill (*J. Bact.*, 1943, **45**, 433; 1942, **43**, 12) described the isolation of the crystalline antibacterial substance, aspergillic acid, $C_{12}H_{20}O_2N_2$ from the culture filtrates. Glister (*Nature*, 1941, **148**, 470) showed that a mould, probably belonging to the *Aspergillus* genus, produces a powerful antibacterial agent with a range considerably greater than that of penicillin. Menzel, Wintersteiner, and Rake (*J. Bact.*, 1943, **46**, 109) concluded that " the active substance elaborated by Glister's unclassified mould is unquestionably identical with aspergillic acid, m. p. 93°, although the cultural characteristics of this mould are different from those of *Aspergillus flavus* ".

Aspergillic acid was examined by Dutcher and Wintersteiner (*J. Biol. Chem.*, 1944, **155**, 359) who suggest that it is a cyclic hydroxamic acid (I) related to pyrazine. Aspergillic acid can be reduced to a neutral deoxyaspergillic acid for which the structure (IX) was suggested by Dutcher and Wintersteiner.



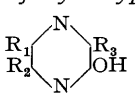

This paper describes a synthesis of a racemic 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine (IX) which was undertaken in order to compare this substance with deoxyaspergillic acid and also as a preliminary step in a contemplated synthesis of aspergillic acid. The experience gained in the review of methods for the synthesis of hydroxy-alkylpyrazines described in Part I (preceding paper) led us to choose the following method for the synthesis of the 3 : 6-di-*sec.*-butyl homologue. Methylethylacetyl chloride (II) was converted into 1-*chloro*-3-*methylpentan*-2-*one* (IV) *via* the diazo-ketone (III). The chloro-ketone was treated in xylene solution with potassium



phthalimide to yield 1-*phthalimido*-3-*methylpentan*-2-*one* (V) which was hydrolysed by means of hydrochloric acid to yield 1-*amino*-3-*methylpentan*-2-*one hydrochloride* (VI). Treatment of the hydrochloride with sodium hydroxide and mercuric chloride gave 2 : 5-di-*sec.*-butylpyrazine (VII) in 11% yield. A very considerable improvement in yield (60%) was achieved by using a modified procedure in which (VI) was treated with sodium hydroxide solution and the reaction product oxidised with hydrogen peroxide; the 2 : 5-di-*sec.*-butylpyrazine was characterised by the preparation of its *chloroplatinate*. Treatment of 2 : 5-di-*sec.*-butylpyrazine in dimethylaniline solution with sodamide gave 2-*amino*-3 : 6-*di*-sec.-*butylpyrazine* (VIII) in high yield. It was characterised by the preparation of a *picrate*, m. p. 134—136°, and several other crystalline derivatives mentioned below. Finally, treatment of the aminopyrazine (VIII) with nitrous acid gave a racemic 2-*hydroxy*-3 : 6-*di*-sec.-*butylpyrazine* (IX), m. p. 122—124°, characterised by the formation of its *hydrochloride*.

In order to characterise the synthetic product (IX) the ultra-violet absorption spectra of a number of hydroxypyrazines have been examined. The absorption spectrum of hydroxypyrazine shows a single maximum at 3160 A., whereas 2-hydroxy-3 : 6-dimethylpyrazine and 2-*hydroxy*-3 : 5 : 6-*trimethylpyrazine* show two maxima at approximately 2300 A. and 3300 A. The absorption spectrum of the racemic 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine is very similar, exhibiting maxima at 2285 A. and 3220 A. Dutcher and Wintersteiner (*loc. cit.*) examined the ultra-violet absorption spectrum of deoxyaspergillic acid and observed a single maximum at 3250 A.; they did not observe a band in the neighbourhood of 2300 A. We have re-examined the absorption spectrum of a specimen of deoxyaspergillic acid, m. p. 99—100° (preliminary softening at 96—97°), given to us by Dr. O. Wintersteiner, and find that apart from differences in intensity it is very similar to that of 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine, exhibiting maxima at 2295 A., and 3250 A. The differences in intensity may be due to lack of purity in the product from natural sources, since Dr. Wintersteiner informs us (private communication) that specimens of deoxyaspergillic acid have been obtained which melt as high as 105—108°.

