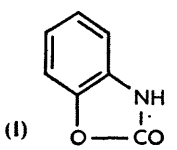
NOTES.

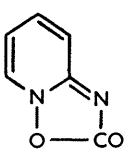
876. N-*Oxides and Related Compounds. Part VI.* Some Derivatives of* 2-*Aminopyridine* 1-*Oxide.*

By A. R. KATRITZKY.

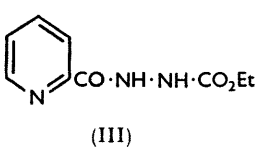
PREPARATIONAL details (cf. ref. 1) are given for 2-aminopyridine 1-oxide hydrochlorides required for other work. As benzoxazolone (I) has antifungal properties,[2] derivatives of



(I)



(II)



(III)

the isoelectronic pyridino-oxadiazolone (II)[3] were made, but later the parent compound was found inactive. Whereas *iso*nicotinoyl hydrazide with carbonyl chloride gives

* Part V, Gardner and Katritzky, preceding paper.

[1] Katritzky, *J.*, 1957, 191.
[2] Virtanen and Hietala, *Acta Chem. Scand.*, 1955, **9**, 1543.
[3] Katritzky, *J.*, 1956, 2063.

2-4′-pyridyl-1-oxa-3 : 4-diazol-5-one,[4] *N*-ethoxycarbonyl-*N*′-picolinoylhydrazine (III) is pyrolysed to *NN*′-dipicolinoylhydrazine.

Experimental.—*2-Ethoxycarbonylaminopyridines.* Ethyl chloroformate (14 c.c.) was added gradually to 2-amino-5-methylpyridine (13·5 g.) in pyridine (60 c.c.) with cooling. After 12 hr., water was added; the resulting *2-ethoxycarbonylamino-5-methylpyridine* (14·9 g., 67%) formed needles (from ethanol), m. p. 144·5—145·5° (Found: C, 60·1; H, 6·7; N, 15·3. $C_9H_{12}O_2N_2$ requires C, 60·0; H, 6·7; N, 15·5%). Similarly prepared were *2-ethoxycarbonylamino-4 : 6-dimethylpyridine* (84%), prisms, m. p. 62—64°, from aqueous ethanol (Found: C, 62·0; H, 7·3. $C_{10}H_{14}O_2N_2$ requires C, 61·9; H, 7·2%); 2 : 6-di(ethoxycarbonylamino)pyridine (32%), prisms, m. p. 132—133°, from ethanol (lit.,[5] m. p. 127°) (Found: C, 52·5; H, 6·0; N, 16·7. Calc. for $C_{11}H_{15}O_4N_3$: C, 52·2; H, 5·9; N, 16·6%); and *2-ethoxycarbonylaminoquinoline* (65%), needles, m. p. 98—100°, from ethanol (Found: C, 66·7; H, 5·6; N, 12·8. $C_{12}H_{12}O_2N_2$ requires C, 66·7; H, 5·6; N, 13·0%).

2-Aminopyridine 1-oxide hydrochlorides. 2-Ethoxycarbonylamino-5-methylpyridine (14·9 g.), acetic acid (32 c.c.), and 30% hydrogen peroxide (13 c.c.) were heated 18 hr. at 70°, then evaporated at 100°/15 mm., and the residue was refluxed for 18 hr. with concentrated hydrochloric acid (20 c.c.). Evaporation and recrystallisation from ethanol gave *2-amino-5-methylpyridine 1-oxide hydrochloride* (6·0 g. 45%), prisms, m. p. 195—198° (Found: C, 45·0; H, 5·8; N, 17·1. $C_6H_9ON_2Cl$ requires C, 44·9; H, 5·6; N, 17·4%). The following were similarly prepared: *2-amino-4 : 6-dimethyl-* (65%), needles, m. p. 230—231° (decomp.) from ethanol (Found: C, 48·6; H, 6·4. $C_7H_{11}ON_2Cl$ requires C, 48·2; H, 6·3%), and *2-amino-6-methyl-pyridine 1-oxide hydrochloride* (67%), prisms (from ethanol), m. p. 212—214° (Found: C, 45·0; H, 5·7; N, 16·9%); *2-aminoquinoline 1-oxide hydrochloride* (56%), needles from ethanol, m. p. 255—257° (decomp.) (Found: C, 55·2; H, 4·7. $C_9H_9ON_2Cl$ requires C, 55·0; H, 4·6%).

2-Ethoxycarbonylaminopyridine 1-oxides. The 2-ethoxycarbonylaminopyridines were oxidised with peracetic acid as described [3] to give: *2-ethoxycarbonylamino-5-methyl-* (83%), prisms, m. p. 90—93° (from ethyl acetate) (Found: N, 14·3. $C_9H_{12}O_3N_2$ requires N, 14·3%), *2-ethoxycarbonylamino-4 : 6-dimethyl-* (86%), needles, m. p. 111—112° (from ethyl acetate) (Found: C, 57·3; H, 6·7; N, 13·1. $C_{10}H_{14}O_3N_2$ requires C, 57·2; H, 6·7; N, 13·3%), and *2 : 6-di(ethoxycarbonylamino)pyridine 1-oxide* (74%), prisms, m. p. 114—116° (from ethyl acetate) (Found: C, 49·5; H, 5·7; N, 15·2. $C_{11}H_{15}O_5N_3$ requires C, 49·1; H, 5·6; N, 15·6%); and *2-ethoxycarbonylaminoquinoline 1-oxide* (91%) plates, m. p. 102—104° (from ethyl acetate) (Found: C, 61·8; H, 5·2; N, 12·2. $C_{12}H_{12}O_3N_2$ requires C, 62·1; H, 5·2; N, 12·1%).

From the oxidation of crude 2-ethoxycarbonylamino-5-methylpyridine a by-product (cf. ref. 3) was obtained: *NN′-di-(5-methyl-2-pyridyl)urea 1 : 1′-dioxide* (7%), m. p. 248—250° [decomp.], from acetic acid (Found: C, 56·8; H, 5·4. $C_{13}H_{14}O_3N_4$ requires C, 56·9; H, 5·1%).

Pyridino-oxadiazolones. Heating the above urethane oxides (cf. ref. 3) gave: *5′-methylpyridino-*, needles, m. p. 197—198° (from ethanol) (Found: C, 56·4; H, 4·2; N, 18·4. $C_7H_6O_2N_2$ requires C, 56·0; H, 4·0; N, 18·7%), *4′ : 6′-dimethylpyridino-*, needles, m. p. 167—168° (from ethanol) (Found: C, 58·7; H, 4·9; N, 16·7. $C_8H_8O_2N_2$ requires C, 58·6; H, 4·9; N, 17·0%), and *quinolino-(1′ : 2′-2 : 3)-1-oxa-2 : 4-diazol-5-one*, needles, m. p. 176—177° (from ethanol) (Found: C, 64·6; H, 3·4; N, 15·7. $C_{10}H_6O_2N_2$ requires C, 64·5; H, 3·2; N, 15·1%).

