615. *Quaternary Ammonium Salts. Part II.* The Formation and Decomposition of Diethylmethylanilinium Salts. Route to* N-*Ethyl*-N-*methylanilines.*

By Hussein A. Fahim and Abdallah M. Fleifel.

Diethylanilines, now obtained in good yields from the primary bases by treatment with ethyl sulphate, give the quaternary diethylmethylanilinium salts more readily with methyl iodide than with methyl sulphate. The quaternary salts from diethyl-*m*- and -*o*-toluidine and methyl iodide can be obtained at the room temperature, but *o*-chloro-*NN*-diethyl-, *NN*-diethyl-*o*-, *m*-, and -*p*-nitro-, and *NN*-diethyl-4-methyl-2-nitro-aniline do not give the quaternary salt under any conditions tried with either reagent. Thermal or alkaline decomposition of the quaterary salts studied takes place smoothly in one direction, to give invariably the *N*-ethyl-*N*-methyl-anilines, except that *NN*-diethyl-*N*-methyl-*p*-phenetidinium iodide gives diethyl-*p*-phenetidine.

Experimental.—The general procedures were those described in Part I.*

NN-Diethyl-*p*-anisidine was obtained (61% yield) when *p*-anisidine (50 g., 1 mol.) and ethyl sulphate (130 g., 2·2 mols.) were heated at 120—130° for 4 hours. *NN*-Diethyl-*N*-methyl-*p*-anisidinium iodide was obtained in quantitative yield when equimolecular amounts of diethyl-*p*-anisidine and methyl iodide reacted overnight at the room temperature; the corresponding *picrate*, obtained in 69·5% yield when equimolecular amounts of the tertiary base and methyl sulphate were heated at 120—130° for 4 hours and the neutralised reaction mixture was treated with saturated picric acid solution, crystallised from water and melted at 108° (Found: C, 51·5; H, 5·2; N, 13·3. $C_{18}H_{22}O_8N_4$ requires C, 51·2; H, 5·2; N, 13·3%).

Diethyl-*o*-anisidine, obtained in 42·5% yield when *o*-anisidine (80 g., 1 mol.) and ethyl sulphate (188 g., 2·2 mols.) were heated at 120—130° for 6 hours, had b. p. 226°. Its *picrate* crystallised from water and melted at 135—136° (Found: C, 49·7; H, 4·9; N, 13·6. $C_{17}H_{20}O_8N_4$ requires C, 50·0; H, 4·9; N, 13·7%). NN-*Diethyl*-N-*methyl*-o-*anisidinium iodide*, obtained in 75·3% yield from the tertiary base and methyl iodide (1 mol. each) at 80° (4 hours), crystallised from methanol–ether and melted at 219—220° (Found: I, 39·9. $C_{12}H_{20}ONI$ requires I, 39·6%). The *picrate*, obtained in 60·8% yield by use of methyl sulphate at 120—130° (7 hours), had m. p. 120—121° (from water) (Found: C, 50·6; H, 5·2; N, 13·4. $C_{18}H_{22}O_8N_4$ requires C, 51·2; H, 5·2; N, 13·3%). The *perchlorate* crystallised from water and melted at 114—115° (Found: Cl, 11·9. $C_{12}H_{20}O_5NCl$ requires Cl, 12·0%).

Unless otherwise stated, the following were similarly prepared.

Diethyl-*p*-phenetidine (58% yield; 7 hours; b. p. 260°) gave the *picrate* (from ethanol), m. p. 110—111° (Found: C, 51·0; H, 5·0; N, 13·4. $C_{18}H_{22}O_8N_4$ requires C, 51·2; H, 5·2; N, 13·3%). NN-*Diethyl*-N-*methylphenetidinium iodide*, obtained in 74·1% yield from the tertiary base and methyl iodide (1 mol. each) at room temperature (2 days), crystallised from methanol–ether and melted at 142—143° (Found: I, 38·6. $C_{13}H_{22}ONI$ requires I, 37·9%). The *picrate*, obtained in 66·7% yield by use of methyl sulphate at 120—130° (4 hours), crystallised from water and melted at 91·5—92·5° (Found: C, 52·2; H, 5·7; N, 13·0. $C_{19}H_{24}O_8N_4$ requires C, 52·3; H, 5·5; N, 12·8%).

NN-Diethyl-*m*-phenetidine (52% yield; 8 hours) gave a *picrate*, m. p. 130—131° (from ethanol) (Found: C, 51·2; H, 5·3; N, 13·2%). N-*Ethyl*-N-*methyl*-m-*phenetidine picrate* crystallised from ethanol and melted at 127° (Found: C, 50·0; H, 5·0; N, 13·5. $C_{17}H_{20}O_8N_4$ requires C, 50·0; H, 4·9; N, 13·7%). NN-*Diethyl*-N-*methylphenetidinium iodide*, obtained in 64·7% yield by keeping the tertiary base and methyl iodide (1 mol. each) at room temperature for 3 days, crystallised from acetone–ether and melted at 137—138° (Found: I, 37·6%). The corresponding *picrate*, obtained in 51·5% yield by use of methyl sulphate (1 mol.) at 120—130° (4 hours), had m. p. 101—102° (from aqueous acetone) (Found: C, 52·3; H, 5·4; N, 12·9%).

NN-Diethyl-*o*-phenetidine (54·6% yield; 7 hours) gave the *picrate*, m. p. 111° (from ethanol) (Found: C, 51·0; H, 5·2; N, 13·3%). NN-*Diethyl*-N-*methyl*-o-*phenetidinium iodide*, obtained in 61·2% yield by use of methyl iodide (1 mol.) at 80° (4 hours), crystallised from methanol–ether and melted at 194—195° (Found: I, 37·4%). The *picrate*, obtained in 45·5% yield by use of methyl sulphate (1·5 mols.) at 120—130° (10 hours), had m. p. 119° (from water) (Found: C, 52·2; H, 5·6; N, 12·7%). The *perchlorate*, crystallised from water, had m. p. 115—116° (Found: Cl, 11·7. $C_{13}H_{22}O_5NCl$ requires Cl, 11·5%).