*Absorption Spectra of Hydroxypyrazines in Ethanol.*



| $R_1$. | $R_2$. | $R_3$. | $\lambda_{m1}$ A. | $\varepsilon_{m1}$. | $\lambda_{m2}$, A. | $\varepsilon_{m2}$. |
|---|---|---|---|---|---|---|
| H | H | H | — | — | 3160 | 4,200 |
| H | Me | Me | 2270 | 7600 | 3230 | 3,600 |
| Me | Me | Me | 2295 | 7900 | 3360 | 7,400 |
| H | CHMeEt | CHMeEt | 2285 | 9600 | 3220 | 10,000 |
| Deoxyaspergillic acid | | (1) | — | — | 3250 | 8,500 |
| ,, | ,, | (2) | 2295 | 6700 | 3250 | 8,000 |

(1) Dutcher and Wintersteiner, *loc. cit.* (2) This paper.

A mixture of racemic 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine (m. p. 122—124°) and deoxyaspergillic acid (m. p. 99—100°) melted at 75—85°. In view of the stereochemical complications, this marked depression cannot of course be taken as evidence that deoxyaspergillic acid has not the structure attributed to it by Dutcher and Wintersteiner. Although two racemic forms of 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine are possible, the synthetic material appears to be a single racemate, fractional crystallisation failing to disclose any sign of heterogeneity. Whilst appreciating that the racemate m. p. 122—124° may not belong to the same optical series as deoxyaspergillic acid, $[\alpha]_D$ + 10°, attempts were made to effect its optical resolution. Since 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine is a weak base (it forms a hydrochloride which is decomposed by water) resolution of the parent 2-amino-3 : 6-di-*sec.*-butylpyrazine was attempted. Like 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine, the 2-amino-compound appears to be a single racemate, extensive fractionation of its picrate, and of several other derivatives, failing to disclose evidence of heterogeneity. 2-Amino-3 : 6-di-*sec.*-butylpyrazine would not form crystalline salts with either *d*-tartaric acid or dibenzoyl *d*-tartaric acid. With *d*-camphorsulphonic acid, however, a crystalline salt was obtained, fractional crystallisation of which gave a d-*camphorsulphonate*, m. p. 109—111°, $[\alpha]_D$ + 24°, in high yield. Decomposition of this salt gave optically inactive 2-amino-3 : 6-di-*sec.*-butylpyrazine. The aminopyrazine formed a crystalline salt with *d*-bromocamphor-π-sulphonic acid which likewise gave in high yield a homogeneous d-*bromocamphor-π-sulphonate*, m. p. 167—169°, $[\alpha]_D$ + 55°, the optical rotation remaining constant after repeated crystallisation. Decomposition of the salt gave 2-amino-3 : 6-di-*sec.*-butylpyrazine, $[\alpha]_D$ + 2°. This slight optical rotation is not

significant since the 2-hydroxy-3 : 6-di-*sec*-butylpyrazine obtained by treatment of this specimen of the amine with nitrous acid was optically inactive. The amino-compound obtained by decomposition of the combined mother liquors from the crystallisation of the *d*-bromocamphor-π-sulphonate was also converted into 2-hydroxy-3 : 6-di-*sec*.-butylpyrazine, m. p. 122—124°, which proved to be optically inactive.