Pyridino-(1′ : 2′-2 : 3)-1-oxa-2 : 4-diazol-5-one did not inhibit the growth of *Microsporum gypseum, M. audonini, M. canis* var. *album, Trichophyton mentagrophytes, T. rubrum, T. sulphureum,* or *Helminthosporium monoceras* in glucose peptone broth in 0·008M-solution.

N-Ethoxycarbonyl-N′-picolylhydrazine. Ethyl chloroformate (1·2 g., 1·05 c.c.) was added during 10 min. to picolinoylhydrazine (1·37 g.) in pyridine (3 c.c.). After 4 hr. water was added, to give the *product* (1·32 g., 72%), prisms, m. p. 126·5—127·5° (from ethanol) (Found: C, 52·1; H, 5·3; N, 19·7. $C_9H_{11}O_3N_3$ requires C, 51·7; H, 5·3; N, 20·1%).

NN′-Dipicolylhydrazine. (*a*) The above hydrazine (2 g.) was heated from 230° to 300° in 15 min., and kept at 300° for 10 min. The residue, crystallised from pentyl alcohol, gave *NN′-dipicolylhydrazine* (0·6 g., 52%), prisms, m. p. 220—223° (from ethanol) (Found: C, 59·6; H, 4·3; N, 23·4. $C_{12}H_{10}O_2N_4$ requires C, 59·5; H, 4·1; N, 23·1%).

[4] Smith, *Science*, 1954, **119**, 514.
[5] Meyer and Malley, *Monatsh.*, 1892, **23**, 407.

(*b*) Potassium nitrite (0·25 g.) in water (2 c.c.) was slowly added to picolinylhydrazine (0·68 g.) in acetic acid (2 c.c.) and ice (10 g.). After 10 min., 30% aqueous potassium carbonate (2 c.c.) was added; after a further 30 min. the base (0·34 g. 56%) was collected; it had m. p. 223—224·5° (from ethanol) (Found: C, 59·8; H, 4·4%) and was identical with the above specimen (infrared spectra and mixed m. p.).

We thank Mrs. K. Crawford of the Sir William Dunn School of Pathology, Oxford, for the biological measurements. This work was done during the tenure of an I.C.I. Research Fellowship.

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, May 23rd,* 1957.]

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877. *The Preparation of Hydronium Forms of Analcite and Chabazite by Ion-exchange.*

By I. R. BEATTIE and A. DYER.

TREATMENT of aluminosilicates with mineral acids usually results in formation of an amorphous solid. However, Barrer *et al.*[1] have found that treatment of the silver form of certain aluminosilicates with a solution of a halide, where the cation is too large to enter the crystals, results in the precipitation of silver halide together with an increase in the pH of the solution. In order to examine this type of reaction further it was decided to treat silver forms of analcite and chabazite with pyridinium chloride solutions, whereby the pH of the solution would be maintained approximately constant in the event of hydrogen-ion exchange.

Experimental.—Silver forms of analcite and chabazite were prepared as described previously.[2] Hydrochloric acid was partially neutralised with pyridine to a pH value of between 5 and 6. Silver chabazite (about 1 g.) was heated under reflux with the pyridine–hydrochloric acid solution (50 ml.) for 1 day. The solid was then filtered off and extracted with pyridine until no further change in weight occurred. In this way all the silver chloride formed during the reaction was removed. The product was examined for hydrogen-ion activity by treatment with aqueous sodium hydroxide. The solid was analysed for residual silver, examined by *X*-ray powder photography, and studied under the microscope. Water content was determined by direct ignition.

With silver analcite the treatment was similar except that the exchange was carried out in a sealed tube at 120°. This process was then repeated after an initial extraction with pyridine had shown limited exchange to have occurred.

During ignition of the exchanged forms it was noted that, contrary to the usual formation of a glassy solid, the residue was a fine powder. Further, although the initial silver forms of the zeolite were discoloured to some extent (presumably by silver or silver oxide) the final product was white. The results of these experiments (Table) indicate that although the removal of

Reactant	*X*-Ray examn. of product	Water (wt.-%)	Exchange (mole-%)	H available (atom-%)
Silver analcite	Typical analcite spacings	17·1	~ 90	~10
Silver chabazite	Typical chabazite spacings	26·4	~100	~80

silver is almost quantitative in both cases, it is probable that with the analcite considerable quantities of amorphous material are formed. This was borne out by the difficulty experienced in obtaining a good *X*-ray powder photograph, long exposures being essential. The small amount of exchange with sodium hydroxide solution is not unexpected, since a silicate, of the formula $(H_3O)_2O,Al_2O_3,4SiO_2,xH_2O$ when amorphous, is to be regarded as $Al_2O_3,4SiO_2,yH_2O$,

[1] Barrer and Raitt, *J.*, 1954, 4641; Barrer and Sammon, *J.*, 1955, 2838; 1956, 675.
[2] Beattie, *Trans. Faraday Soc.*, 1954, **50**, 581.

showing no evidence of hydrogen ions. Apparently the very stable chabazite structure is much less affected by this exchange. In view of the presence of amorphous material, water-content measurements must be treated with caution.

Discussion.—Silicate glasses undergo very rapid exchange with hydrogen ions in water,[3,4] yielding a strongly alkaline solution. With zeolites, such as analcite, the equivalent reaction does not occur, despite the great facility with which these minerals undergo ion exchange. The difference in behaviour is probably due to presence of terminal oxygens in the glass. A hydrogen or hydronium ion adjacent to an Si–O grouping will presumably, by covalent linking, become Si–O–H. The activity of hydrogen ions within the silicate may then be extremely small, so that the equilibrium for the exchange would lie on the side of a hydrogen glass. In this way hydrogen-ion exchange could occur even in alkaline solution. In the zeolites now studied there are no terminal oxygen atoms, the structures being a three-dimensional array of aluminium and silicon tetrahedrally surrounded by four oxygen atoms, with each oxygen linked to either two silicon or a silicon and an aluminium atom. Examination of the behaviour in neutral solution of silicates containing a terminal oxygen atom could be of value in considering the structure of glass. The amount of hydrogen-ion exchange might then be indicative of the presence of singly-linked oxygen atoms.

It is well known that aluminium does, in fact, enhance the resistance of many glasses to corrosion. It has also been shown [4] that the diffusion coefficient for sodium-ion migration is lowered if, for a given glass composition, silicon is partially replaced by aluminium. For every aluminium atom so introduced there would be one less terminal oxygen atom. However, the calculation of the diffusion coefficient assumes the equilibrium position to be that of a hydrogen glass, the concentration of sodium ions at time infinity being zero. An erroneous infinity value (due to only partial hydrogen-ion exchange) would lead to an incorrect diffusion coefficient, since this is found from the relation

$$Q = 2A(C - C_\infty)[(Dt)/\pi]^{\frac{1}{2}}$$

where Q = quantity of material which has diffused across the plane $x = 0$ up to time t; D = diffusion coefficient; C = concentration of diffusing material initially; C_∞ = concentration of diffusing material at time infinity; and A = surface area of the solid.

KING'S COLLEGE, STRAND, LONDON, W.C.2. [*Received, February 22nd*, 1957.]