NN-Diethyl-*p*-toluidine, obtained in 91·3% yield at 120—130° (6 hours), gave a *picrate*, 110° (from ethanol) (Found: C, 52·0; H, 5·2; N, 14·5. $C_{17}H_{20}O_7N_4$ requires C, 52·0; H, 5·1; N, 14·3%). *Diethylmethyl*-p-*toluidinium iodide*, obtained in 59·4% yield by use of methyl iodide at room temperature (overnight) and crystallised from ethanol–ether, had m. p. 165° (Found: I, 41·8. $C_{12}H_{20}NI$ requires I, 41·6%). The *picrate*, obtained in 53% yield from the tertiary base (1 mol.) and methyl sulphate (2 mols.) at 120—130° (2 hours), crystallised from water and melted at 105—106° (Found: C, 52·9; H, 5·3; N, 13·8. $C_{18}H_{22}O_7N_4$ requires C, 53·2; H, 5·4; N, 13·8%).

* The following paper is to be regarded as Part I: *J.*, 1950, 3529.

NN-Diethyl-*m*-toluidine (84% yield; 6 hours) gave the *picrate*, m. p. 124° (from ethanol) (Found: C, 52·2; H, 5·0; N, 14·3%). *Diethylmethyl*-m-*toluidinium iodide*, obtained in 57·7% yield from the tertiary base and methyl iodide (1 mol. each) at room temperature (2 weeks) (no quaternary salt could be isolated when the temperature was raised), crystallised from acetone–ether and melted at 109—110° (Found: I, 41·2%). The *picrate*, obtained in 48% yield by use of methyl sulphate (2 mols.) at 120—130° (24 hours), had m. p. 136—137° (from water) (Found: C, 53·4; H, 5·4; N, 13·9%).

NN-Diethyl-*o*-toluidine (35% yield; 6 hours) gave the *picrate*, m. p. 181—182° (from ethanol) (Found: C, 52·3; H, 5·0; N, 14·2%). *Diethylmethyl*-o-*toluidinium iodide*, obtained in 14·4% yield from the tertiary base and methyl iodide at room temperature (2 months) (no quaternary salt could be isolated when the temperature was raised), crystallised from methanol–ether and melted at 137—138° (Found: I, 41·8%). The *picrate*, obtained in 8% yield from the tertiary base and methyl sulphate (6 mols.) at 120—130° (32 hours), had m. p. 129° (from water) (Found: C, 53·1; H, 5·3; N, 13·9%).

p-*Bromo*-NN-*diethylanilinium picrate* crystallised from ethanol and melted at 163° (Found: C, 42·6; H, 4·0; N, 12·4; Br, 17·7. $C_{18}H_{17}O_7N_4Br$ requires C, 42·0; H, 3·7; N, 12·3; Br, 17·5%). p-*Bromo*-NN-*diethyl*-N-*methylanilinium iodide*, obtained in 75% yield by use of methyl iodide (1 mol.) at about 100° (1 hour) and crystallised from methanol–ether, melted at 189—190° (Found: total halogen, 56·2. $C_{11}H_{17}NBrI$ requires total halogen, 55·9%). The *picrate*, obtained from the iodide and crystallised from ethanol, melted at 165—166° (Found: C, 43·7; H, 3·9; N, 12·0; Br, 17·2. $C_{17}H_{19}O_7N_4Br$ requires C, 43·3; H, 4·0; N, 11·9; Br, 17·0%). The *perchlorate* crystallised from water and melted at 180—181° (Found: total halogen, 34·0. $C_{11}H_{17}O_4NBrCl$ requires total halogen, 33·7%).

m-Bromo-*NN*-diethylaniline (59·3% yield; 7 hours) gave the *picrate* which crystallised from ethanol and melted at 118° (Found: C, 42·3; H, 3·9; N, 12·0; Br, 17·8%). m-*Bromo*-NN-*diethyl*-N-*methylanilinium iodide*, obtained in 37·5% yield by use of methyl iodide (1 mol.) at about 100° (8 hours) and crystallised from methanol–ether, had m. p. 184—185° (Found: total halogen, 56·3%). The *picrate*, obtained from the iodide, crystallised from ethanol and melted at 125—126° (Found: C, 42·7; H, 3·8; N, 12·0; Br, 17·1%). The *perchlorate* had m. p. 105—106° (from water) (Found: total halogen, 33·5%).

o-Chloro- (47·5% yield; 8 hours) and *o*-nitro-*NN*-diethylaniline (53% yield; 8 hours) and *NN*-diethyl-2-nitro-4-methylaniline (65·8% yield; 10 hours) were also prepared.

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616. *The Fluorination of Some Nitrides and Cyanides.*

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PARTLY with a view to the preparation of nitrogen trifluoride, some experiments have been carried out on the fluorination of a few nitrides and cyanides.

Magnesium nitride did not react even with undiluted fluorine, either at room temperature or when the copper reaction tube was heated to about 400°. Boron nitride, on the other hand, reacted vigorously, as reported by Moissan and Lebeau (*Compt. rend.*, 1900, **130**, 1436) who did not, however, determine the fate of the nitrogen: fractionation of the gaseous reaction product gave only boron trifluoride.

Reactions between cyanides and fluorine have been reported by Moissan (*Ann. Chim. physique*, 1891, **24**, 262) who did not investigate the reaction products, and by Ruff and Geise (*Ber.*, 1936, **69**, 598), who obtained a variety of products from silver cyanide, including carbon tetrafluoride, perfluoromethylamine ($CF_3{\cdot}NF_2$) inseparably mixed with perfluoroethane, and compounds of composition $C_2N_2F_6$ and $C_2N_2F_8$. The reaction between gaseous fluorine and solid potassium ferro- and ferri-cyanide, and between gaseous hydrogen cyanide and solid cobalt trifluoride have now been studied. The ferro- and ferri-cyanides were chosen since they can readily be obtained pure and dry. Both react readily with fluorine diluted with nitrogen, and give a large number of gaseous products, some of which rapidly attack both mercury and tap grease and make manipulation rather difficult. Only two definite compounds have been isolated from these mixtures, *viz.*, carbon tetrafluoride and perfluoromethylamine; no hexafluoroethane was found, so that the perfluoromethylamine could be isolated. This compound has also been obtained by Haszeldine (*J.*, 1950, 1966) as a by-product in the fluorination of methylaniline, and by fluorination of methylamine, both by cobalt trifluoride. Since the boiling points of perfluoroethane and perfluoromethylamine are −78·2° and −77·0°, respectively, separation by fractional distillation is impracticable. The vapour pressure of perfluoromethylamine, measured from −135° to −75° and, above its m. p. of −122·1° follows the equation, $\log_{10} p_{mm.} = 7{\cdot}474 - 901{\cdot}0/T$, which gives the latent heat of vaporisation as 4·12 kcals./mole, and the Trouton constant as 21·0. The vapour pressure below the m. p.