In view of this lack of success attending the use of camphor-sulphonic acid salts, it seemed desirable to introduce an acidic function into 2-amino-3 : 6-di-*sec*.-butylpyrazine and to attempt resolution of the resulting acid with a suitable optically active base. Treatment of the amine with succinic anhydride gave 2-*succinimido*-3 : 6-*di*-sec.-*butylpyrazine*, m. p. 99—101°. This compound proved to be very labile under hydrolytic conditions, treatment with dilute barium hydroxide solution causing quantitative conversion into the parent amine. When treated with aqueous-alcoholic sodium carbonate solution, 2-succinimido-3 : 6-di-*sec*.-butylpyrazine gave 2-*succinamido*-3 : 6-*di*-sec.-*butylpyrazine*, m. p. 121°, in low yield. The replacement of succinic anhydride by phthalic anhydride proved advantageous, fusion of the amine with the latter giving 2-*phthalimido*-3 : 6-*di*-sec.-*butylpyrazine*, m. p. 111—112°, in excellent yield; hydrolysis of the latter with dilute alkali yielded 2-*phthalamido*-3 : 6-*di*-sec.-*butylpyrazine*, m. p. 130° (X). The phthalamic rather than the succinamic acid was chosen for resolution experiments because of ease of preparation and greater stability. The phthalamic acid gave a *brucine* salt, m. p. 160—161°, which, after repeated crystallisation, had a slight lævorotation. Decomposition of this salt regenerated the optically inactive phthalamic acid and brucine. Attempts to form a crystalline quinine salt of the phthalamic acid were unsuccessful.

We believe that the close similarity in the ultra-violet absorption spectra of the racemic 2-hydroxy-3 : 6-di-*sec*.-butylpyrazine and deoxyaspergillic acid indicates that the latter is a hydroxypyrazine derivative. A satisfactory explanation for the difficulties encountered in the attempted resolution of 2-amino-3 : 6-di-*sec*.-butylpyrazine and its bearing upon the structure of deoxyaspergillic acid must await further investigation.

## Experimental.

1-*Chloro*-3-*methylpentan*-2-*one*.—Methylethylacetic acid (*Org. Synth.*, V, 75) was converted into its acid chloride using the method described by Brown (*J. Amer. Chem. Soc.*, 1938, **60**, 1325; cf. Hudson and Hauser, *ibid.*, 1941, **63**, 3156). The acid chloride, b. p. 117° (yield 70—75%), was characterised by the preparation of methylethylacetamide which separated from ether as small needles, m. p. 111—112°. Methylethylacetyl chloride (40 g.) in dry ether (100 c.c.) was added slowly to a dry solution of diazomethane in ether (700 c.c., prepared from 80 g. of nitrosomethylurea) with shaking and cooling with ice-water. The reaction vessel was fitted with a soda-lime tube and the solution left for 15 hours. The solution was then cooled in ice and treated with a stream of dry hydrogen chloride (2—3 hours). The reaction mixture was left overnight and washed first with saturated sodium carbonate solution until the ether phase was neutral and then with water, and dried ($Na_2SO_4$). The ether was removed and the light brown oil distilled under reduced pressure to give a main fraction, b. p. 60—70°/15 mm., which on redistillation yielded 1-*chloro*-3-*methylpentan*-2-*one* as a colourless oil, b. p. 62—64°/14 mm., $n_D^{17°}$ 1·4385 (yield, 69—79%). The chloro-ketone has a penetrating, but not markedly lachrymatory, odour (Found : C, 54·0; H, 8·3. $C_6H_{11}OCl$ requires C, 53·6; H, 8·2%).

1-*Phthalimido*-3-*methylpentan*-2-*one*.—A mixture of 1-chloro-3-methylpentan-2-one (20 g.), dry xylene (35 c.c.), and potassium phthalimide (30 g.) was heated at 140—150° (bath temp.) with stirring for 4 hours. After cooling, the mixture was diluted with hot benzene and filtered. The filtrate was concentrated under reduced pressure and then treated with light petroleum (b. p. 40—60°). The crystalline solid which separated on cooling (24·5 g., m. p. 80—83°) was collected and recrystallised from light petroleum (b. p. 40—60°) to give 1-*phthalimido*-3-*methylpentan*-2-*one* as long fine needles, m. p. 84—86°, not raised by further recrystallisation (yield, 65%) (Found : C, 68·6; H, 6·3; N, 5·4. $C_{14}H_{15}O_3N$ requires C, 68·6; H, 6·1; N, 5·7%).