[3] Douglas and Isard, *J. Soc. Glass Tech.*, 1949, **33**, 289.
[4] Beattie, *Trans. Faraday Soc.*, 1953, **49**, 1059.

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878. *The Formation of Peroxymonosulphuric Acid and Peroxydisulphuric Acid in Solutions of Sulphuric Acid Irradiated by* ^{60}Co *Radiation.*

By M. DANIELS, J. LYON, and J. WEISS.

SUGGESTIONS that during the radiolysis of aqueous sulphate [1] or sulphuric acid solution [2] the solutes can participate in free-radical reactions have recently received indirect support.[3] However, direct evidence has hitherto been absent; recent results with pure sulphuric acid solutions [4] can only be interpreted as a consequence of direct absorption of energy by the sulphuric acid.

[1] Allen, Hochanadel, Ghormley, and Davis, *J. Phys. Chem.*, 1952, **56**, 575.
[2] Allen, *Radiation Res.*, 1954, **1**, 85.
[3] Sworski, *J. Amer. Chem. Soc.*, 1956, **78**, 1768.
[4] Hochanadel, Ghormley, and Sworski, *ibid.*, 1955, **77**, 3215.

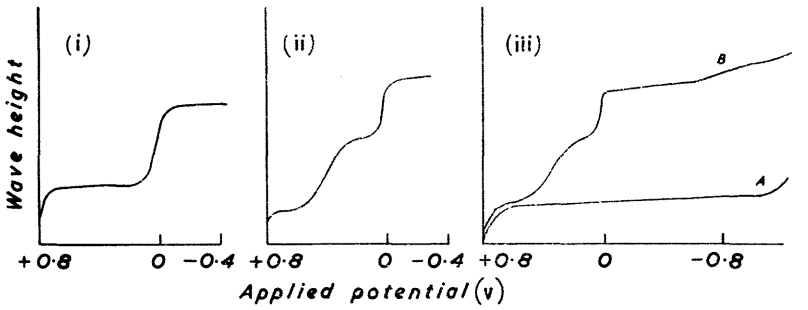
The present work demonstrates the existence of peroxymonosulphuric acid and peroxydisulphuric acid in solutions of sulphuric acid, irradiated in presence of air; their formation provides clear evidence of radical attack on the sulphuric acid molecule or its anions.

Analysis of mixtures of small amounts of peroxymono- and peroxydi-sulphuric acid in presence of hydrogen peroxide—which is always formed in irradiated, aerated aqueous solutions—is complicated by interrelation by hydrolysis and mutual interference by induced reactions.[5,6] Several independent methods have therefore been used.

In the polarogram hydrogen peroxide gives a well-defined, broad wave at −1·3 to −0·5 v (against the standard calomel electrode) [7] and peroxydisulphuric acid a sharp wave at +0·1 v).[8,9] Caro's acid has not been investigated previously, but it should give a wave at a still more positive potential.

Polarograms were obtained by the usual methods, a Cambridge pen-recording instrument being used. Fig. 1 shows the results for (i) a solution of peroxydisulphuric acid (4×10^{-4}M), (ii) a similar solution after partial hydrolysis, and (iii) an un-irradiated and an irradiated 2·5M-solution of sulphuric acid. In the last, the peroxydisulphate wave can be

FIG. 1.



(i), *Potassium peroxydisulphate* (4×10^{-4}M). (ii), *Solution* (i) *after hydrolysis.* (iii), 2·5M-*Sulphuric acid*: (*A*), *unirradiated*; (*B*), *irradiated.*

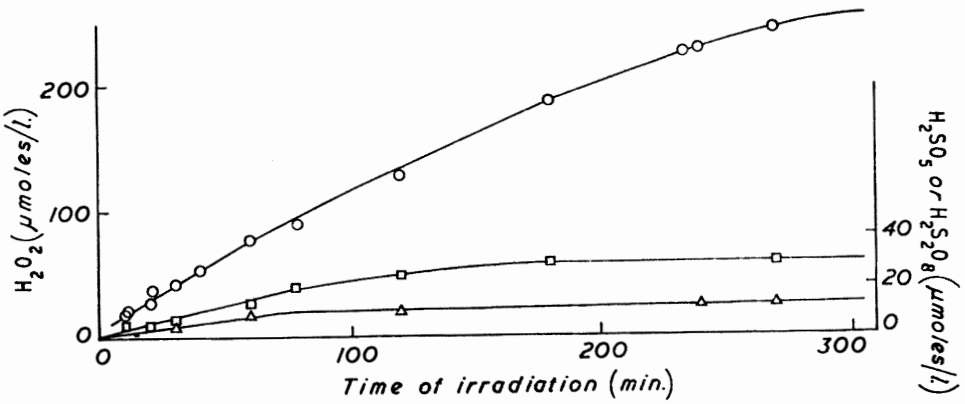
readily identified; there is also a broader wave at a half-wave potential of +0·4 v and this is also found in hydrolysed solutions of peroxydisulphate. If the second wave is accepted as being due to Caro's acid, *viz.*, $H_2S_2O_8 + H_2O \longrightarrow H_2SO_5 + H_2SO_4$, this would indicate the presence of this compound in irradiated solutions of sulphuric acid. Hydrogen peroxide can be identified and estimated separately by the specific titanium sulphate reagent.[10] Csanyi and Solymosi's method [11] is suitable for other micro-estimations; this involves addition of arsenite to the acid solution to remove the Caro's acid; the hydrogen peroxide can then be estimated cerimetrically and excess of arsenite back-titrated with ceric salt, with osmium tetroxide as catalyst. Finally, the peroxydisulphuric acid is hydrolysed with hot sulphuric acid in the presence of arsenite, and the consumption of the latter is again estimated by ceric titration. By a combination of these methods, hydrogen peroxide and peroxymono- and peroxydi-sulphuric acid have been determined in solutions of sulphuric acid irradiated (^{60}Co) in presence of air. Some typical results are shown in Fig. 2. In 0·4M-sulphuric acid the yields of the per-acids are relatively low, but still significant,

[5] Gleu, *Z. analyt. Chem.*, 1931, **195**, 61.
[6] Berry, *Analyst*, 1933, **58**, 464.
[7] Kolthoff and Lingane, "Polarography," Interscience Publ., Inc., New York, 1952.
[8] Kolthoff, Guss, May, and Medalia, *J. Polymer Sci.*, 1946, **1**, 340.
[9] Bernard, *Compt. rend.*, 1933, **236**, 2412.
[10] Eisenberg, *Ind. Eng. Chem. Anal.*, 1943, **15**, 327.
[11] Csanyi and Solymosi, *Z. analyt. Chem.*, 1954, **142**, 423.

e.g., at a dose of $2{\cdot}4 \times 10^{-5}$ mole ev/ml. there were found 5·6 μmoles/l. of peroxymono-acid, 3·2 μmoles/l. of peroxydi-acid, and 316 μmoles/l. of hydrogen peroxide. The yields of the products are generally in the sequence: $H_2O_2 > H_2SO_5 > H_2S_2O_8$, the absolute values being dependent on the concentration of sulphuric acid. The yields of both peroxymono- and peroxydi-sulphuric acid, though not that of hydrogen peroxide, appear to reach a stationary state after a certain dose of radiation.