(*i.e.*, of the solid) is given, less accurately, by $\log_{10} p_{mm.} = 7{\cdot}95 - 970/T$. The triple-point pressure was $32{\cdot}_2$ mm.

The fluorination of anhydrous hydrogen cyanide, by cobalt trifluoride at 200—250°, with nitrogen as diluent, also gave a variety of products. No single substance except carbon tetrafluoride could be isolated by fractional distillation. No perfluoromethylamine could be isolated since it was mixed with hexafluoroethane. A fraction b. p. −38·0° to −39·1°, of molecular weight 161—171, evidently consisted mainly of $C_2N_2F_6$ (*M*, 166; Ruff and Geise, *loc. cit.*) together with some $C_2N_2F_8$ (*M*, 204). A very complex mixture of compounds of higher molecular weight containing carbon, nitrogen, and fluorine was also obtained; it was unreactive to all reagents tested except hot potassium.

Since the fluorination of hydrocarbons substituted by CF_3 groups gives higher yields of fluorocarbons and fewer by-products than the fluorination of unsubstituted hydrocarbons, it was expected that treatment of trifluoromethyl cyanide with cobalt trifluoride would give a substantial yield of perfluoroethylamine, $C_2F_5{\cdot}NF_2$. In fact, the major product was hexafluoroethane, but perfluoroethylamine, b. p. −34·3°, was also obtained. This substance is unreactive and non-basic, like perfluoromethylamine; its vapour pressure, measured from −102° to −37°, is given by: $\log_{10} p_{mm.} = 7{\cdot}435 - 1088/T$, which gives the latent heat of vaporisation as 4·98 kcals./mole, and the Trouton constant as 20·8. The liquid forms a glass when cooled in liquid oxygen. It is interesting that the boiling point is somewhat higher than the value −37·0° found by Thompson and Emeléus (*J.*, 1949, 3080) for the isomeric secondary compound perfluorodimethylamine $(CF_3)_2NF$, prepared by the cobalt fluoride fluorination of trimethylamine.

Experimental.—Fluorinations with gaseous fluorine were carried out in apparatus constructed from copper tube, and those with cobalt trifluoride in a horizontal tubular reactor containing 20 lb. of cobalt trifluoride which could be stirred by a set of paddles and electrically heated to 450°. The various reaction products were separated, as far as possible, in a low-temperature fractional-distillation apparatus of the type described by Booth and Bozarth (*Ind. Eng. Chem.*, 1937, **29**, 470) and Booth and McNabney (*ibid.*, *Anal.*, 1944, **16**, 131), in which the head of the column is automatically cooled by small squirts of liquid oxygen to such a temperature as to maintain a pressure of one atmosphere. Vapour pressures and m. p.s were determined in a Stock apparatus, temperatures being measured by suitable vapour-pressure thermometers and copper–constantan thermocouples standardised against the mercury, carbon dioxide, and liquid oxygen fixed points. Molecular weights of gases were measured by means of a quartz-fibre suspension gas-density balance of standard type with electromagnetic control. The balance beam contained a short (1 cm.) permanent magnet, and under the thermostat tank containing the balance was a large, flat solenoid consisting of about 10,000 turns of enamelled copper wire (S.W.G. 34) on a wood former.

Hydrogen cyanide. This was fluorinated by cobalt trifluoride at 200—250° in the presence of 2—3 volumes of nitrogen. Any hydrogen fluoride formed was removed by passing the reaction products over sodium fluoride before they were condensed in traps cooled in liquid oxygen. Numerous fractional distillations of the volatile product gave: (*a*) b. p. −129°, *M*, 88 (CF_4), (*b*) a white solid subliming at 1 atm., *M*, 80—90, which was not investigated, (*c*) b. p. −77·6° to −78·9°, *M*, 124—128 ($CF_4 + CF_3{\cdot}NF_2$), (*d*) b. p. −38·0° to −39·1°, *M*, 161—171, and (*e*) residues b. p. −38° to +30°. Fraction (*d*), on careful distillation was divided into three approximately equal sub-fractions boiling within 1·1°, of *M* 161, 168, and 171 in order of increasing b. p. The middle fraction on analysis had the composition $C_2N_2F_{6\cdot4}$ and probably consisted mainly of $C_2N_2F_6$.

Trifluoromethyl cyanide. This was similarly diluted with nitrogen and fluorinated with cobalt trifluoride. In one experiment 9·5 l. of the cyanide gave, on fractionation of the product, (*a*) 6·48 l., b. p. −79·1° to −76·2°, *M*, 132 (C_2F_6, b. p. −78·2°, *M*, 138), (*b*) 1·16 l., b. p. −35·7° to −34·3°, *M*, 172 (C_2F_7N requires *M*, 171), and (*c*) 21 c.c., b. p. −35° to +40°. Very little carbon tetrafluoride was formed. Fraction (*a*) was evidently mainly hexafluoroethane, though the low molecular weight indicated that some perfluoromethylamine may have been present. Fraction (*b*), *perfluoroethylamine*, was redistilled for analysis and vapour-pressure measurement [Found: F, 77·6; N, 8·0%; *M*, 172. C_2NF_7 requires F, 77·8; N, 8·2%; *M*, 171].