1-*Amino*-3-*methylpentan*-2-*one Hydrochloride*.—The phthalimido-ketone (10·8 g.) was heated under reflux with hydrochloric acid (120 c.c.; 20%) for 24 hours. The solution was allowed to cool, and the separated phthalic acid filtered off and washed with a little ice-water. The filtrate and washings were combined and evaporated to dryness under reduced pressure. Ice-water (50 c.c.) was added and the mixture filtered and again evaporated to dryness. The residue was dissolved in warm methanol (20 c.c.) and diluted with an equal volume of dry ether. The solution was cooled to — 20°; the hydrochloride then separated as shining plates. A further crop was obtained from the mother liquors (yield, 87%). Recrystallisation from methanol–ether with refrigeration gave 1-*amino*-3-*methylpentan*-2-*one hydrochloride* as plates which sintered at 130—140° and were completely molten at 160°, a property not changed by further recrystallisation (Found : Cl, 23·8. $C_6H_{14}ONCl$ requires Cl, 23·4%).

2 : 5-*Di*-sec.-*butylpyrazine*.—(*a*) A solution of the amino-ketone hydrochloride (6 g.) in ice-water (25 c.c.) was cooled (ice-water) and treated with sodium hydroxide solution (50 c.c.; 33%). The oil which separated was isolated by means of ether and dissolved in methanol. The solution was cooled to 0°, treated with hydrogen peroxide (5 c.c.; 30%), and set aside for 4 hours. Palladised charcoal (0·5 g. 5%) was added and the mixture set aside overnight. After filtration, the methyl alcohol was removed under reduced pressure, and the residue treated with water and thrice extracted with chloroform. The combined extracts were dried ($Na_2SO_4$) and evaporated, and the oil was distilled under reduced pressure

to give 2 : 5-di-*sec.*-butylpyrazine as a light yellow oil, b. p. 112—117°/13 mm. (yield, 60%). The *chloroplatinate* separated from methanol as orange-red needles, m. p. 183° (decomp.) [Found : C, 36·3; H, 5·4; Pt, 24·5, 24·8; Cl, 26·3. $(C_{12}H_{20}N_2)_2,H_2PtCl_6$ requires C, 36·3; H, 5·3; Pt, 24·6; Cl, 26·8%].

(*b*) A solution of 1-amino-3-methylpentan-2-one hydrochloride (15·2 g.) in water (15 c.c.) was treated with sodium hydroxide solution (250 c.c.; 33%) with ice-cooling. Finely powdered mercuric chloride (40 g.) was added and the mixture steam distilled. The distillate (500 c.c.) was treated with mercuric chloride solution and the mercurichloride which separated was collected. The mercurichloride was distilled with potassium hydroxide solution (50%; 30 c.c.) and the oily distillate collected, dried (KOH), and distilled to give 2 : 5-di-*sec.*-butylpyrazine as a light yellow coloured oil, b. p. 113°/11 mm. (yield, 11%). Its chloroplatinate separated from methanol as orange-red needles, m. p. 183° (decomp.) not depressed when mixed with the specimen described under (*a*).