The mere presence of peroxydisulphuric acid seems a strong indication of the intermediate formation of HSO_4 radicals, with subsequent dimerisation.

FIG. 2. *Irradiation of* 2M*-solutions of sulphuric acid with* ^{60}Co *γ-rays. Yields of products as functions of dose: dose rate,* 1×10^{-7} *mole* ev/*ml./min.* ⊙ H_2O_2 □ H_2SO_5 △ $H_2S_2O_8$.



It is now apparent, that radical reactions with sulphuric acid cannot be neglected in the interpretation of radiolytic processes in sulphuric acid solutions, especially when the reactions of the radical so produced (*e.g.* HSO_4) are different from those of its precursor (OH). It cannot yet be definitely concluded whether the sulphuric acid molecule is concerned in this reaction, *viz.* $OH + H_2SO_4 \longrightarrow H_2O + HSO_4$, or the bisulphate ion, $OH + HSO_4^- \longrightarrow OH^- + HSO_4$, although there is some evidence, that the sulphate ion can probably be excluded.

Work is in progress to elucidate the behaviour of dilute and concentrated solutions of sulphuric acid and the rôle of oxygen in these systems.

Thanks are due to King's College for the award of the Levine Studentship (J. L.), to Pilkington Bros. (J. L.), and to the Director of the Atomic Energy Research Establishment, Harwell, for support and for permission to publish this Communication.

KING'S COLLEGE, NEWCASTLE UPON TYNE, 1. [*Received, April* 23*rd*, 1957.]

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879. *The Reactions of Gaseous Fluorine and Chlorine with Liquid* n-*Butane and* iso*Butane.*

By P. C. ANSON and J. M. TEDDER.

n-BUTANE and *iso*butane have been fluorinated and chlorinated by bubbling a mixture of the gaseous halogen and nitrogen through the liquid hydrocarbon illuminated by visible light. The reactions were carried out at four temperatures and the products estimated by gas-phase chromatography. The results are summarised in the Table. The relative

rates of substitution of the different hydrogen atoms are thus in the expected order, tertiary > secondary > primary for both reactions, but fluorination is considerably less selective than chlorination. Chlorination becomes less selective as the temperature is

The proportions of primary to secondary or tertiary halide obtained by reaction of liquid butane and iso*butane with mixtures of gaseous nitrogen and fluorine or chlorine.*

[The extent of halogenation was about 15% for fluorine and about 7% for chlorine. The composition of gaseous mixture was F_2 (or Cl_2) : N_2 = 1 : 4. Figures in parentheses are the number of runs at each temperature.]

Hydrocarbon	Temp.	Proportion in product fluorn.	Proportion in product chlorn.	Hydrocarbon	Temp.	Proportion in product fluorn.	Proportion in product chlorn.
n-Butane	−101°	1·34 (1)	0·28 (1)	*n*-Butane	−33°	1·32 (2)	0·48 (1)
,, ...	− 80	1·21 (9)	0·32 (3)	*iso*Butane	−80	4·01 (3)	0·92 (2)
,, ...	− 67	1·18 (2)	0·39 (1)	,, ...	−33	—	2·28 (1)

raised but fluorination appears to be unaffected. We believe that the apparent insensitivity of this fluorination to changes in temperature is due to the reaction's occurring at quite high temperature in the gas phase of the bubbles. As a bubble forms at the inlet some butane will evaporate into it (vapour pressure [1] of butane at −60° is 43 mm.) and then react almost instantaneously. The heat of reaction will warm the bubble and thereby increase the rate of evaporation of the hydrocarbon. This butane will in turn react and raise the temperature of the bubble still further (the latent heat of vaporisation [2] of butane is 5·3 kcal./mole compared with approximately 100 kcal./mole for the heat of the reaction [3]). It is possible, therefore, that the bulk of the reaction may occur in the vapour phase at temperatures very much higher than the surrounding liquid. In agreement with this, the distribution of the products in fluorination at −80° was considerably affected by slight changes in the sinter at the inlet, *i.e.*, changes in the site at which the bubbles are formed had a greater effect on the reaction than a 70° change in temperature.

The chlorination probably also occurs partly in the gas phase, but the heat of reaction is much less (*ca.* 25 kcal./mole), and some of the reaction may occur in the liquid. This belief is supported by some chlorinations in solvent. A dilute solution of chlorine in tetrachloroethane was added to a dilute solution of butane in the same solvent. The solution was irradiated for half an hour at −35° ± 5° before being analysed. The distribution of monochlorides (primary : secondary = 0·53) was not greatly different from that obtained with gaseous chlorine. An attempt to apply the same procedure to fluorine was thwarted by the insolubility of fluorine in either tetrachloroethane or carbon tetrachloride.

The present work failed to give results for a really quantitative comparison of fluorination and chlorination, but it is the first precise study of aliphatic mono-fluorination. Attention has now been turned to gas-phase reactions.

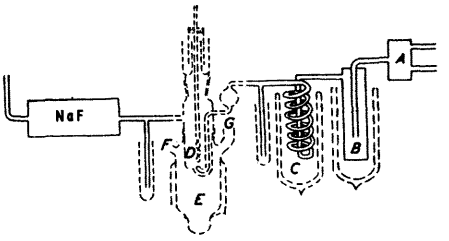
Apparatus (*see Figure*).—Fluorine (from a generator) or chlorine (from a cylinder) was mixed with a metered flow of " oxygen free " nitrogen in vessel *A* and then passed through trap *B* (at −80°) and coil *C* in which the gas was cooled to the reaction temperature. In " Pyrex " reaction vessel *D* the inlet tube ended in a coarse sinter. Vessel *D* fitted into a second glass vessel *E*, the lower half of which formed a silvered Dewar flask. A low-boiling solvent [ethylene, b. p. −101°; " Arcton 3 " (CF_3Cl), b. p. −81°; hydrogen bromide, b. p. −67°; ammonia, b. p. −33°) was condensed into *E* through inlet *F*, and its level in *E* kept above the level of the hydrocarbon inside vessel *D*. The outside of *E* was illuminated by two 100-watt lamps.

The products from fluorinations were poured into a cold vessel containing anhydrous sodium fluoride and samples were taken directly from this vessel for injection into the gas-phase

[1] Wackher, Linn, and Grosse, *Ind. Eng. Chem.*, 1945, **37**, 464.
[2] Aston and Messerly, *J. Amer. Chem. Soc.*, 1940, **62**, 1917.
[3] Tedder, *Chemistry and Industry*, 1955, 508.

chromatography column. Products of chlorinations were left in the reaction vessel for ½ hr. after the supply of chlorine had been stopped, while the nitrogen stream continued and entrained out any unchanged chlorine and the hydrogen chloride formed.