Analysis. Several attempts to analyse gases containing carbon, nitrogen, and fluorine by heating them in a sealed tube with metallic potassium resulted in explosions. The method finally adopted was to reflux potassium in a U-tube *in vacuo* until all gases had been pumped off, then to allow the weighed sample of gas to react in small doses with boiling potassium. Nitrogen was pumped off by a Topler pump and measured in a gas burette, and fluoride and cyanide determined in the contents of the U-tube after cooling and decomposition with alcohol. Some of the nitrogen appeared as gas and the rest as cyanide.

The authors thank the Director of Research, Imperial Smelting Corporation Ltd., Avonmouth, for kindly permitting the use of his laboratories. One of us (J. H.) thanks the Imperial Smelting Corporation for a maintenance grant.

THE UNIVERSITY, BRISTOL. [*Received, February 16th*, 1951.]

617. *Characterisation of Monoalkyl Ethers of Ethylene and Diethylene Glycols.*

By E. S. Lane.

The reagents hitherto proposed (Veraguth and Diehl, *J. Amer. Chem. Soc.*, 1940, **62**, 233; Seikel and Huntress, *ibid.*, 1941, **63**, 593; Manning and Mason, *ibid.*, 1940, **62**, 3136) for the characterisation of monoalkyl ethers of ethylene and diethylene glycols have not proved entirely satisfactory. It has now been found that the allophanates of these glycols are readily prepared and crystallised. Allophanates have previously been used for the characterisation of a variety of alcohols (Paul and Riobe, *Compt. rend.*, 1947, **224**, 474; Gaddis and Butz, *J. Amer. Chem. Soc.*, 1947, **69**, 117; Naves, *Helv. Chim. Acta*, 1946, **29**, 553, 1447; Karrer and Hoffmann, *ibid.*, 1940, **23**, 1126; Blohm and Becker, *J. Amer. Chem. Soc.*, 1950, **72**, 5342). The method of preparation used is based on that used by Werner and Gray (*Sci. Proc. Roy. Dublin Soc.*, 1946, **24**, 77; 1947, **24**, 209). Attention is drawn to Spielman, Barnes, and Close's modification (*J. Amer. Chem. Soc.* 1950, **72**, 2520), which is convenient when the required allophanate (*e.g.*, that of 2-phenoxyethanol) is sparingly soluble in water. The allophanate of 2-2′-methoxyethoxyethanol is low-melting.

Experimental.—M. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss of Oxford.

2-*Methoxyethyl Allophanate.*—2-Methoxyethanol (" Methyl Cellosolve ") (15·2 g.) and dioxan (150 ml.) were stirred together, and anhydrous sodium cyanate (39 g.) added portionwise during 2 hours, while a stream of dry hydrogen chloride was passed through the mixture. Solvent and acid were removed under reduced pressure, and the solid residue was extracted with ether. The extracted material (21 g.) was recrystallised (charcoal) from ether, to give 2-*methoxyethyl allophanate*, m. p. 163° (Found: C, 37·05; H, 6·6; N, 17·4. $C_5H_{10}O_4N_2$ requires C, 37·1; H, 6·2; N, 17·3%).

2-*Ethoxyethyl allophanate*, similarly prepared, had m. p. 143—145° (11·1 g. from 18 g. of alcohol) (Found: C, 41·4; H, 6·6; N, 15·7. $C_6H_{12}O_4N_2$ requires C, 41·0; H, 6·8; N, 15·9%).

2-*Butoxyethyl Allophanate.*—2-Butoxyethanol (12 g.) and benzene (100 ml.) were stirred together while anhydrous sodium cyanate (25 g.) was added portionwise during 2 hours and a stream of anhydrous hydrogen chloride was passed in. The reaction mixture was evaporated to dryness. The residue (15·2 g.) was insoluble in water but easily soluble in methanol. Recrystallised from 9 : 1 water–methanol, it gave the *allophanate* as soft colourless crystals, m. p. 118° (Found: C, 47·2; H, 7·7; N, 13·5. $C_8H_{16}O_4N_2$ requires C, 47·1; H, 7·85; N, 13·7%).

2-*Phenoxyethyl Allophanate.*—2-Phenoxyethanol (13·8 g.) and glacial acetic acid (100 ml.) were stirred together while anhydrous sodium cyanate (19·5 g.) was added portionwise during 2 hours. The reaction mixture was stirred at room temperature for a further 2 hours, then poured into water, and the insoluble *allophanate* filtered off. It recrystallised from ethylene glycol monoacetate as colourless crystals, m. p. 219—220° (4·3 g.) (Found: C, 53·5; H, 5·3; N, 12·5. $C_{10}H_{12}O_4N_2$ requires C, 53·6; H, 5·4; N, 12·5%).

2-2′-*Methoxyethoxyethyl Allophanate.*—Prepared as above in dioxan, this was a slightly discoloured semi-solid material which could not be recrystallised owing to its excessive solubility.

2-2′-*Ethoxyethoxyethyl Allophanate.*—Prepared in dioxan (3 hours), this *allophanate* had m. p. 102—104° (Found: C, 43·7; H, 7·15; N, 12·9. $C_8H_{16}O_5N_2$ requires C, 43·7; H, 7·3; N, 12·7%).

2-2′-*Butoxyethoxyethyl Allophanate.*—2-2′-Butoxyethoxyethanol (16 g.) and benzene (100 ml.) were stirred together while anhydrous sodium cyanate (20 g.) was added portionwise during 1 hour and a stream of dry hydrogen chloride was passed through the mixture. The reaction mixture was heated (to remove acid) and filtered through sintered glass, and the filtrate evaporated. The residue was extracted with acetone, the solution filtered, and the filtrate evaporated to dryness. The solid (16·9 g.) was easily soluble in solvents but not in cold water. Recrystallisation from aqueous acetone gave the *allophanate*, m. p. 88° (Found: C, 48·5; H, 8·2; N, 11·0. $C_{10}H_{20}O_5N_2$ requires C, 48·4; H, 8·1; N, 11·3%).

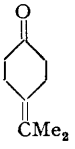
The author is indebted to The Director, Atomic Energy Research Establishment, for permission to publish this note.

