332. 1 : 3 : 7 : 8-*Tetramethylxanthine.*

By H. Bader and J. D. Downer.

In order to compare their pharmacological properties caffeine and its 8-methyl derivative (1 : 3 : 7 : 8-tetramethylxanthine) have been synthesized by the method of Cook *et al.* (*J.*, 1949, 1071; 1950, 1884). The preparation of 1-methyl-2-thioxanthine required for caffeine has been simplified with improved yield (62%) by omitting the isolation of the intermediate 4-amino-5-carbethoxyglyoxaline and its *N'*-methylthioureido-derivative, and using pyridine as a solvent.

Experimental.—Diazomethane (21 g.) in ether (750 c.c.) was added to ethyl 4-amino-2-methylglyoxaline-5-carboxylate (18·8 g.) in methanol (100 c.c.) and kept at room temperature for 4 days. The solvents were removed *in vacuo*; the residue crystallized from benzene as colourless needles of *ethyl 4-amino-1 : 2-dimethylglyoxaline-5-carboxylate* (17·1 g., 84%), m. p. 121° (Found : C, 51·7; H, 6·9. $C_8H_{13}O_2N_3$ requires C, 52·4; H, 7·15%). (For light absorption properties, see Bader, Downer, and Driver, *J.*, 1950, 2775.)

This dimethylglyoxaline (16·9 g.), methyl *iso*thiocyanate (10 g.), and pyridine (20 c.c.) were refluxed for 2 hr., cooled, and filtered. The resulting *ethyl 1 : 2-dimethyl-4-N'-methylthioureido-glyoxaline-5-carboxylate* (15·6 g., 66%), m. p. 164°, crystallized from ethanol as colourless needles, m. p. 166·5° (Found : C, 47·0; H, 6·45; N, 22·3. $C_{10}H_{16}O_2N_4S$ requires C, 46·85; H, 6·3; N, 21·9%).

This (15·1 g.) was dissolved in aqueous ammonia (450 c.c. of 30%) at 60° and the crude xanthine [11·55 g., 93%; m. p. 345° (decomp.)] precipitated by addition of 30% aqueous acetic acid. Repeated precipitation with acetic acid of its solution in aqueous ammonia gave colourless needles of *1 : 7 : 8-trimethyl-2-thioxanthine*, 365° (decomp.) (Found : C, 45·65; H, 4·75; N, 26·2. $C_8H_{10}ON_4S$ requires C, 45·7; H, 4·8; N, 26·6%).

Hydrogen peroxide (50 c.c.; 80-vol.) was added in portions to a suspension of 1 : 7 : 8-trimethyl-2-thioxanthine (11·1 g.) in concentrated aqueous ammonia (100 c.c.) with vigorous stirring, and the mixture brought to the boil. When the reaction had subsided hydrogen peroxide (50 c.c.; 80-vol.) was added, stirring continued for 10 min. and the crude xanthine (7·35 g., 70%; m. p. 338°) precipitated with acetic acid. Recrystallization from methanol gave colourless needles of *1 : 7 : 8-trimethylxanthine*, m. p. 344° (decomp.) (Found : C, 49·1; H, 5·0; N, 28·6. $C_8H_{10}O_2N_4$ requires C, 49·5; H, 5·2; N, 28·85%).

Diazomethane (7·5 g.) in ether (250 c.c.) was added to a suspension of the preceding xanthine (7·2 g.) in methanol (100 c.c.) at 0° and the whole kept at room temperature for 18 hr. The solvent was concentrated *in vacuo* to 20 c.c., whereupon needles of 1 : 3 : 7 : 8-tetramethylxanthine (8-methylcaffeine) (6·2 g., 80%), m. p. 209° undepressed by authentic material, were deposited.

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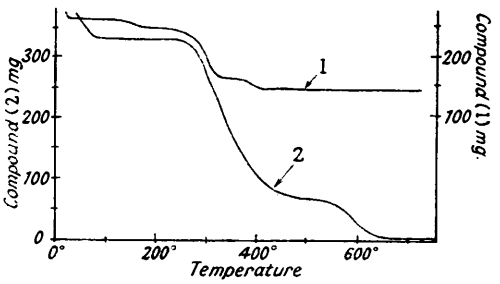
333. *Thermogravimetric Curves for the Decomposition of Octa-ammino-μ-amino-μ-nitrodicobaltic Sulphate and Dichlorobisethylenediaminocobaltic Hexachlorostibnate.*

By D. Gibbons.

The precipitates obtained by use of Belcher and Gibbon's new reagents (see title) for the determination of sulphate (*J.*, 1952, 4216) and antimony (*J.*, 1952, 4775) have been examined by Professor C. Duval by means of his thermogravimetric balance. The curves obtained are shown in the Figure: (1) is for the decomposition of octa-ammino-μ-amino-

μ-nitrodicobaltic sulphate, and (2) for that of dichlorobisethylenediaminocobaltic hexachlorostibnate. Both show well-defined horizontal portions extending on each side of the



drying ranges previously recommended, so that the safety limits may be extended to 25—122° and 75—225°, respectively.

I thank Professor Duval for permission to reproduce these curves.

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334. C-*Methylation of* 4 : 6-*Dihydroxycoumaran*-3-*one.*

By T. P. C. MULHOLLAND and G. WARD.