Gas-phase Chromatography.—A conventional chromatography column, of 9 mm. " Pyrex " tubing, was packed with Celite 545 and dinonyl phthalate, according to James and Martin's method.[4] The effective length was 7 ft. The fractions were detected after elution by the change in thermal conductivity of the gas stream as measured by the usual katharometer device. The whole column and the katharometers were maintained at a constant temperature



Thick lines represent copper; broken lines glass.

according to the products being analysed. The carrier gas was " oxygen free " nitrogen flowing at 30 c.c./min. The products were identified by comparing their elution times with synthetic mixtures of authentic fluoro- and chloro-butanes. By studying synthetic mixtures it was confirmed that the areas under the peaks of the chromatogram were proportional to the weight of isomers injected. No products formed by fission of carbon bonds were detected, and the total yield of polyhalogenated compounds was less than 0·1% under the conditions described. Small amounts of butenes may have been formed but these could not be separated from the large excess of unchanged butane. An average of five chromatograms was obtained for each halogenation.

The authors thank Imperial Chemical Industries (General Chemicals Division) for the loan of a fluorine generator and for supplies of " Arcton 3," the British Petroleum Company for a gift of *n*-butane, and the Director of the Chemical Research Laboratory, Teddington, for assistance in supplying *n*-butane and *iso*butane. One of them (P. C. A.) is indebted to the D.S.I.R. for a maintenance grant.

THE UNIVERSITY, SHEFFIELD. [*Received, May 13th,* 1957.]

[4] James and Martin, *Biochem. J.*, 1952, **50**, 679.

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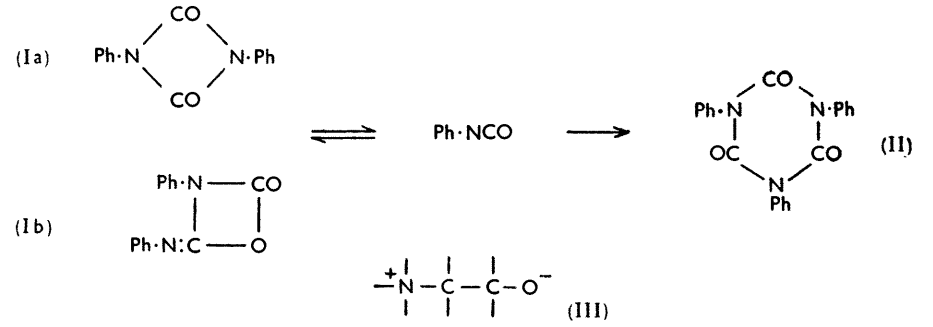
880. *The Polymerisation of Aromatic* iso*Cyanates.*

By J. IDRIS JONES and N. G. SAVILL.

THE chemistry of *iso*cyanates was recently reviewed by Arnold, Nelson, and Verbanc.[1] Catalysts such as pyridine, methylpyridines, triethylamine, *N*-methylmorpholine,[2] and triethylphosphine and other alkyl- or dialkylaryl-phosphines induce dimerisation of phenyl *iso*cyanate. The symmetrical structure (Ia) was originally assigned to the dimer, but an alternative (Ib) has been postulated and some support presented. Crystallographic and infrared studies support structure (Ia), but it is possible that a catalysed rearrangement occurs in solution. When heated with a small amount of potassium acetate phenyl *iso*cyanate gives the trimer (II); sodium benzoate in dimethylformamide is also a useful catalyst for the trimerisation.[3]

[1] Arnold, Nelson, and Verbanc, *Chem. Rev.*, 1957, **57**, 47; *J. Chem. Educ.*, 1957, **34**, 158.
[2] Kogon, *J. Amer. Chem. Soc.*, 1956, **78**, 4911.
[3] Balon, Barthel, Kehr, Langerak, Pelley, Simons, Smeltz, and Stallmann, Abs. Papers, 130th Meeting, Amer. Chem. Soc. Atlantic City, N.J. Sept. 1956, p. 15P.

In an attempt to prepare *N*-substituted oxazolid-2-ones by condensation of epoxides with aromatic *iso*cyanates, a trace of pyridine being used as catalyst, it was discovered that trimerisation of the *iso*cyanate occurred exclusively under these conditions. Thus, phenyl *iso*cyanate in solution in ethylene oxide, propylene oxide, styrene oxide, or epichlorohydrin with a trace of pyridine gave high yields of triphenyl *iso*cyanurate (II)



when kept; no reaction occurred in absence of pyridine. Tertiary bases open the epoxide ring [4] and the catalytic action in this case is believed to be due to the initial formation of structure (III). Cetylpyridinium chloride also had some catalytic activity, a 48% yield of trimer being obtained in 1 month with 2% of this catalyst. Whilst the dimerisation is reversible [2] the trimerisation is irreversible, and when phenyl *iso*cyanate dimer was dissolved in epichlorohydrin containing a catalytic amount of pyridine, the product was triphenyl *iso*cyanurate.

The behaviour of diphenylyl and 1- and 2-naphthyl *iso*cyanates has also been studied. With epichlorohydrin and a small amount of pyridine, and careful exclusion of moisture, some trimerisation always occurred. The m. p.s reported by Raiford and Freyermuth [5] for the corresponding dimers obtained by polymerisation with triethylphosphine [270° (decomp.), ~296° (sublimes), and 196—197°, compared with 374°, 335°, and 344°] support the trimeric structures, as do the infrared absorption spectra. Kogon [2] observed that triphenyl *iso*cyanurate and other tri-(*ortho*-substituted aryl) *iso*cyanurates have one carbonyl absorption band at 1703—1694 cm.$^{-1}$. We find that triphenyl *iso*cyanurate gives a single absorption band at 1711 cm.$^{-1}$; the other three products give single peaks in the same region (see Table). The spectrum of dimeric phenyl *iso*cyanate, on the other hand, exhibits a twin carbonyl absorption band at 1773 and 1756 cm.$^{-1}$. In contrast to the spectra of tri-(*para*-substituted aryl) *iso*cyanurates [2]—three main absorption peaks in the range 1766—1680 cm.$^{-1}$—that of trisdiphenylyl *iso*cyanurate had a single band at 1709 cm.$^{-1}$.

Trimer of	M. p.	C=O band (cm.$^{-1}$)	Found (%), C	H	N	Requires (%), C	H	N
Phenyl *iso*cyanate	285°	1711	70·3	4·2	11·8	70·6	4·2	11·8
Diphenylyl *iso*cyanate	374	1709	79·8	4·8	7·1	80·0	4·7	7·2
1-Naphthyl ,, ...	335	1713	77·8	4·3	7·9	78·1	4·2	8·3
2-Naphthyl ,, ...	344	1700	77·7	4·0	8·3	78·1	4·2	8·3

The dimeric and trimeric forms of 2 : 4-di*iso*cyanatotoluene have been prepared.[1,3,6,7] We have found that in propylene oxide or epichlorohydrin, with pyridine as catalyst, this di*iso*cyanate is converted into a resin. Presumably, some of the *ortho* as well as the *para*

[4] Bradley, Forrest, and Stephenson, *J.*, 1951, 1592.
[5] Raiford and Freyermuth, *J. Org. Chem.*, 1943, **8**, 230.
[6] Saunders and Hardy, *J. Amer. Chem. Soc.*, 1953, **75**, 5439.
[7] Seifken, *Annalen*, 1949, **562**, 75.