2-*Amino*-3 : 6-*di*-sec.-*butylpyrazine*.—A solution of 2 : 5-di-*sec.*-butylpyrazine (4·2 g.) in freshly distilled dimethylaniline (10 c.c.) was added to finely powdered, freshly prepared sodamide (4·0 g.). The mixture was heated at 165° (bath temp.) for 2 hours with vigorous mechanical stirring. The mixture was cooled and poured on crushed ice. The aqueous phase was saturated with potassium carbonate and the mixture thrice extracted with ether. The ethereal extract was dried ($Na_2SO_4$) and the ether removed. Dimethylaniline was removed at 15 mm. and the remaining oil distilled to give the aminopyrazine, b. p. 110—120°/1 mm. (yield, 60—65%). Purification was achieved by conversion into the *picrate* which separated from methanol or ethanol as yellow needles, m. p. 134—136° (Found : C, 49·6; H, 5·6; N, 19·7. $C_{18}H_{24}O_7N_6$ requires C, 49·5; H, 5·5; N, 19·3%). Decomposition of the picrate by treatment with lithium hydroxide solution (cf. Burger, *J. Amer. Chem. Soc.*, 1945, **67**, 1615) and isolation of the product by means of ether followed by distillation gave 2-*amino*-3 : 6-di*sec.*-*butylpyrazine* as a colourless oil, b. p. 112—114°/0·5 mm. (97% yield) (Found : C, 69·3; H, 10·1; N, 20·1. $C_{12}H_{21}N_3$ requires C, 69·6; H, 10·1; N, 20·3%). A sample of the once-distilled base (3·7 g., b. p. 110—120°/1 mm.) was treated with successive portions of ethanolic picric acid, each containing approximately 0·5 g. of picric acid to give seven crops of picrate each of which melted within the range 131—136°. Each crop gave no depression in m. p. when mixed with the preceding one; the total picrate recovered (6·75 g.) represents 85% of the initial base.

2-*Hydroxy*-3 : 6-*di*-sec.-*butylpyrazine*.—A solution of 2-amino-3 : 6-di-*sec.*-butylpyrazine (2·1 g.) in N-hydrochloric acid (50 c.c.) was treated with sodium nitrite (2·0 g.) added in small portions with shaking, the mixture being cooled in ice-water. The mixture was kept at room temperature for 2—3 hours, warmed to 50—60° for five minutes, cooled, and neutralised by addition of sodium bicarbonate. The mixture was extracted with ether and the extract repeatedly washed with N-sodium hydroxide solution. The alkaline extract was acidified to litmus with dilute hydrochloric acid. After cooling to 0°, the solid was collected (1·55 g.), washed with water, and crystallised from aqueous methanol from which 2-*hydroxy*-3 : 6-*di*-sec.-*butylpyrazine* separated as prismatic needles (or as prisms from concentrated solutions), m. p. 122—123°. 2-Hydroxy-3 : 6-di-*sec.*-butylpyrazine sublimes rapidly at 120°/0·005 mm. It is readily soluble in cold ether, light petroleum, benzene, chloroform and acetone, insoluble in cold water, slightly soluble in hot water, and readily soluble in cold 3N-sodium hydroxide and 3N-hydrochloric acid. In admixture with an equal quantity of deoxyaspergillic acid (m. p. 99—100°) it melted at 75—85° (Found : C, 69·0; H, 9·4; N, 13·5. $C_{12}H_{20}ON_2$ requires C, 69·2; H, 9·6; N, 13·5%).

The *hydrochloride* was obtained by treating a dry ethereal solution of the hydroxy-pyrazine with dry hydrogen chloride; it separates from ethanol–ether as small prismatic needles, m. p. 173—175°. (Found : C, 59·6; H, 8·6; N, 11·1. $C_{12}H_{21}ON_2Cl$ requires C, 58·9; H, 8·6; N, 11·45%). When a solution of the hydrochloride in ethanol is diluted with water, 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine separates, m. p. 122—123°.

2-(2-*Bromopropionamido*)butan-3-*one*.—A solution of 2-aminobutan-3-one hydrochloride (Fargher and Pyman, *J.*, 1919, 233) (18·2 g.) in water (80 c.c.) was added rapidly to a well stirred ice-cooled suspension of powdered calcium carbonate (50 g.) in dry chloroform (150 c.c.). To this mixture was added a solution of 2-bromopropionyl bromide (50 g.) in dry chloroform (100 c.c.). After being stirred for 5 minutes the mixture was filtered and the chloroform layer separated, washed with water, and evaporated under reduced pressure. The residue crystallised on trituration with light petroleum; after four recrystallisations from benzene–light petroleum 2-(2-*bromopropionamido*)*butan*-3-*one* was obtained as prismatic needles, m. p. 77—79° (Found : C, 38·1; H, 5·3. $C_7H_{12}O_2NBr$ requires C, 37·9; H, 5·4%).