FOR synthesis of compounds related to dechlorogriseofulvin (MacMillan, *J.*, in the press), 4 : 6-dimethoxycoumaranone was required in quantity. Although this was achieved by a slight modification of the method of Drumm, MacMahon, and Ryan (*Proc. Roy. Irish Acad.*, 1924, **36**, 149), methylation of 4 : 6-dihydroxycoumaranone with methyl sulphate under their conditions gave an impure product which could not be fractionated by crystallisation. Chromatography showed it to consist of 4 : 6-dimethoxycoumaranone and a ketone $C_{11}H_{12}O_4$ containing one *C*-methyl group.

On the assumption that the latter compound was a *C*-methyl derivative of 4 : 6-dimethoxycoumaranone, the ready reaction with benzaldehyde to give a benzylidene derivative, and the condensation in the presence of alkali to give a compound $C_{22}H_{22}O_7$ showed that *C*-methylation had taken place in the phloroglucinol nucleus giving 4 : 6-dimethoxy-5(or 7)-methylcoumaranone. The 5-methyl structure was established by unambiguous synthesis from 4-hydroxy-2 : 6-dimethoxytoluene *via* ω-chloro-2-hydroxy-4 : 6-dimethoxy-5-methylacetophenone. The 7-methyl isomer was also synthesised. Neither coumaranone gave the violet colour with concentrated nitric acid given by dechlorogriseofulvin (MacMillan, *loc. cit.*) and 4 : 6-dimethoxycoumaranone.

Experimental.—Some microanalyses are by Mr. W. Brown.

Methylation of 4 : 6-*dihydroxycoumaranone.* (i) A suspension of 4 : 6-dihydroxycoumaranone (50 g.) in water (125 ml.) was treated with potassium hydroxide (35 g.) in water (70 ml.). Methyl sulphate (118 ml.) was added dropwise to the stirred mixture at 25° during 2 hours, the pH being maintained at 7—8 by addition of more alkali. More methyl sulphate (20 ml.) and alkali were then added, the pH being raised to 8—10 towards the end of the reaction. The insoluble product was washed with cold methanol and crystallised twice from benzene, giving 4 : 6-dimethoxycoumaranone (24 g.), m. p. 134—137°. Further crystallisation raised the m. p. to 138—139° (Found : C, 61·75; H, 5·4. Calc. for $C_{10}H_{10}O_4$: C, 61·8; H, 5·2%).

(ii) Methylation of 4 : 6-dihydroxycoumaranone (50 g.) by the method of Drumm *et al.* (*loc. cit.*) gave 54 g. of crude neutral product. This (10 g.) was chromatographed in warm benzene (200 ml.) on acid-washed alumina (21 × 3 cm.). Two bands and a mixed interband showing blue fluorescence in ultra-violet light were eluted with benzene (at *ca.* 40—50°

for the second band). On recovery, the second band gave 4 : 6-dimethoxycoumaranone (3·2 g.), m. p. 134—138° alone or mixed with an authentic specimen. The first band gave 4 : 6-*dimethoxy-5-methylcoumaranone* (1·8 g.) which was washed with light petroleum and crystallised from dilute ethanol (charcoal) in colourless needles, m. p. 146—147° [Found : C, 63·3, 63·7; H, 6·0, 6·1; OMe, 27·6; *C*-Me, 6·6%; *M* (Rast), 197. $C_{11}H_{12}O_4$ requires C, 63·45; H, 5·8; 2OMe, 29·8; 1*C*-Me, 7·2%; *M*, 208]. Absorption in EtOH : Max. at 327, 277, ~235 mμ (log ε 3·80, 4·20, ~3·97). The infra-red spectrum showed the presence of a carbonyl group absorbing at 1689 cm.$^{-1}$ but no semicarbazone, phenylhydrazone, or *p*-nitrophenylhydrazone could be prepared. The 2 : 4-*dinitrophenylhydrazone* formed red needles (from nitrobenzene), m. p. 237—239° (Found : C, 52·4; H, 3·75; N, 14·4. $C_{17}H_{16}O_7N_4$ requires C, 52·6; H, 4·2; N, 14·4%).

Saturation of a mixture of the ketone (200 mg.) and benzaldehyde (100 mg.) in acetic acid (7 ml.) with hydrogen chloride at 10° caused separation of a complex from which the *benzylidene* derivative (175 mg.) was obtained by washing with water. It crystallised from ethanol in pale yellow needles, m. p. 175—175·5° (Found : C, 73·0; H, 5·3. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%).

A solution of the ketone (100 mg.) in 3N-sodium hydroxide (10 ml.) and methanol (10 ml.) was heated under reflux in nitrogen for 5 hr. The solid (90 mg.) which separated on cooling crystallised from light petroleum in colourless needles, m. p. 175—175·5°, of 2-(4 : 6-*dimethoxy-5-methyl-3-coumaronyl*)-4 : 6-*dimethoxy-5-methylcoumaran-3-one* [Found : C, 66·3; H, 5·5; OMe, 31·1; *C*-Me, 7·3%; *M* (Rast), 438. $C_{22}H_{22}O_7$ requires C, 66·3; H, 5·6; 4OMe, 31·15; 2*C*-Me, 7·5%; *M*, 398). Absorption in EtOH : Max. at 324, 279, [254, 249], 234 mμ (log ε 3·73, 4·24, [4·10, 4·10], 4·31). The infra-red spectrum showed carbonyl absorption at 1700 cm.$^{-1}$ and absence of hydroxyl groups. The compound did not react with Brady's reagent and was unsaturated to neutral permanganate.

4 : 6-*Dimethoxy-5-methylcoumaranone*. (i) 4-Hydroxy-2 : 6-dimethoxytoluene (100 mg.) was converted by Horvath's procedure (*Monatsh.*, 1951, **82**, 901) into ω-*chloro-2-hydroxy*-4 : 6-*dimethoxy-5-methylacetophenone* (130 mg.), which crystallised from ethanol in needles, m. p. 114° (Found : C, 53·6; H, 5·6; Cl, 14·4. $C_{11}H_{13}O_4Cl$ requires C, 54·0; H, 5·4; Cl, 14·5%).