A.E.R.E., Harwell, near Didcot, Berks. [*Received, April 4th*, 1951.]

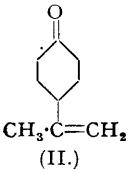
618. *The Preparation of* 4-iso*Propylidene*cyclo*hexanone and its Derivatives.*

By K. G. Lewis.

Recently Frank and McPherson (*J. Amer. Chem. Soc.*, 1949, **71**, 1387) prepared 4-*iso*propylidene*cyclo*hexanone (I) by distillation of γ-carboxy-γ-*iso*propenylpimelic acid with barium carbonate, proved its structure by ozonolysis to acetone and *cyclo*hexane-1 : 4-dione and by its conversion into γ-terpineol, and characterised it by means of a semicarbazone and a 2 : 4-dinitrophenylhydrazone. The last derivative, prepared in hot alcoholic hydrochloric acid, was orange which was unexpectedly dark in view of the non-conjugation of the carbonyl group and the ethylenic bond. It was also found that a Thorpe reaction, expected to yield (I), gave a substance which yielded the same 2 : 4-dinitrophenylhydrazone but a different semicarbazone. Frank and McPherson suggested the presence, in the second ketone, of some of the 4-*iso*propenyl isomer (II).



(I.)



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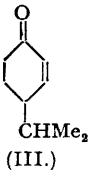

(III.)

The present author has found the same 2 : 4-dinitrophenylhydrazone to be formed from 4-*iso*propyl*cyclo*hex-2-enone (III). The discrepancies are resolved by recollecting the effect of strong acid on the unconjugated system (I). Formation of the hydrazone in hot acid, as practised by Frank and McPherson, gives the derivative of (III) from either (I) or (III); in the cold (cf. Birch, *J.*, 1946, 595), (I) gives a different 2 : 4-dinitrophenylhydrazone with the expected properties. The Thorpe reaction referred to above involves final hydrolysis with hot acid for 6 hours : Frank and McPherson's second ketone was therefore (III). The difference of the semicarbazones is thus explained. The identities of the dinitrophenylhydrazones have been confirmed by absorption spectra.

Experimental.—(M. p.s are uncorrected.)

4-iso*Propylidene*cyclo*hexanone*. This was prepared as recorded by Frank and McPherson (*loc. cit.*) and had b. p. 92—94°/13 mm., n_D^{22} 1·4819.

(*a*) The 2 : 4-dinitrophenylhydrazone, prepared according to Shriner and Fuson (" The Systematic Identification of Organic Compounds," John Wiley & Sons, New York, 2nd edn. 1940, p. 143), yielded deep orange-red plates, m. p. 132—134°, from alcohol. The mixed m. p. with authentic (±)-4-*iso*propyl*cyclo*hex-2-enone 2 : 4-dinitrophenylhydrazone (m. p. 136°) was 134—136°. The absorption max. in alcohol was at 3760 Å (ε 28,600).

(*b*) The ketone (0·5 g.) in alcohol (10 ml.) was added to 2 : 4-dinitrophenylhydrazine (0·5 g.) in alcohol (5 ml.) and concentrated sulphuric acid (0·5 ml.) and the mixture was kept cool. The resulting 2 : 4-dinitrophenylhydrazone was filtered off, washed with 5% sodium carbonate and water, and crystallised as golden-yellow plates, m. p. 122—124°, from alcohol. The absorption max. in alcohol was at 3650 Å (ε 22,500).

(*c*) The semicarbazone had m. p. 196—198° (from 90% alcohol), depressed when mixed with (±)-4-*iso*propyl*cyclo*hex-2-enone semicarbazone, m. p. 190—192°.

(±)-4-iso*Propyl*cyclo*hex-2-enone*. This was prepared by the racemisation of natural (−)-4-*iso*propyl*cyclo*hex-2-enone (cryptone) by Gillespie and Macbeth's method (*J.*, 1939, 1531). The 2 : 4-dinitrophenylhydrazone, deep orange-red plates, had m. p. 136° (from alcohol) (Gillespie and Macbeth record m. p. 130—131°; Birch, *loc. cit.*, gives m. p. 135—136°). The absorption max. in alcohol was at 3760 Å (ε 29,300). The semicarbazone had m. p. 190—192° (from 90% alcohol) (Gillespie and Macbeth record m. p. 188°).

The author thanks Professor A. K. Macbeth, of the University of Adelaide, and Mr. P. A. Berry for the sample of (−)-4-*iso*propyl*cyclo*hex-2-enone, also Mr. J. Ferguson, of the Chemistry Department, University of Sydney, for determination of the ultra-violet absorption spectra, and the Commonwealth Science Research Fund for financial assistance.

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[*Received, May 21st*, 1951.]

619. *Paper Chromatography of the Cardiac Glycosides.*

By C. H. Hassall and S. L. Martin.

The recent publication by Schindler and Reichstein (*Helv. Chim. Acta*, 1951, **34**, 108) of a method for paper chromatography of cardiac glycosides utilising a stationary phase of formamide and various combinations of benzene and chloroform prompts us to describe now the results of our investigations using different procedures. As did the Swiss workers we found considerable variation in the behaviour of different glycosides. However, by using a variety of solvent mixtures, it has been possible to apply the technique to the separation and identification of the cardiac glycosides which have been investigated.