2-*Hydroxy*-3 : 5 : 6-*trimethylpyrazine*.—A solution of 2-(2-bromopropionamido)butan-3-one (5·0 g.) in dry ethanol (30 c.c.) containing sodium iodide (0·5 g.) was saturated with dry ammonia at 0° and kept at room temperature for 48 hours. The solvent was removed under reduced pressure and the gummy residue extracted with hot benzene. Concentration of the benzene extract gave a crop of red needles (1·0 g.), m. p. 196—198°, which was purified by sublimation at 120°/0·01 mm.; the *pyrazine* was thus obtained as colourless needles, m. p. 197—199° (Found : C, 60·9; H, 7·1; N, 20·1. $C_7H_{10}ON_2$ requires C, 60·9; H, 7·2; N, 20·3%).

2-*Amino*-3 : 6-*di*-sec.-*butylpyrazine* d-*Camphor*-β-*sulphonate*.—A mixture of 2-amino-3 : 6-di-*sec.*-butylpyrazine (0·877 g.) and *d*-camphor-β-sulphonic acid (0·992 g.) was dissolved in a warm mixture of water (10 c.c.) and methanol (2 c.c.). Since the salt did not separate on cooling, the solvent was removed under reduced pressure and the residual gum dissolved in ethyl acetate (1 c.c.) and ether (15 c.c.). The solution was repeatedly agitated; after three days crystal formation was observed, and on agitation a massive crystalline deposit rapidly separated. The prismatic crystals (1·15 g.), m. p. 104—108°, were collected (crop *A*) and the mother liquor concentrated to give a second crop of prisms, m. p. 101—105° (0·5 g.) (crop *B*). Crops *A* and *B* together represent 85% of the theoretical yield of salt. Crop *A* (0·5 g.) was thrice recrystallised from ether–light petroleum (b. p. 40—60°) to yield 2-*amino*-3 : 6-*di*-sec.-*butylpyrazine* d-*camphor*-β-*sulphonate* (0·25 g.) as prisms, m. p. 109—111°, $[\alpha]_D^{21°}$ + 24° (*l*, 1; *c*, 2·1 in chloroform), not altered by further recrystallisation (Found : C, 60·4; H, 8·6; N, 9·6. $C_{22}H_{37}O_4N_3S$ requires C, 60·1; H, 8·4; N, 9·6%). Crop *B* was thrice crystallised from ether–light petroleum (b. p.

40—60°) to yield 0·3 g. of the same salt, m. p. 108—111°, $[\alpha]_D^{20°}$ + 22·5° (*l*, 1; *c*, 2·6 in chloroform). Concentration of the mother liquors from crops *A* and *B* followed by recrystallisation, gave a further quantity (0·35 g.) of the same salt, m. p. 108—111°, $[\alpha]_D^{20°}$ + 23° (*l*, 1; *c*, 3·0 in chloroform). Decomposition of the salt, $[\alpha]_D$ + 23°, by shaking with sodium hydroxide solution (10%) followed by chloroform extraction gave the parent amino-pyrazine, $[\alpha]_D^{16°}$ ± 0° (*l*, 1; *c*, 3·0 in chloroform); it was characterised by its picrate, m. p. 134—136°.