(ii) Ring closure of the above chloroacetophenone (130 mg.) in ethanol (20 ml.) with sodium acetate (200 mg.) in the usual way gave 4 : 6-dimethoxy-5-methylcoumaranone (60 mg.), needles, m. p. 146—147° (from ethanol) (Found : C, 63·4; H, 5·8. Calc. for $C_{11}H_{12}O_4$: C, 63·45; H, 5·8%). The identity with material obtained from methylation of 4 : 6-dihydroxycoumaranone was confirmed by mixed m. p., infra-red and ultra-violet absorption spectra, and formation of the same benzylidene derivative, m. p. and mixed m. p. 175° (Found : C, 73·2; H, 5·6. Calc. for $C_{18}H_{16}O_4$: C, 73·0; H, 5·4%).

4 : 6-*Dimethoxy-7-methylcoumaranone* was prepared from 2-hydroxy-4 : 6-dimethoxytoluene by the method described above. The intermediate ω-*chloro-2-hydroxy*-4 : 6-*dimethoxy-3-methylacetophenone* (34% yield), pale yellow needles, had m. p. 184—184·5° (from ethanol) (Found : C, 53·9; H, 5·1; Cl, 13·9%). Although the compound did not react with Brady's reagent or give a colour with ferric chloride or titanous chloride (Weygand and Csendes, *Ber.*, 1952, **85**, 45), the infra-red absorption spectrum showed a strongly bonded hydroxyl band at 2670 cm.$^{-1}$ and carbonyl absorption with frequency lowered to 1630 cm.$^{-1}$. 4 : 6-*Dimethoxy-7-methylcoumaranone* (59% yield) crystallised from ethanol in colourless needles, m. p. 177—178° (Found : C, 63·2; H, 5·9. $C_{11}H_{12}O_4$ requires C, 63·45; H, 5·8%). Absorption in EtOH : Max. at 320, 288, 234 mμ (log ε 3·50, 4·14, 3·95). The *benzylidene* derivative, obtained as described above, crystallised from ethanol in yellow needles, m. p. 244—245° (Found : C, 72·6; H, 5·3. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%).

The authors thank Dr. L. A. Duncanson for the infra-red absorption spectra, Dr. T. H. H. Quibell for a specimen, and Dr. F. Stansfield for details of an unpublished method of preparation, of 4-hydroxy-2 : 6-dimethoxytoluene.

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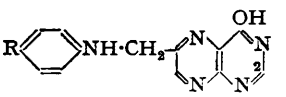
335. *Some Pteridines related to Folic Acid. Part I. 2-Deamino-analogues.*

By D. J. Brown.

2-Deaminofolic acid {I; R = $CO{\cdot}NH{\cdot}CH{\cdot}CO_2H){\cdot}[CH_2]_2{\cdot}CO_2H$} and several related compounds having simpler side chains were prepared by condensing the appropriate primary amine with 6-bromomethyl-4-hydroxypteridine. The last-mentioned intermediate, and the corresponding 7-isomer, were prepared by direct bromination of 4-hydroxy-6(and 7)-methylpteridine by a procedure based on the successful ω-brominations of similar methylpteridines (Boothe *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 27; Waller *et al.*, *ibid.*, 1950, **72**, 4630; Tschesche, Köhncke, and Korte, *Z. Naturforsch.*, 1950, **5**, 132; *Chem. Ber.*, 1951, **84**, 485). The 6-bromo-compound in sodium hydroxide solution quickly gives an amorphous polymeric substance of unknown structure. The 7-isomer gives a similar substance more slowly.

The folic acid analogues were tested for folic acid activity. The determination of their metal-binding stability constants is described elsewhere (Albert, *Biochem. J.*, in the press).

(I) 

2-Deaminofolic acid, tested with *Strept. faecalis* R and *Lactobacillus casei* showed inhibitory, but no growth-promoting, activity. It was inactive as an inhibitor of the Walker rat carcinosarcoma 256, and, unlike xanthopterin, caused no hypertrophy of the rat kidney. It showed no capacity, as does " aminopterin," to arrest cell division in embryonic chick cells growing *in vitro*.

Experimental.—Analyses were by Mr. P. R. W. Baker, Beckenham. Each substance was purified until it showed only one spot on a paper chromatogram viewed in light of mainly 254 mμ.

6-Bromomethyl-4-hydroxypteridine. To a hot solution of 4-hydroxy-6-methylpteridine (18 g.; Albert, Brown, and Cheeseman, *J.*, 1952, 4219) in acetic acid (615 ml.) was added bromine (6·6 ml.) in acetic acid (60 ml.). The whole was refluxed until, about 8 min. later, boiling became more vigorous and the colour of the solution darkened rapidly. Immediately the flask was cooled in ice–water to about 45° and the solvent was removed in a vacuum at 40—45°. The dark green sticky residue was shaken with ice-cold water (35 ml.) for 10 min., and the solid which remained was filtered off and washed with water (20 ml.) and then with ethanol (3 × 20 ml.) (yield, 86%). When dried at 110° for 10 min. it became purple. Recrystallization from ethanol (80 parts) with charcoal (0·25 part) gave a 75—80% recovery of crystalline material suitable for further syntheses. Two more recrystallizations gave colourless needles of *6-bromomethyl-4-hydroxypteridine quartohydrobromide*, decomp. >200° [Found: C, 32·3; H, 1·9; N, 21·4; Br, 37·8. $(C_7H_5ON_4Br)_3,(C_7H_5ON_4Br,HBr)$ requires C, 32·2; H, 2·0; N, 21·4; Br, 38·2%]. It is unstable to cold alkali, all the bromine appearing as ion within 2 min. The aqueous solution is strongly acid.