$100 \times R_F$ *Values of cardiac glycosides.*[1,2]

Solvent	Digilanid A		Digilanid B		Digilanid C		Digitoxin		Digoxin		Urechitoxin		Convallotoxin	
	R_{FF}	R_{FC}	R_{FF}	R_{FC}	R_{FF}	R_{FC}	R_{FF}	R_{FC}	R_{FF}	R_{FC}	R_{FF}	R_{FC}	R_{FF}	R_{FC}
Ethyl acetate–water	52	36	0	—	0	—	94	92	86	68	85	82	36	31
Ethyl acetate–water [3]	74	62	0	—	0	—	87	82	0	—	80	74	36	21
Ethyl acetate–2·55N-aqueous sodium benzoate	0	—	28	27	0,11	0,6	0,91	0,88	0,80	0,67	0,46	0,44	0,24	0,13
Water–ethyl acetate	0·5	0·4	0·7	0·6	1·1	1	0	—	0·8	0·7	84	78	70	68
2·55N-Sodium benzoate–ethyl acetate	95	91	95	88	94	84	95	94	97	94	96	94	97	94
0·286N-Sodium benzoate–ethyl acetate	76	66	87	85	85,0·4	78,0·3	0	—	0·9	0·8	86	84	87	85
n-Butyl alcohol–water	87	82	76	74	82	78	93	90	88	86	76	72	66	62
n-Butyl alcohol–water [3]	92	89	92	87	96	93	95	88	96	92	81	75	73	63
Water–*n*-butyl alcohol	22	11	0	—	55	51	4·3	3·6	20	10	30	16	68	62
Ethyl oxalate–water	43	40	0	—	0	—	87	86	0·7	0·6	98	96	21	15
Water–ethyl oxalate	77	73	76	72	71	67	73	66	71	68	79	76	79	77
Ethyl methyl ketone–water	79	56	93	88	55	43	79	56	72	66	89	79	96	91
Water–ethyl methyl ketone	83	80	93	90	94	93	70	60	74	57	89	86	94	89
Water–ethyl methyl ketone [3]	95	92	87	84	98	97	95	92	98	96	97	94	90	88
Chloroform–water	0,39	0,20	0,13	0,7	0,6	0,3·4	0,73	0,64	0,46	0,36	0,62	0,44	0,5	0,2·8
Chloroform–water [3]	0,31	0,15	0	—	0,4·6	0,3·1	0,65	0,60	0,52	0,37	0,59	0,53	0,5	0,2·5

[1] With all combinations of solvent studied R_F value for gitoxin = 0·0. [2] The solvent front moved 20—30 cm. [3] Temp. 12°; in all other cases 34·5° ± 0·5°.

The table summarises the R_F values obtained with the representative series of glycosides studied. R_F values were calculated by using the front (R_{FF}) and centre (R_{FC}) of spots as reference points. They give an indication of the degree of longitudinal spread. In preliminary experiments, it was found that careful control of temperature was generally necessary for satisfactory results. In particular instances, *e.g.*, digoxin, digitoxin, it was possible to vary R_F values to obtain a better separation of constituents of a mixture by utilising this temperature effect. When good equilibrium conditions were maintained, there was normally satisfactory agreement between R_F values obtained in different experiments at a given temperature. In the two cases where significant variation between replicates occurred (digoxin, digilanid A) there was better agreement between R_{FF} than between R_{FC} values.

When ethyl acetate–sodium benzoate–water was used, two spots were obtained with single starting compounds. This also occurred with chloroform–water for all cases except gitoxin. Similar effects have been described elsewhere (Partridge, *Biochem. J.*, 1947, **42**, 244; Peterson and Reinecke, *J. Amer. Chem. Soc.*, 1950, **72**, 3598). The evidence suggests that this result may arise from the formation of artefacts in the course of chromatography.

As the table of R_F values indicates, all the glycosides investigated may be identified by this procedure when suitable solvents are employed. Technical difficulties are frequently encountered in the cardiac glycoside series in the separation of individuals on a preparative scale by the standard procedures of crystallisation, fractional elution chromatography, or partition. It appears likely that the chromatopile procedure (Mitchell and Haskins, *Science*, 1949, **110**, 278) could be applied with advantage to such cases when indications obtained from paper-strip chromatography are favourable; as an example, this method has been applied successfully to the separation of the digitalis glycosides gitoxin, digitoxin, and digoxin.

Experimental.—Apparatus. A small-scale modification of the standard pattern of apparatus used for descending paper chromatography has been employed. Four strips of filter paper (2 × 45 cm., Whatman No. 1), weighted at the free end with paper clips, were supported by the top segment (2·5 × 2·5

cm.) of a movable glass-rod frame with the other ends placed in a glass cup (2 × 3 cm.) fixed to the frame centrally below the top segment. The mounted frame was placed in a glass cylinder (45 × 7 cm.) permanently closed at the bottom and containing both liquid phases (in separate containers). The cylinder was closed by a large stopper carrying a small stoppered tube through which solvent could be introduced into the solvent cup.

Large-scale runs carried out with a stainless-steel tank similar to that described by Woiwod (*J. Gen. Bact.*, 1949, **3**, 312) gave R_F values which in some cases were consistently slightly higher than those obtained with the smaller apparatus and recorded in the table above.

Procedure. Both forms of apparatus were maintained at 34·5° ± 0·5° in an air thermostat. The glycoside solutions used were 1% (w/v) in methyl alcohol or methyl alcohol–chloroform. Normally two drops of solution (40—60 μg.) were applied with a micropipette giving a spot of approx. 0·3-cm. radius. The chromatography was carried out in a manner similar to that described by Jermyn and Isherwood (*Biochem. J.*, 1949, **44**, 402). The solvent front was allowed to move 20—30 cm. in the small apparatus and up to 50 cm. in the large one. The time required varied with the solvent from 1 to 10 hours.

The location of the spots was indicated by lightly spraying the dry papers with aqueous 5·5N-potassium hydroxide and then with 2% *m*-dinitrobenzene in ethyl alcohol (Raymond, *Analyst*, 1939, **64**, 113; Marlow, *J. Biol. Chem.*, 1950, **183**, 167). When necessary the light blue colours obtained were intensified by spraying again with aqueous potassium hydroxide. In the case of gitoxin, only faint colours are obtained and the test is not always reliable. The position of the gitoxin may be confirmed by applying the Keller–Kiliani reagent to extracts of strip sections or by utilising the colour obtained with hydrogen chloride (Mesnard and Deveze, *Bull. Trav. Soc. pharm. Bordeaux*, 1950, **88**, 109).

The length of the spot increases with the amount of glycoside used although in the cases studied the position of the spot front does not show significant variation due to this factor. It is probable that this contributes to the better reproducibility shown by R_{FF} values in a series of experiments in which there was some variation in the amount of glycoside used (40—60 μg.).