*iso*cyanate groups have been involved in the polymerisation, the resin appearing to be highly cross-linked.

Experimental.—Trimerisation of phenyl iso*cyanate.* Phenyl *iso*cyanate (10 g.) in epichlorohydrin (8 g.) with 1 drop of pyridine was kept at room temperature for 2 days. The crystalline product (10 g.) obtained was triphenyl *iso*cyanurate, m. p. 285° (lit. 282°). Similarly a quantitative yield of the *iso*cyanurate was obtained from the *iso*cyanate (5 g.) after 3 days at 0° in ethylene oxide (10 g.) containing 2 drops of pyridine. In both cases there was slight contamination from the product of the pyridine–epoxide reaction. Extensive trimerisation was also observed in propylene oxide and styrene oxide with pyridine as catalyst. Phenyl *iso*cyanate (5 g.) was unaffected in dry benzene, chloroform, or light petroleum (b. p. 60—80°) (10 g.) with 1 drop of pyridine. In pyridine (5 g.) with 2 drops of propylene oxide the *iso*cyanate (5 g.) trimerised to the extent of 92% in 24 hr. Phenyl *iso*cyanate with 2% by weight of cetylpyridinium chloride gave 48% of trimer after 1 month.

Conversion of dimer into trimer. Phenyl *iso*cyanate dimer (1 g.) was dissolved in warm epichlorohydrin (5 g.) containing 1 drop of pyridine. After 5 days at room temperature some trimer had separated. This was removed, and addition of light petroleum (b. p. 60—80°) to the filtrate caused precipitation of more trimer, m. p. 273—274°. Chromatography on alumina gave altogether 0·85 g. of triphenyl *iso*cyanurate, m. p. 282°.

Polymerisation of diphenylyl and 1- *and* 2-*naphthyl* iso*cyanates.* The *iso*cyanate (5 g.) from a sealed ampoule was dissolved in epichlorohydrin (10 g.) to which was added 2 drops of pyridine. With diphenylyl *iso*cyanate extensive deposition of crystals occurred during 24 hr.; with 1- and 2-naphthyl *iso*cyanate only after 1 month was there appreciable crystallisation. Despite precautions to exclude moisture, some water was picked up during the working up, which involved addition of light petroleum (b. p. 60—80°) followed by extraction of the precipitated solids with hot acetone. It was subsequently found that the starting materials had also been exposed to moisture before being sealed. The presence of ureas complicated separation of the trimers. Thus, some *sym*-bisdiphenylyl-, -di-1-naphthyl-, and -di-2-naphthyl-ureas, m. p.s 321°, 298°, and 310°, were recovered, dimethylformamide proving a useful solvent for crystallisation. From the acetone-soluble portions the trimeric *iso*cyanates were isolated in low yields ($\gtrsim$22%).

Polymerisation of 2 : 4-*di*iso*cyanatotoluene.* A firm gel was obtained when the di*iso*cyanate (4·8 g.) was set aside for 24 hr. in propylene oxide (10 ml.) containing 1 drop of pyridine. On removal of the solvent at 100° *in vacuo* a completely insoluble resin was obtained. 2 : 4-Di-*iso*cyanatotoluene (7 g.) in epichlorohydrin (10 ml.) containing 1 drop of pyridine gave a similar insoluble polymer during 24 hr. at room temperature.

Infrared absorption spectra. The compounds were examined as mulls in Nujol, a modified Hilger D 209 double-beam instrument being used.

This work is published by permission of the Director of the Laboratory. The authors are indebted to Mr. W. Kynaston for the infrared absorption data.

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881. *Some α- and β-*DL-*Aspartyl Peptides.*

By Y. LIWSCHITZ and A. ZILKHA.

PEPTIDES composed of two amino-acids, each of which contains an asymmetric carbon atom, should exist in two racemic forms. The fact that in only relatively few instances were both actually isolated may be due either to the preferential formation of one racemic form under the conditions of the reaction, or to the formation of mixed crystals.[1] We have now isolated the two stereoisomeric racemates of β-DL-aspartyl-DL-α-aminobutyric acid and of β-DL-aspartyl-DL-valine, and of their ethyl esters and *N*-benzyl derivatives.

Synthesis of ethyl (*N*-benzyl-α-DL-aspartyl)-DL-α-aminobutyrate from the mixed

[1] Fischer, " Untersuchungen ueber Aminosaeuren, Polypeptide und Proteine (1899—1906)," Julius Springer, Berlin, 1906, p. 42.

anhydride of *N*-benzyl-DL-aspartic acid and chloroformic acid [2] gave a 30% yield of material of m. p. 86°, together with an isomeric compound (A), m. p. 186° in, 15% yield. The latter differed from ethyl (*N*-benzyl-β-DL-aspartyl)-DL-α-amino-*n*-butyrate (B) prepared by the maleic anhydride method,[3] and so must be a second modification of either the α- or the β-isomer. This was confirmed as follows.

Both the free dipeptide ester and the dipeptide derived from substance (A) gave a negative biuret reaction and a blue spot with ninhydrin on paper chromatograms, in contradistinction to the α-isomer which gave a positive biuret reaction and a purple spot. α-Isomers of all known ethyl esters of (*N*-benzyl-DL-aspartyl)-dipeptides melt at least 50° below the corresponding β-derivatives and are more soluble in water and ethanol. Thus in accordance with previous findings,[2,4] substance (A) belongs to the β-series.

Coupling DL-valine ethyl ester with the same mixed anhydride of *N*-benzyl-DL-aspartic acid yielded the *N*-benzyl-dipeptide ester (B) (13%; m. p. 170°) (no α-derivative could be isolated) which represented a second racemic modification of the β-isomer according to the above criteria; the substance (A) obtained in our previous work [3] melted at 179—181°.

It has been shown [5-7] that the infrared spectra of optically " pure " (LL, DD) dipeptides differ markedly from those of the " mixed " (LD, DL) diastereoisomers, especially in the appearance of strong additional bands in the spectra of the latter. On this basis it seems that the higher-melting isomers, designated (A), are of the " mixed " type. Strong bands in the spectrum of ethyl (*N*-benzyl-β-aspartyl)-α-aminobutyrate (A) but not in that of the (B) compound occur at 3·0, 3·3, 6·6, and 7·6 μ. In ethyl (*N*-benzyl-α-aspartyl)-α-aminobutyrate, the C=O stretching band appears at 5·95 and not at 6·0 μ, as for all β-derivatives. Strong bands present in the spectrum of (*N*-benzyl-β-aspartyl)valine ethyl ester (A), but not in that of the (B) isomer, appear at 3·3 and 7·4 μ.

β-Alanine ethyl ester coupled to yield almost exclusively the (*N*-benzyl-α-DL-aspartyl)-β-alanine ester from which the free dipeptide was prepared in the usual manner.

Use of a 4-molar excess of the amino-ester in the coupling reaction resulted in preferential formation of α-dipeptides. Thus (*N*-benzyl-α-DL-aspartyl)-DL-alanine ethyl ester was formed with the use of an excess of DL-alanine ester, but not when merely equivalent amounts were used.