7-Bromomethyl-4-hydroxypteridine. 4-Hydroxy-7-methylpteridine (Albert *et al.*, *loc. cit.*) was brominated in the same way (yield, 76%) but the reaction mixture was cooled at once after the addition of bromine. It was recrystallized twice from ethanol (150 parts) with carbon, to give colourless leaflets of *7-bromomethyl-4-hydroxypteridine* (65% recovery), decomp. >170° (Found: N, 23·45; Br, 32·9. $C_7H_5ON_4Br$ requires N, 23·25; Br, 33·1%). This compound was but little changed by cold alkali after 5 min. Complete liberation of bromine as ion required 2 hr.' heating in water at 100° (pH <1 after a few min.).

6-Anilinomethyl-4-hydroxypteridine (I; R = H). 6-Bromomethyl-4-hydroxypteridine quartohydrobromide (2·3 g.), dissolved in boiling ethanol (180 ml.), was refluxed with aniline (2·5 ml.) for 2 hr. After refrigeration the crystalline product was filtered off, washed with ethanol, dried (yield, 67%), dissolved in sodium hydroxide solution (1%; 33 ml.), and reprecipitated by hydrochloric acid (pH 3—4). Recrystallization from 75 ml. of 6 : 4 amyl alcohol–dimethylformamide gave deep yellow crystals of *6-anilinomethyl-4-hydroxypteridine*, decomp.

>250° (Found: C, 62·2; H, 4·5; N, 27·4. $C_{13}H_{11}ON_5$ requires C, 61·65; H, 4·4; N, 27·65%), soluble in about 4000 parts of boiling water.

6-p-*Anisidinomethyl- and* 6-(2 : 5-*dimethoxyanilinomethyl*)-4-*hydroxypteridine.* The bromo-compound reacted similarly with *p*-anisidine. The yield was 70%. One recrystallization from amyl alcohol (1000 ml.) gave deep orange needles of 6-p-*anisidinomethyl*-4-*hydroxypteridine*, decomp. 240—260° (Found: C, 59·2; H, 4·4; N, 25·0. $C_{14}H_{13}O_2N_5$ requires C, 59·3; H, 4·6; N, 24·7%), soluble in about 3500 parts of boiling water.

The crude greenish-yellow solid obtained from 2 : 5-dimethoxyaniline, when recrystallized twice from water (1200 parts; carbon), gave yellow needles (15%) of 6-(2 : 5-*dimethoxyanilinomethyl*)-4-*hydroxypteridine hemihydrate* (dried at 120°) [Found: C, 55·5; H, 5·0; N, 21·7. $(C_{15}H_{15}O_3N_5)_2,H_2O$ requires C, 55·9; H, 5·0; N, 21·7%], soluble in dimethylformamide and acetic acid.

6-p-*Carboxyanilinomethyl*-4-*hydroxypteridine* (R = CO_2H). The bromo-compound (1·9 g.) and *p*-aminobenzoic acid (2·8 g.) reacted similarly. The crude product was ground with water (30 ml.) containing sodium hydroxide added to pH 4. The dried material was dissolved in warm dimethylformamide (40 ml.), and warm water (12 ml.) was added. The solution was brought to the boil, treated with carbon, and allowed to crystallize (yield, 28%). Repetition gave yellow needles of 6-p-*carboxyanilinomethyl*-4-*hydroxypteridine*, decomp. *ca.* 300° (Found: C, 56·55; H, 3·7; N, 23·55. $C_{14}H_{11}O_3N_5$ requires N, 56·7; H, 3·7; N, 23·55%). It dissolved in 2-ethoxyethanol.

4-*Hydroxy*-6-p-*sulphoanilinomethylpteridine.* 6-Bromomethyl-4-hydroxypteridine quarto-hydrobromide (3 g.) in ethanol (270 ml.) was refluxed with finely ground sodium sulphanilate (4·5 g.) for 2 hr. After refrigeration (12 hr.) the greenish solid was filtered off and dissolved in sodium hydroxide solution (0·5%; 100 ml.), and 2N-hydrochloric acid added to pH 2—3. After 1 hr. at 0°, the yellow crystals were filtered off (yield, 33%). Recrystallization from water (50 parts; carbon) gave yellow needles (75% recovery) of the *sodium* salt of 4-hydroxy-6-*p*-sulphoanilinomethylpteridine dihydrate, best dried in a vacuum (P_2O_5) at 20° (prolonged boiling in water caused decomposition) (Found: C, 17·8; S, 8·1. $C_{13}H_{10}O_4N_5SNa,2H_2O$ requires N, 17·9; S, 8·2%), soluble in about 200 parts of water at 20°.