2-*Amino*-3 : 6-*di*-sec.-*butylpyrazine* d-*Bromocamphor*-π-*sulphonate*.—A solution of ammonium *d*-bromocamphor-π-sulphonate {m. p. 278° decomp., $[\alpha]_D^{18°}$ + 85° (*l*, 1; *c*, 3·8 in water) $[\alpha]_D^{18·5°}$ + 94° (*l*, 1; *c*, 3·1 in methanol)} (1·0 g.) in water (10 c.c.) was boiled with 0·5N-barium hydroxide solution (10 c.c.) until ammonia evolution ceased. The solution was cooled and exactly neutralised with 0·5N-sulphuric acid, and the barium sulphate was removed. The filtrate was evaporated at 30° under reduced pressure to a viscous syrup, which was dried over phosphoric oxide in a vacuum. A solution of 2-amino-3 : 6-di-*sec*.-butylpyrazine (0·63 g.) in chloroform (20 c.c.) was added to the syrupy sulphonic acid. Crystallisation of the salt did not occur using either chloroform or ethyl acetate as solvent but was achieved from ether–light petroleum (b. p. 40—60°) from which a crop of heavy prisms separated, m. p. 156—161°, $[\alpha]_D^{18°}$ + 55° (*l*, 1; *c*, 3·0 in chloroform) (1·2 g. or 82%), which on crystallisation attained the constant m. p. 167—169°, $[\alpha]_D^{18°}$ + 55° (*l*, 1; *c*, 2·5 in chloroform), not altered by further recrystallisations (Found: C, 51·6; H, 7·0; N, 7·8. $C_{22}H_{36}O_4N_3BrS$ requires C, 51·1; H, 7·0; N, 8·1%). The base (0·15 g.) regenerated from a specimen of salt (0·57 g.), m. p. 164—167°, $[\alpha]_D^{18°}$ + 55°, had $[\alpha]_D^{18°}$ + 2° (*l*, 0·5; *c*, 3·0), a value within the limits of experimental error. This specimen of the base was treated with nitrous acid to give 2-hydroxy-3 : 6-di-*sec*.-butylpyrazine (0·1 g.), m. p. 121—122°, $[\alpha]_D^{18°}$ ± 0° (*l*, 0·5; *c*, 5·5 in ethanol). Similarly, the base regenerated from the combined mother liquors of the twice recrystallised salt was converted into the hydroxy-pyrazine (0·15 g.), m. p. 118—120°, $[\alpha]_D^{20°}$ ± 0° (*l*, 0·5; *c*, 3·0 in ethanol), which after a single recrystallisation from aqueous ethanol had m. p. 121—122°.

2-*Succinimido*-3 : 6-*di*-sec.-*butylpyrazine*.—A mixture of succinic anhydride (0·55 g.) and 2-amino-3 : 6-di-*sec*.-butylpyrazine (1·1 g.) was heated at 120—125° for 45 minutes. After cooling, the reaction mixture was dissolved in chloroform and the solution washed with 3N-sodium hydroxide, then with water, and dried ($Na_2SO_4$). The chloroform was removed, the resulting gum crystallising on cooling; recrystallisation from *n*-hexane gave 2-*succinimido*-3 : 6-*di*-sec.-*butylpyrazine* as prisms, m. p. 99—101° (yield, 62%). It is readily soluble in the common organic solvents with the exception of light petroleum, and is insoluble in water, 3N-sodium hydroxide, and 3N-hydrochloric acid (Found: C, 66·6; H, 8·0; N, 14·2. $C_{16}H_{23}O_2N_3$ requires C, 66·4; H, 8·0; N, 14·5%).

The succinimido-derivative (0·3 g.) in ethanol (5 c.c.) was treated with 0·5N-barium hydroxide (15 c.c.) and refluxed for 30 minutes. The ethanol was removed by distillation and the oil which separated was isolated by means of chloroform. Distillation at 100°/15 mm. gave 2-amino-3 : 6-di-*sec*.-butylpyrazine (0·19 g.) characterised as its picrate which separated from ethanol as needles, m. p. 133—135° not depressed when mixed with the authentic specimen of m. p. 134—136°.