Efforts to obtain the free α-DL-aspartyl-DL-alanine were unsuccessful, and on hydrogenolysis of (*N*-benzyl-α-DL-aspartyl)-DL-alanine (which could not be isolated from the mixture after hydrolysis of the ester) the peptide bond was completely disrupted and only the two component amino-acids were detected on paper-chromatograms. That the peptide bond was still intact after the hydrolysis was unequivocally proved by the absence of a positive ninhydrin-reacting substance.

Experimental—M. p.s were determined in a Fisher–Johns apparatus and the ascending method of paper partition chromatography was used (80% phenol). Infrared absorption spectra were examined in potassium bromide discs with a Baird double-beam instrument.

Ethyl (N-*benzyl*-β-DL-*aspartyl*)-DL-α-*aminobutyrate* (*A*) *and ethyl* (N-*benzyl*-α-DL-*aspartyl*)-DL-α-*aminobutyrate*. To a cooled solution of the mixed anhydride of *N*-benzyl-DL-aspartic and chloroformic acid [2] (from 4·4 g. of *N*-benzyl-DL-aspartic acid) were added triethylamine (2 g.) and then ethyl DL-α-aminobutyrate (2·6 g.). After the mixture had been kept overnight at room temperature, triethylamine hydrochloride was filtered off and the solution evaporated *in vacuo* to dryness. The residue was dissolved in acetone (30 ml.) and left at 0° for 4 days. There separated *ethyl* (N-*benzyl*-β-DL-*aspartyl*)-DL-α-*aminobutyrate* (*A*) (1 g., 15%), m. p. 181°,

[2] Liwschitz and Zilkha, *J. Amer. Chem. Soc.*, 1954, **76**, 3698.
[3] *Idem, ibid.*, 1955, **77**, 1265.
[4] LeQuesne and Young, *J.*, 1952, 24.
[5] Otey and Greenstein, *Arch. Biochem. Biophys.*, 1954, **53**, 501.
[6] Ellenbogen, *J. Amer. Chem. Soc.*, 1956, **78**, 369.
[7] Blackburn and Tetley, *Biochim. Biophys. Acta*, 1956, **20**, 423.

raised to 186° on recrystallization from ethanol or water (Found: C, 60·6; H, 7·1; N, 8·2. $C_{17}H_{24}O_5N_2$ requires C, 60·6; H, 7·1; N, 8·3%).

To the filtrate was added dry ether until the appearance of cloudiness. Storage at 0° for 1 week gave the *N*-benzyl-α-dipeptide ester, m. p. 80° (2 g., 30%). After two recrystallizations from water it melted at 86°. It gave a positive bluish biuret reaction (Found: C, 60·2; H, 7·0; N, 8·3%).

Ethyl α-DL-*aspartyl*-DL-α-*aminobutyrate*. This *compound*, obtained in almost quantitative yield by hydrogenolysis of the preceding compound,[2] had m. p. 187° (from water–acetone) and gave positive ninhydrin and biuret reactions [Found: N, 11·1; N (Van Slyke), 5·6. $C_{10}H_{18}O_5N_2$ requires N, 11·4; N (Van Slyke), 5·7%].

α-DL-*Aspartyl*-DL-α-*aminobutyric acid*. Ethyl (*N*-benzyl-α-DL-aspartyl)-DL-α-aminobutyrate (1·6 g.) was left in N-lithium hydroxide (14 ml.) for 90 min. at room temperature. The solution was then acidified with hydrochloric acid and evaporated to dryness *in vacuo*. The residue was dissolved in glacial acetic acid (50 ml.) and hydrogenated with 0·3 g. of catalyst. Filtration, evaporation *in vacuo*, dissolution of the residue in hot absolute ethanol, re-evaporation, and recrystallization from water–acetone yielded the free *dipeptide*, m. p. 202° (0·45 g., 43%), giving a bluish biuret reaction and a purple spot on paper chromatograms (R_F 0·31) [Found: C, 43·5; H, 6·4; N, 12·5; N (Van Slyke), 6·3. $C_8H_{14}O_5N_2$ requires C, 44·0; H, 6·4; N, 12·8; N (Van Slyke), 6·4%].

Ethyl β-DL-*aspartyl*-DL-α-*aminobutyrate* (*A*). Hydrogenolysis as for the corresponding α-derivative gave an almost quantitative yield of this ester as *monohydrate* (from aqueous ethanol), m. p. 114°, giving a negative biuret and a positive ninhydrin test [Found : N, 10·6; N (Van Slyke), 5·4. $C_{10}H_{18}O_5N_2,H_2O$ requires N, 10·6; N (Van Slyke), 5·3%].

β-DL-*Aspartyl*-DL-α-*aminobutyric acid* (*A*). Ethyl (*N*-benzyl-β-DL-aspartyl)-DL-α-aminobutyrate (A) (0·5 g.) was left in N-sodium hydroxide (5 ml.) for 2 hr. at room temperature. After acidification with hydrochloric acid the solution was evaporated to dryness. The residue was taken up in glacial acetic acid (20 ml.) and catalyst (0·2 g.) added. Hydrogenolysis was carried out for 6 hr. The recovered *dipeptide* had m. p. 208° (0·12 g., 30%), with a negative biuret reaction and giving a bluish spot on paper chromatograms (R_F 0·39) [Found: C, 43·0; H, 6·3; N, 12·4; N (Van Slyke), 6·3%)].

(N-*Benzyl*-β-DL-*aspartyl*)-DL-*valine ethyl ester* (B). To a cooled solution of the mixed anhydride from 4·4 g. of *N*-benzyl-DL-aspartic acid was added DL-valine ethyl ester (5·8 g.). Treatment was then continued as in the coupling with ethyl DL-α-aminobutyrate but the mixture was left at 0° for 2 weeks, giving an *ester* (0·9 g., 13%), m. p. 170° (from ethanol) (Found: C, 61·8; H, 7·4; N, 7·9. $C_{18}H_{26}O_5N_2$ requires C, 61·6; H, 7·4; N, 8·0%).

β-DL-*Aspartyl*-DL-*valine ethyl ester* (*B*), obtained in almost quantitative yield by hydrogenolysis, had m. p. 118° (from ethanol–ether) and gave a positive ninhydrin but a negative biuret reaction [Found: C, 47·3; H, 7·7; N, 10·2; N (Van Slyke), 5·1. $C_{11}H_{20}O_5N_2,H_2O$ requires C, 47·2; H, 7·9; N, 10·0; N (Van Slyke), 5·0%].

β-DL-*Aspartyl*-DL-*valine* (*B*). The *N*-benzyl-dipeptide ester (0·8 g.) was left in N-lithium hydroxide (7 ml.) for 2 hr. at room temperature, acidified with hydrochloric acid, and evaporated *in vacuo*. Further treatment and isolation as above gave the acid (0·2 g., 38%), m. p. 224° (from water–acetone) [negative biuret reaction and a blue spot on paper chromatograms (R_F 0·43)] [Found: C, 45·8; H, 6·9; N, 11·7; N (Van Slyke), 6·0. Calc. for $C_9H_{16}O_5N_2$: C, 46·5; H, 6·9; N, 12·1; N (Van Slyke), 6·0%].