2-*Deaminofolic acid.* To a solution of *p*-aminobenzoylglutamic acid (4 g.) (Tschesche *et al.*, *loc. cit.*, 1951) in ethanol (200 ml.) and aqueous potassium hydroxide solution (0·8N; 14·4 ml.) at 50—60° was added finely ground 6-bromomethyl-4-hydroxypteridine quartohydrobromide (3·2 g.). The mixture was at once placed under reflux in a boiling-water bath and vigorously shaken for 5 min. After 2 hr.' heating it was filtered hot and was refrigerated (after scratching if an oil was first deposited) for 24 hr. The solid was washed with alcohol (5 ml.) and dried in warm air (*ca.* 40°) and then for 5 min. at 110° (yield, 44%). It was twice recrystallized from preheated water (100 parts; carbon); rapid cooling of the filtrate gave, after refrigeration, 50% recovery. The light yellow crystalline 2-*deaminofolic acid* decomposed at ~170°. It was anhydrous after being dried at 90° in a vacuum, but hygroscopic (Found: C, 53·5; H, 4·2; N, 19·6. $C_{19}H_{18}O_6N_6$ requires C, 53·5; H, 4·25; N, 19·7%). It darkened slowly at 110° and the aqueous solution rapidly above *ca.* 80°. Small variations in the conditions led to loss of yield and quality of the product.

The author thanks Dr. R. H. Nimmo-Smith of the Microbiology Unit, Oxford, Professor A. Haddow of The Chester Beatty Research Institute, London, and Dr. W. Jacobson of the Strangeways Research Laboratory, Cambridge, who very kindly undertook the various biological tests.

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336. *Pyrimidine.*

By Norman Whittaker.

Pyrimidine was first obtained, and in 15—20% overall yield, by Gabriel and Colman (*Ber.*, 1899, **32**, 1525) from 6-methyluracil by a route involving reductive dechlorination of the 2 : 4-dichloro-6-methylpyrimidine with zinc dust and water to 4-methylpyrimidine. Gabriel (*Ber.*, 1900, **33**, 3666) similarly obtained pyrimidine directly by reducing 2 : 4 : 6-trichloropyrimidine, but 2 : 4 : 5 : 6-tetrachloropyrimidine (Emery, *Ber.*, 1901, **34**, 4180) gave a poor yield under the same conditions. More recently catalytic desulphurisation by Raney nickel of mercaptopyrimidines (Cavalieri and Bendich, *J. Amer. Chem. Soc.*, 1950, **72**, 2587; Boarland, McOmie, and Timms, *J.*, 1952, 4691) has been investigated, but with little success.

Magnesium oxide has been found useful in maintaining a neutral pH during the catalytic reductive dechlorination of simple chloropyrimidines by palladium catalysts and hydrogen (Whittaker, *J.*, 1951, 1565; see also Lythgoe and Rayner, *ibid.*, 1951, 2323; Boarland *et al.*, *loc. cit.*). By this means catalytic dechlorination of 2 : 4-dichloropyrimidine has now been effected on a half-molar scale with hydrogen under pressure, to give 75—80% yields of pyrimidine as a colourless hygroscopic solid, m. p. 22·5°, b. p. 124°/758 mm. This material was used for the spectrographic studies of a colleague, Dr. T. S. G. Jones, the results of which have been quoted by Boarland and McOmie (*J.*, 1952, 3716). Caustic alkali has no appreciable effect in the cold on pyrimidine (cf. Lythgoe and Rayner, *loc. cit.*) and is recommended for use in the isolation of pyrimidine from the reduction liquors to decompose the impurities present.

In an attempt to prepare 5-bromopyrimidine by the catalytic dechlorination of 5-bromo-2 : 4-dichloropyrimidine there was no break in the reduction curve until 3 mols. of hydrogen had been absorbed, and the product was again pyrimidine.

Experimental.—Pyrimidine. Pure magnesium oxide (freshly ignited; 50 g.) and palladium–charcoal (*ca.* 3% of Pd; 21 g.) were added to a suspension of 2 : 4-dichloropyrimidine (crystallised; 84 g.) in ethanol (420 ml.) and water (840 ml.), and the mixture agitated at room temperature under hydrogen at 30—40 lb. pressure. Absorption of hydrogen was complete after 80 min. The filtered liquid was distilled in steam and an excess of aqueous mercuric chloride added to the acidified distillate (pH 6) to give pyrimidine mercurichloride (172 g.). This was distilled with sodium sulphide (nonahydrate; 200 g.), and the aqueous distillate saturated with potassium hydroxide at 0—5°, solid pyrimidine separating. After warming to room temperature the upper pyrimidine layer was separated, and the lower aqueous layer (smelling strongly of ammonia) extracted with a little ether. The extract and the pyrimidine layer were combined, dried (KOH), and fractionated through a short packed column, to give pyrimidine (35 g., 78%), b. p. 123·5—124°/762 mm., m. p. 20·5—22·5°. The product was dissolved in water (50 ml.), treated with potassium hydroxide as described above, distilled over a little phosphoric oxide, and fractionally distilled, to give pure pyrimidine (31 g.), b. p. 124°/758 mm., m. p. 22·5°.

Pyrimidine methiodide (2·4 g.), m. p. 136—137°, separated from a solution of pyrimidine (1 g.) in methanol (2 ml.) containing methyl iodide (2 ml.) at room temperature. Recrystallised from ethanol it formed pale yellow plates of the same m. p. (Found : C, 27·0; H, 2·95; N, 13·2; I, 57·3. $C_5H_7N_2I$ requires C, 27·05; H, 3·15; N, 12·6; I, 57·2%).

5-Bromo-2 : 4-dichloropyrimidine. This was prepared by heating 5-bromouracil (10 g.), phosphoryl chloride (50 ml.), and diethylaniline (12 ml.) under reflux for 100 min. The product was isolated as described for 2 : 4-dichloro-5-nitropyrimidine (Whittaker, *loc. cit.*) as a colourless oil (10·5 g., 88%), b. p. 112—113°/12 mm., which solidified at room temperature (Found : N, 12·1; Ag halide, 211·4. Calc. for $C_4HN_2BrCl_2$: N, 12·3; Ag halide, 208·5%).