Chromatopile chromatography. A mixture of gitoxin (20 mg.), digitoxin (30 mg.), and digoxin (20 mg.) was applied in chloroform–methanol to three filter papers (Whatman No. 1, 11 cm.) which were introduced into the top of a pile compressed to 18·7 cm. in the form of the commercially available chromatopile apparatus (Mitchell and Haskins, *loc. cit.*). Chromatography was carried out by the standard procedure at 34·5° with ethyl acetate–water. The apparatus was allowed to come to equilibrium overnight in an enclosed vessel containing both phases of the solvent mixture. Qualitative examination of sections of the papers at the end of the experiment indicated R_F values for the individual glycosides similar to those obtained on paper strips. The glycosides concentrated on the periphery of the papers. The identity and purity of the three constituents separated in this way was confirmed by extraction from the paper at different locations, recrystallisation, and comparison on paper-strip chromatograms with pure products.

We are indebted to Roche Products Ltd., Prof. A. Stoll, and Burroughs Wellcome & Co. (U.S.A.) Inc. for samples of authentic glycosides, and to Roche Products Ltd. and the Chemical Society for grants.

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[*Received, May 25th*, 1951.]

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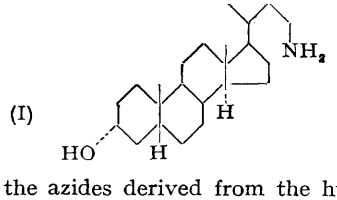
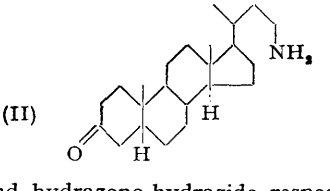
620. *Basic Derivatives of Steroids. 23-Amino-3α-hydroxy- and 23-Amino-3-keto-norcholane.*

By MARJORIE L. HILTON and M. WEBB.

THE synthesis, from cholic and deoxycholic acids, of certain basic derivatives of norcholane which possessed bacteriostatic properties was recorded in a previous paper (James, Smith, Stacey, and Webb, *J.*, 1946, 665). This work has now been extended to the preparation from lithocholic acid of 23-amino-3α-hydroxy- (I) and 23-amino-3-keto-norcholane (II) by decom-





position of the azides derived from the hydrazide and hydrazono-hydrazide respectively (cf. Caldwell, *J. Amer. Chem. Soc.*, 1938, **60**, 991; 1939, **61**, 3584).

The bacteriostatic concentrations of the hydrochlorides of (I) and (II) against *Staph. aureus* (Oxford, Strain D), determined by the serial dilution method in a glucose–broth medium (pH 7), were respectively 1 : 256,000 and 1 : 64,000 after 48 hours at 37°. Both compounds were inactive when tested against the Gram-negative organism *Aerobact. aerogenes*.

Experimental.—Lithocholic acid. Methyl cholate was converted into methyl 3α-(β-carboxypropionoxy)-7 : 12-diketocholanate which was then reduced in 5-g. quantities to lithocholic acid, m. p. 184° (Heusser and Wuthier, *Helv. Chim. Acta*, 1947, **30**, 2165).

Lithocholylhydrazine. A mixture of methyl lithocholate (1·95 g.) and absolute hydrazine hydrate (25 ml.) was boiled under reflux for 5 hours. The excess hydrazine hydrate was then removed by evaporation under reduced pressure and the solid residue dried *in vacuo* over concentrated sulphuric acid. Crystallisation from ethanol, gave *lithocholylhydrazine* (1·5 g.) as white needles, m. p. 214—217° (sintering at 211°), $[\alpha]_D^{18}$ +36° (*c*, 1·0 in ethanol) (Found : C, 73·4; H, 10·9; N, 7·0. $C_{24}H_{42}O_2N_2$ requires C, 73·8; H, 10·8; N, 7·2%).

23-*Amino*-3α-*hydroxynorcholane hydrochloride*.—A solution of sodium nitrite (0·4 g.) in water (5 ml.) was added slowly with stirring to a solution of the hydrazide (1·5 g.) in 5N-hydrochloric acid (50 ml.) and acetic acid (80 ml.) at 0° to −5°, until excess of nitrous acid was detected (starch–iodide paper). After 30 minutes, the suspension was poured into ice-water (200 ml.), and the azide collected by filtration, washed with ice-water, and transferred, while still moist, into acetic acid (50 ml.). The suspension was heated on a steam-bath until the solid had dissolved and the evolution of gases had ceased (*ca.* 2 hours). The solution was cooled to 0° and made alkaline to litmus with sodium hydroxide, and the precipitated amine collected (centrifuge), washed with ice-water, and dried (P_2O_5–NaOH). Dry hydrogen chloride was passed through a solution of the crude amine in dry chloroform until no further precipitation of the hydrochloride occurred. The supernatant liquid was decanted and the gelatinous precipitate triturated with acetone until solid. Crystallisation from ethanol–acetone (1 : 3) gave 23-*amino*-3α-*hydroxynorcholane hydrochloride* (0·6 g.) as needles, m. p. >300° (decomp.), $[\alpha]_D^{19}$ +37·5° (*c*, 1·02 in ethanol) (Found, after drying at 180° : C, 72·1; H, 10·6; N, 3·7. $C_{23}H_{42}ONCl$ requires C, 71·9; H, 10·9; N, 3·65%).

3-*Ketocholanic acid*.—Lithocholic acid was oxidized with chromic acid according to Wieland and Dane's method (*Z. physiol. Chem.*, 1932, **212**, 48). The reaction product was poured into water, and the resulting emulsion extracted with ether. The ethereal extract was dried ($MgSO_4$) and evaporated *in vacuo*. The residual syrup was triturated with methanol until solid. Recrystallisation from methanol afforded 3-ketocholanic acid (1·45 g.; m. p. 139°).

Hydrazone of 3-*ketocholanylhydrazine.* A solution of methyl 3-ketocholanate (1·35 g.) in absolute ethanol–hydrazine hydrate (25 ml. each) was boiled under reflux for 12 hours. The solution was filtered, evaporated under reduced pressure, and dried *in vacuo* over concentrated sulphuric acid. Trituration of the syrup with ethanol yielded a gelatinous solid which hardened on treatment with ether, to give 3-ketocholanylhydrazine hydrazone (1·0 g.) as a white amorphous powder.