2-*Succinamido*-3 : 6-*di*-sec.-*butylpyrazine* [N-(3 : 6-*Di*-sec.-*butyl*-2-*pyrazyl*)*succinamic Acid*].—A solution of the succinimido-derivative (0·25 g.) in methanol (2 c.c.) and sodium carbonate solution (10%; 3 c.c.) was heated under reflux for 1 hour. The mixture was diluted with an equal volume of water and extracted with ether. Evaporation of the ether gave a viscous oil which on treatment with ethanolic picric acid gave the picrate of 2-amino-3 : 6-di-*sec*.-butylpyrazine, m. p. and mixed m. p. 133—135° (0·13 g.). The aqueous phase was acidified to Congo-red with hydrochloric acid and the solution evaporated at 30° under reduced pressure to a small bulk. The resinous solid separating was dissolved in cold N-sodium hydroxide solution and the solution again acidified to Congo-red. Careful evaporation of the solution gave a crystalline solid (0·14 g.), m. p. 119—121°. Crystallisation of this from aqueous methanol gave 2-*succinamido*-3 : 6-*di*-sec.-*butylpyrazine* as prisms, m. p. 121—122° (Found: equiv., 312. $C_{16}H_{25}O_3N_3$ requires equiv., 307).

2-*Phthalimido*-3 : 6-*di*-sec.-*butylpyrazine*.—A mixture of 2-amino-3 : 6-di-*sec*.-butylpyrazine (1·0 g.) and phthalic anhydride (0·8 g.) was slowly heated to 180° (bath temp.) and maintained at 170—180° for 5 minutes. The cold reaction product was dissolved in chloroform, and the solution washed successively with N-sodium hydroxide solution and water, and dried. The solvent was removed, and crystallisation induced by the addition of light petroleum and cooling. Recrystallisation from light petroleum (b. p. 40—60°) gave 2-*phthalimido*-3 : 6-*di*-sec.-*butylpyrazine* as rosettes of prismatic needles, m. p. 111—112° (yield, 83%) (Found: C, 71·2; H, 6·8; N, 12·1. $C_{20}H_{23}O_2N_3$ requires C, 71·2; H, 6·8; N, 12·5%).

2-*Phthalamido*-3 : 6-*di*-sec.-*butylpyrazine* [N-(3 : 6-*Di*-sec.-*butyl*-2-*pyrazyl*)*phthalamic Acid*].—A solution of the phthalimido-derivative (1·35 g.) in ethanol (15 c.c.) and potassium hydroxide solution (5%; 15 c.c.) was heated under reflux for 1½ hours. The ethanol was removed by distillation, and the solution diluted with an equal volume of water and acidified to Congo-red with dilute hydrochloric acid. The precipitated acid was collected (1·3 g., m. p. 128—129°) and crystallised from aqueous alcohol from which 2-*phthalamido*-3 : 6-*di*-sec.-*butylpyrazine* separated as small needles, m. p. 130° (Found: equiv., 350. $C_{20}H_{25}O_3N_3$ requires equiv., 355). The phthalamic acid was readily hydrolysed to 2-amino-3 : 6-di-*sec*.-butylpyrazine by refluxing for 30 minutes with 5N-hydrochloric acid; the base was c haracterised as its picrate which separated as yellow needles from ethanol, m. p. 134—136°.

A solution of the phthalamic acid (0·75 g.) and brucine {0·85 g.; m. p. 174—176°, $[\alpha]_D^{18°}$ − 109° (*l*, 1; *c*, 2·45 in chloroform)} in acetone (25 c.c.) containing a little ether was set aside for several hours; the separated brucine salt was then collected (m. p. 158—159°; 1·4 g., 90%). Fractional crystallisation from chloroform–ethyl acetate gave a constant-melting *salt*, m. p. 160—161° (0·45 g.), $[\alpha]_D^{20°}$ − 10° (*l*, 0·5; *c*, 4·2 in chloroform) (Found: N, 9·3. $C_{43}H_{51}O_7N_5$ requires N, 9·35%). Decomposition of the salt (0·15 g.) by dilute hydrochloric acid gave the phthalamic acid (50 mg.), m. p. 129—130°, $[\alpha]_D^{20°}$ ± 0° (*l*, 1; *c*, 12·9 in alcohol).

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