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337. *Cumyl Phenyl Ether.*

By A. M. Spivey.

During work on the separation of a mixture of phenol, αα-dimethylbenzyl alcohol, and acetophenone by fractional distillation under reduced pressure it was observed that, after most of the phenol and all of the acetophenone had distilled, a higher-boiling residue remained. This residue was a single, neutral compound, degraded by boiling 48% hydrobromic acid to a mixture of phenol and α-methylstyrene, the latter presumably resulting from dehydration of the preformed αα-dimethylbenzyl alcohol. This fact and the microanalysis indicate that the compound is cumyl phenyl ether, resulting from the condensation of phenol and the carbinol. The ease of its formation in good yield suggests that this type of condensation might be common between phenols and tertiary aromatic alcohols.

Several unsuccessful attempts, other than the direct condensation of the two components, were made to synthesise the ether and it may well be that direct condensation is the only route to this type of compound. α-Chlorocumene (Hoffman, *J. Amer. Chem. Soc.*, 1929, **51**, 2546) was treated with sodium phenoxide in ethanol but gave only a mixture of α-methylstyrene and phenol. Powell and Adam's method (*J. Amer. Chem. Soc.*, 1920, **42**, 656) for preparing benzyl phenyl ether was then applied, and a mixture of α-chlorocumene, phenol, and potassium carbonate in acetone was boiled under reflux but only phenol, α-methylstyrene, and *p*-cumylphenol could be isolated. The other known method for preparing alkyl aryl ethers, *viz.*, the warming of dry diazobenzene sulphate with αα-dimethylbenzyl alcohol gave only α-methylstyrene, probably because the acid-catalysed dehydration of the carbinol proceeded faster and at a lower temperature than the reaction forming the ether. Finally cumyl phenyl ether was synthesised in 20% yield by heating under reflux at reduced pressure a mixture of phenol and the carbinol, and was identical with the first specimen isolated. The reason for this low yield, compared with the higher yield obtained in the larger experiment in the presence of acetophenone, was not investigated, but it was shown that there was no reaction when phenol and acetophenone were boiled under reflux under similar conditions.

When most of this work had been completed it was noticed that Zal'kind and Kurlina (*J. Gen. Chem., Russia*, 1950, **20**, 2158) had observed the condensation between benzyl alcohol and phenol in the presence of acidic condensing agents. These authors, however, also isolated appreciable amounts of dibenzyl ether, *o*- and *p*-hydroxyphenylmethanes, and *o*- and *p*-benzylbenzyl alcohols as well as benzyl phenyl ether.

Experimental.—A mixture of phenol (125 g.), αα-dimethylbenzyl alcohol (50 g.), and acetophenone (25 g.) was fractionally distilled at 20 mm. through a column (122 × 2·3 cm.) packed with 4-mm. glass Fenske helices. At first pure phenol distilled but later fractions contained increasing amounts of acetophenone with traces of the carbinol and the last fraction to be collected contained a small amount of α-methylstyrene. At this stage, when 68% of the phenol and all the acetophenone (determined by infra-red analysis) had distilled, difficulty was experienced in maintaining the reflux, and distillation was therefore stopped. The residue crystallised to an almost colourless solid (35·4 g.), m. p. 46·5—48°; the total yield, including material recovered from the column, was 51 g. (66% on the carbinol). *Cumyl phenyl ether* formed needles (from ethanol), m. p. 47—48° (Found: C, 84·6; H, 7·5. $C_{15}H_{16}O$ requires C, 84·9; H, 7·6%) It was insoluble in aqueous acids and alkalis and soluble in most organic solvents.

Action of 48% hydrobromic acid on the ether. The ether (2 g.) was boiled under reflux with 48% hydrobromic acid (50 c.c.) for 2 hr., the mixture was diluted with water and extracted thrice with ether, and the combined ethereal extracts were extracted twice with 10% aqueous sodium hydroxide. The remaining ether solution was dried ($CaCl_2$) and concentrated to yield a mixture (0·75 g.) of the two dimers of α-methylstyrene, 4-methyl-2 : 4-diphenylpent-2-ene and 1 : 1 : 3-trimethyl-3-phenylindane (infra-red analysis), the unsaturated dimer predominating. The alkaline extract was acidified and extracted thrice with ether. The ethereal extract was dried (Na_2SO_4) and evaporated yielding a phenol whose 3 : 5-dinitrobenzoate (needles; m. p. 143·5—144·5°) did not depress the m. p. of an authentic specimen of phenyl 3 : 5-dinitrobenzoate.

Direct preparation of cumyl phenyl ether. A mixture of phenol (4·7 g.) and αα-dimethylbenzyl alcohol (6·8 g.) was boiled under reflux at 80 mm. for 12 hr. The mixture was distilled through a 6″ Vigreux column, and the fraction (6 g.), b. p. 80—85°/13 mm. consisting of phenol and α-methylstyrene, collected. The residue (2·0 g.; 20%) was recrystallised from ethanol giving the ether as needles, m. p. 47°, identical with the first specimen obtained from the mixture of phenol, the alcohol, and acetophenone.

The author is indebted to Mr. J. C. Hawkes for carrying out the infra-red analyses described and to the Directors for permission to publish this work.