23-*Amino*-3-*ketonorcholane hydrochloride.* Sodium nitrite (0·5 g.) in water (5 ml.) was added slowly with stirring to a solution of the foregoing hydrazone (905 mg.) in 5N-hydrochloric acid (25 ml.)–acetic acid (80 ml.) at 0°, until excess of nitrous acid was detected (starch–iodide paper). After 30 minutes at 0° the solution was poured into ice-water (200 ml.), and the precipitated azide collected, washed with ice-water, and transferred into glacial acetic acid (30 ml.). The suspension was heated on a steam-bath until evolution of gases had ceased (1½ hours); the resulting solution was cooled to 0° and neutralised with sodium hydroxide. The emulsion thus obtained was extracted with chloroform and the extract washed with water and dried ($MgSO_4$). Dry hydrogen chloride was passed for 10 minutes through the cooled solution which was then evaporated to dryness under reduced pressure at room temperature. A white solid remained which was triturated with acetone, washed twice with acetone, and collected (centrifuge). Crystallisation from ethanol–light petroleum and recrystallisation from acetone–water gave 23-*amino*-3-*ketonorcholane hydrochloride* as colourless needles (100 mg.), m. p. 236° (decomp.), $[\alpha]_D^{21}$ +54·7° (*c*, 1·13 in ethanol) (Found, after drying at 180° : C, 72·7; H, 10·0; N, 3·5. $C_{23}H_{40}ONCl$ requires C, 72·4; H, 10·5; N, 3·7%).

The authors thank Professor M. Stacey, F.R.S., for his interest in this work. One of them (M. L. H.) is indebted to the Department of Scientific and Industrial Research for a grant.

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[*Received, June 12th*, 1951.]

621. *The Preparation of Acid Anhydrides.*

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It has been shown (Klinger and Schmitz, *Ber.*, 1891, **24**, 1271; 1276; Basse and Klinger, *Ber.*, 1898, **31**, 1217) that the action of sodium on acid chlorides in dry ether is abnormal and leads to esters of unsaturated glycols $RCO_2 \cdot CR{:}CR \cdot O_2CR$. Vavoglis (*Ber.*, 1937, **70**, 2391) obtained ethyl benzoate from benzoyl chloride and zinc or iron in dry ether. Pearl, Evans, and Dehn (*J. Amer. Chem. Soc.*, 1938, **60**, 2478) produced a similar result by using sodium and ether but found that potassium in dry xylene gave the corresponding anhydride from benzoyl, succinoyl, or phthaloyl chlorides; evidently oxidation of a free radical occurs in this reaction; toluene-*p*-sulphonyl chloride yielded di-*p*-tolyl disulphone; no reference to the early work in this field is given.

Ralston and Selby (*J. Amer. Chem. Soc.*, 1939, **61**, 1019) extended the work of Klinger and his collaborators to higher fatty acid chlorides and obtained similar products.

No work appears to have been done on the action of metallic oxides on acid chlorides. Investigation showed that the reaction proceeds, as expected, according to the equation:

$$2R \cdot COCl + M_2O\ (M'O) \longrightarrow (R \cdot CO)_2O + 2MCl\ (M'Cl_2)$$

Silver and yellow mercuric oxides reacted readily; lime gave a poor yield of anhydride; and cupric oxide, although it caused a vigorous reaction, did not furnish a solid product. The reaction is improved by using an excess of the metallic oxide whereby all the acid chloride is removed, otherwise the final separation is difficult.

Experimental.—Benzoic anhydride. (1) Dry silver oxide (21 g.) was added in small amounts to benzoyl chloride (24·5 g.) with rapid stirring (mercury seal). The two-necked flask was cooled in ice. Much heat, causing white fumes, developed. When addition was complete, pure dry benzene (40 ml.) was added and the mixture was refluxed for 1 hour. After filtration the solvent was removed and the brown oily residue distilled in a vacuum, to remove benzoyl chloride. The solid residue (13 g.) was dissolved in ether, and the solution warmed with norite for ½ hour, filtered, and freed from the ether. Benzoic anhydride (9 g.), m. p. 41—42°, was obtained. Recrystallization from light petroleum (b. p. 60—80°) gave colourless needles, m. p. 42°. Hydrolysis furnished benzoic acid, m. p. 121°.

(2) Benzoyl chloride (24 g.) and dry benzene (20 ml.) were similarly treated with dry yellow mercuric oxide (21 g.), added slowly with stirring and cooling. Benzene (20 ml.) was then added and the mixture refluxed for ½ hour, then filtered, and the solvent removed. Benzoic anhydride (9 g.), m. p. 40—42°, remained. Extraction of the mercuric chloride with dry ether and recrystallization of the extract from light petroleum (b. p. 60—80°) gave colourless needles, m. p. 42° (2 g.). The anhydride, on hydrolysis, yielded benzoic acid, m. p. 121°.

(3) Benzoyl chloride (24·2 g.), benzene (20 ml.), and dry lime (10 g.) were refluxed for 4 hours. After filtration and removal of the benzene, colourless crystals (3 g.), m. p. 41—42°, of benzoic anhydride were obtained.

p-*Toluic anhydride.* (1) *p*-Toluoyl chloride (10 g.) in dry benzene (20 ml.) was added, with stirring, to dry silver oxide (10 g.) cooled in ice. After addition of benzene (20 ml.) and refluxing for 1 hour the silver chloride was filtered off, the solvent removed, and the residue (7·5 g.) recrystallized from light petroleum (b. p. 60—80°). Colourless needles (5 g.), m. p. 95°, of *p*-toluic anhydride separated. Hydrolysis gave *p*-toluic acid, m. p. 181°.

(2) *p*-Toluoyl chloride (15·6 g.) in dry benzene (20 ml.) was similarly run in to a flask containing a slight excess of dry yellow mercuric oxide. After similar treatment colourless crystals (5·7 g.), m. p. 95°, were obtained which were hydrolysed to *p*-toluic acid.

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[*Received, July 3rd*, 1951.]