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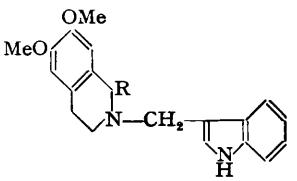
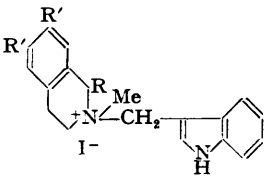
338. *Synthesis of* 1-*Alkyl*-1 : 2 : 3 : 4-*tetrahydro*-2-3′-*indolylmethyl*-6 : 7-*dimethoxy*isoquinolines *and the Ready Cleavage of their Methiodides.*

By J. M. OSBOND.

TOXIFERINE I has been shown to be the most potent curarising agent known (cf. Paton and Perry, *Brit. J. Pharmacol.*, 1951, **6**, 299). The complete structure of this alkaloid, which belongs to the calabash curare group, is not known, but it possesses a monoquaternary nitrogen in a tetrahydro*iso*quinoline ring, and a secondary non-basic nitrogen in an indole ring (Schmidt and Karrer, *Helv. Chim. Acta*, 1947, **30**, 1162). On this basis Craig and Tarbell (*J. Amer. Chem. Soc.*, 1949, **71**, 462) prepared 1 : 2 : 3 : 4-tetrahydro-2-3′-indolylmethyl*iso*quinoline methiodide (II; R = R′ = H) as a possible analogue (cf., however, Schmidt, Ebnother, and Karrer, *ibid.*, 1950, **33**, 1486), but this had only minimal activity. With a view to obtain a compound of greater activity the iodide (II; R = Et, R′ = OMe) has been synthesised in the hope that inclusion of two methoxy-groups in the tetrahydro*iso*quinoline moiety would enhance activity as in the bistetrahydro*iso*quinolylalkane dimethiodide series (cf. Craig, *Chem. Reviews*, 1949, **42**, 285; Taylor, *J.*, 1951, 1150).



(I)



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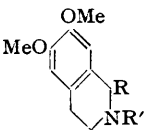
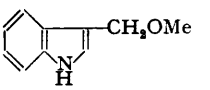


(III)



(IV)

1-Ethyl-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy*iso*quinoline (III; R = Et, R′ = H), prepared by catalytic reduction of the corresponding dihydro*iso*quinoline (cf. Dey and Govindachari, *Arch Pharm.*, 1939, **277**, 177), with indole and formaldehyde in aqueous acetic acid (cf. Kuhn and Stein, *Ber.*, 1937, **70**, 567) gave 1-ethyl-1 : 2 : 3 : 4-tetrahydro-2-3′-indolylmethyl-6 : 7-dimethoxy*iso*quinoline (I; R = Et). Treatment of this with excess of methyl iodide in benzene at room temperature gave a yellow oil which solidified. Considerable care had to be exercised in crystallising this methiodide (II; R′ = OMe, R = Et) for, although it was readily obtained pure by dissolution in cold methanol, from which it separated as small needles, in boiling methanol it gave the hydriodide of 1-ethyl-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-2-methyl*iso*quinoline (III; R = Et, R′ = Me). Cleavage of the Mannich base methiodide occurred even when a methanolic solution of the methiodide was set aside overnight at room temperature. From the methanolic mother-liquors the other fission product, 3-methoxymethylindole (IV), was obtained.

The instability of quaternary salts of 3-indolylmethylamines in alkaline medium is well known (Madinaveitia, *J.*, 1937, 1927; Geissman and Armen, *J. Amer. Chem. Soc.*, 1952, **74**, 3916) and is utilised in the tryptophan synthesis (cf. Snyder and Smith, *ibid.*, 1944, **66**,

350; Snyder and Eliel, *ibid.*, 1948, **70**, 3855) but cleavage does not appear to take place in neutral solution (cf. Snyder and Eliel, *ibid.*, 1948, **70**, 1703; Snyder, Thompson and Hinman, *ibid.*, 1952, **74**, 2009; Craig and Tarbell, *loc. cit.*; Geissman and Armen, *loc. cit.*). The instability of the methiodide (II; R′ = OMe, R = Et) in *neutral* conditions may possibly be due to the two methoxy-groups or the bulky ethyl group. We therefore treated 1 : 2 : 3 : 4-tetrahydro-2-3′-indolylmethyl-6 : 7-dimethoxy-1-methyl*iso*quinoline (I; R = Me) (Osbond, *J.*, 1951, 3464) in a similar way with methyl iodide in benzene at room temperature; the methiodide could not be obtained crystalline, but when in warm methanol it gave the hydriodide of 1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1 : 2-dimethyl*iso*quinoline (III; R = R′ = Me).

Dr. W. D. M. Paton reports that (II; R = Et, R′ = OMe), when injected intravenously (3 mg./kg.) into a cat under chloralose anaesthesia, has ganglionic blocking action, being *ca.* one-tenth as active as hexamethonium, with a transient depressor effect on the blood pressure; it reduced the pressor response to 0·5 mg. of nicotine considerably. There was no neuromuscular blocking, atropine, or adrenolytic action in doses up to 3 mg./kg.

Experimental.—1-*Ethyl*-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*isoquinoline *hydrochloride*. 1-Ethyl-3 : 4-dihydro-6 : 7-dimethoxy*iso*quinoline (6·27 g.) (Spath and Polgar, *Monatsh.*, 1929, **51**, 190) was hydrogenated in methanol (200 c.c.) in the presence of platinum oxide at room temperature and atmospheric pressure. After overnight shaking the catalyst was filtered off and the filtrate was taken to dryness and treated with concentrated hydrochloric acid. The hydrochloride separated from ethanol as prisms (5·5 g.), m. p. 214—215° (Found: C, 60·7; H, 8·0; N, 5·6. Calc. for $C_{13}H_{19}O_2N$,HCl: C, 60·6; H, 7·8; N, 5·4%). Dey and Govindachari (*loc. cit.*) record m. p. 214°.

1-*Ethyl*-1 : 2 : 3 : 4-*tetrahydro*-2-3′-*indolylmethyl*-6 : 7-*dimethoxy*isoquinoline. 1-Ethyl-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy*iso*quinoline hydrochloride (2·57 g., 1 mol.) was dissolved in water and made alkaline with 2N-sodium hydroxide and the base was extracted with ether (2 × 25 c.c.), washed with water, and dried (K_2CO_3). After removal of the ether the base was dissolved in aqueous acetic acid (10 c.c.; 50%); indole (1·17 g., 1·1 mol.) and then aqueous formaldehyde (0·75 c.c.; 40%; 1 mol.) were added successively at room temperature. The solution became warm and cloudy at once and gradually some amorphous solid separated. After 36 hr. at room temperature the mixture was extracted with ether, the aqueous layer made strongly alkaline, and the basic material extracted twice with ether. The ether was removed and the clear reddish gum was dissolved in benzene and diluted with light petroleum (b. p. 40—60°) and scratched, whereupon a white solid (1·63 g.) gradually crystallised. Two recrystallisations from benzene–light petroleum (b. p. 40—60°) and finally from *iso*propyl alcohol afforded the *base* as colourless prisms (0·9 g.), m. p. 132—133° (Found: C, 75·2; H, 7·4; N, 7·9. $C_{22}H_{26}O_2N_2$ requires C, 75·4; H, 7·5; N, 8·0%).

Preparation and decomposition of 1-*ethyl*-1 : 2 : 3 : 4-*tetrahydro*-2-3′-*indolylmethyl*-6 : 7-*dimethoxy*isoquinoline *methiodide*. (*a*) 1-Ethyl-1 : 2 : 3 : 4-tetrahydro-2-3′-indolylmethyl-6 : 7-dimethoxy*iso*quinoline (0·24 g.) was dissolved in methyl iodide (1·5 c.c.) at room temperature and set aside. After a few min. an oil began to separate. After 2 hr. light petroleum (b. p. 40—60°) was added and the supernatant liquor was decanted. The residual gum was dissolved in methanol at room temperature, and light petroleum (b. p. 40—60°) was added; the yellow oil which separated solidified when scratched (m. p. 90—110°). The *methiodide* was dissolved in methanol at room temperature and, on scratching, small colourless needles separated, having m. p. 110° (Found, on specimen dried over KOH at 0°: C, 52·6; H, 6·4; N, 5·3; H_2O, 5·7. $C_{23}H_{29}O_2N_2I$,1·75H_2O requires C, 52·7; H, 6·1; N, 5·3; H_2O, 6·0. Found, in sample dried at 100° *in vacuo*: C, 55·5; H, 6·1; N, 5·9. $C_{23}H_{29}O_2N_2I$ requires C, 56·1; H, 5·9; N, 5·7%). (*b*) The crude reaction product as obtained above was dissolved in boiling methanol and diluted with ether from which 1-*ethyl*-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-2-*methyl*isoquinoline *hydriodide* separated as clumps of prisms, m. p. 212—214° (Found: C, 46·0; H, 6·1; N, 4·1. $C_{14}H_{21}O_2N$,HI requires C, 46·3; H, 6·1; N, 3·85%). The methanol mother-liquor was taken to dryness and the residue was extracted three times with boiling ether. The ethereal extracts were combined, filtered, and taken to dryness. The yellow crystalline material, m. p. 85—90°, was recrystallised from light petroleum (b. p. 40—60°) twice, to afford 3-methoxymethylindole as pale yellow prisms, m. p. 95—96° (Found: C, 74·5; H, 7·0. Calc. for $C_{10}H_{11}ON$: C, 74·5; H, 6·9%). Madinaveitia (*loc. cit.*) gives m. p. 99—100°. Geissman and Armen (*loc. cit.*) give m. p. 98—99°.

When the methanol mother-liquor from (*a*) was kept at room temperature overnight, 1-ethyl-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-2-methyl*iso*quinoline hydriodide, m. p. 212—213°, separated.

Preparation and decomposition of 1-*ethyl*-1 : 2 : 3 : 4-*tetrahydro*-2-3′-*indolylmethyl*-6 : 7-*dimethoxy*iso*quinoline methiodide*. 1-Ethyl-1 : 2 : 3 : 4-tetrahydro-2-3′-indolylmethyl-6 : 7-dimethoxy*iso*quinoline (0·57 g.; Osbond, *loc. cit.*) was dissolved in methyl iodide (2 c.c.) and set aside at room temperature for 2 hr. Ether was added to the solution and the methiodide collected. When, however, it was recrystallised from boiling methanol, small white nodules of 1-*ethyl*-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-2-*methyl*iso*quinoline hydriodide* (0·28 g.), m. p. 204—207°, were obtained. One further recrystallisation from methanol ether gave the pure hydriodide as colourless prisms, m. p. 207—210° (Found : C, 44·8; H, 5·8; N, 4·2. $C_{13}H_{19}O_2N$,HI requires C, 44·7; H, 5·8; N, 4·0%). The picrate, prepared from a solution of the hydriodide by the addition of aqueous sodium picrate, separated from alcohol as yellow needles, m. p. 210° (Found : C, 50·3; H, 4·65; N, 12·4. Calc. for $C_{13}H_{19}O_2N,C_6H_3O_7N_3$: C, 50·7; H, 4·9; N, 12·4%). Spath and Passl (*Ber.*, 1929, **62**, 1021) give m. p. 212—213°.

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