(N-*Benzyl*-α-DL-*aspartyl*)-β-*alanine ethyl ester*. To a cooled solution of the mixed anhydride prepared from 11·2 g. of *N*-benzyl-DL-aspartic acid was added β-alanine ethyl ester (11·7 g.). After 2 days at 0°, some (*N*-benzyl-β-DL-aspartyl)-β-alanine ethyl ester (1·1 g., 7%; m. p. 197°), identified by mixed m. p., was removed and the filtrate evaporated *in vacuo*. The residue was taken up in hot acetone (50 ml.) and left at 0° for 2 days. The ester which crystallized was filtered off and washed with acetone; it (10 g., 63%) had m. p. 132°. Recrystallization from ethanol raised the m. p. to 140°. The *ester* gave a positive biuret reaction (Found: C, 59·8; H, 6·8; N, 8·8. $C_{16}H_{22}O_5N_2$ requires C, 59·6; H, 6·8; N, 8·7%).

β-DL-*Aspartyl*-β-*alanine ethyl ester*, obtained in almost quantitative yield by hydrogenolysis of the preceding compound, had m. p. 188° (from ethanol), and gave positive ninhydrin and biuret reactions (Found: C, 46·9; H, 6·8; N, 12·0. $C_9H_{16}O_5N_2$ requires C, 46·5; H, 6·9; N, 11·9%).

α-DL-*Aspartyl*-β-*alanine*. (*N*-Benzyl-α-DL-aspartyl)-β-alanine ethyl ester (3 g.) was left in

N-sodium hydroxide (21 ml.) for 1 hr. at room temperature. After acidification with hydrochloric acid, the *dipeptide* was obtained in the usual manner (0·5 g., 26%), having m. p. 196° (from water–acetone). It gave a positive biuret reaction and a purple spot on paper chromatograms (R_F 0·36) [Found: C, 41·1; H, 6·1; N, 13·6; N (Van Slyke), 6·9. $C_7H_{12}O_5N_2$ requires C, 41·1; H, 5·9; N, 13·7; N (Van Slyke), 6·9%].

(N-*Benzyl*-α-DL-*aspartyl*)-DL-*alanine ethyl ester*. To a cooled solution of the mixed anhydride from 6·6 g. (0·03 mole) of *N*-benzyl-DL-aspartic acid, was added DL-alanine ethyl ester (14 g., 0·12 mole). The mixture was left for 48 hr. at room temperature and then evaporated *in vacuo*. The residue was taken up in acetone (40 ml.) and left at 0° for 4 days. The crystals were filtered off (1·6 g.; m. p. 140°). Dry ether was added to the filtrate until cloudiness and the whole left at 0° for several more days. The resulting, still somewhat sticky precipitate was washed with acetone and filtered off. An additional 1·1 g. were obtained (total yield of both fractions 28%). On recrystallization from ethanol the m. p. was raised to 144°. In contrast to the β-isomer this *ester* gave a bluish biuret reaction and reacted negatively to copper carbonate (Found: C, 59·6; H, 6·9; N, 8·8. $C_{16}H_{22}O_5N_2$ requires C, 59·6; H, 6·8; N, 8·7%).

α-DL-*Aspartyl*-DL-*alanine ethyl ester*, obtained in almost quantitative yield by hydrogenolysis of the preceding compound, had m. p. 188° (from water–acetone) and gave positive biuret and ninhydrin reactions [Found: C, 45·7; H, 6·8; N, 11·8; N (Van Slyke), 6·1. $C_9H_{16}O_5N_2$ requires C, 46·5; H, 6·9; N, 11·9; N (Van Slyke), 6·0%].

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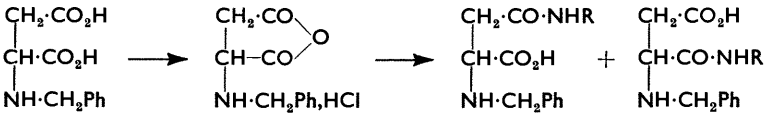
882. *Preparation of Aspartyl Amides and Peptides* via N-*Benzyl*-DL-*aspartic Anhydride Hydrochloride.*

By A. ZILKHA and Y. LIWSCHITZ.

AN additional method for the preparation of aspartyl amides and peptides is based on the use of *N*-benzyl-DL-aspartic anhydride hydrochloride. Treatment of *N*-benzyl-DL-aspartic acid with acetic anhydride causes acetylation of the secondary amino-group in addition to the ring closure,[1] but using cold acetyl chloride–acetic acid (1 : 1) affords *N*-benzyl-DL-aspartic anhydride hydrochloride in 80% yield. If the proportion of acetyl chloride to acetic acid is 3 : 1, the product is *N*-benzyl-DL-aspartic acid hydrochloride, whose identity was proved by comparison with a sample prepared by evaporation *in vacuo* of a solution of *N*-benzyl-DL-aspartic acid in hydrochloric acid.



Reaction of this anhydride with amines and free amino-acid esters in water or acetone gave mainly β-derivatives, accompanied, in some cases, by the α-isomer. The preferential formation of β-amides and peptides when bulky groups are involved is probably due to steric effects, since in the reaction with ammonia, only α-asparagine was isolated.

Reaction with ethyl DL-α-aminobutyrate in acetone afforded two racemic modifications of the β-peptide in addition to the α-isomer.[2] In this and similar instances the isomers were separated by fractional crystallization from ethanol.

Known substances [3–5] were identified by mixed m. p.s and the nature of the linkage in

[1] Liwschitz, Zilkha, and Amiel, *J. Amer. Chem. Soc.*, 1956, **78**, 3067.
[2] Liwschitz and Zilkha, preceding note.

new amides or peptides was determined by the biuret reaction,[6] reaction with copper carbonate,[7] and the colour with ninhydrin on paper chromatograms.[8]

Experimental.—M. p.s were determined in a Fisher–Johns apparatus.

N-*Benzyl*-DL-*aspartic anhydride hydrochloride*. *N*-Benzyl-DL-aspartic acid (11·2 g.) was dissolved in acetyl chloride (40 ml.) and acetic acid (40 ml.) and left overnight at room temperature. The salt which crystallized was filtered off and washed with a little acetic acid and ether: it (8·6 g., 80%) had m. p. 157°; it must be protected from moisture and should always be used freshly prepared (Found: N, 5·5; Cl, 14·6. $C_{11}H_{12}O_3NCl$ requires N, 5·8; Cl, 14·7%).

N-*Benzyl*-DL-*aspartic acid hydrochloride*. (*a*) *N*-Benzyl-DL-aspartic acid (11·2 g.) was dissolved in acetyl chloride (60 ml.) and acetic acid (20 ml.). Precipitation began almost at once. After 1 hr. at room temperature, the *salt* was filtered off and washed with ether; it (13 g.) had m. p. 87° (Found: N, 5·1; Cl, 13·5. $C_{11}H_{14}O_4NCl$ requires N, 5·4; Cl, 13·5%). (*b*) *N*-Benzyl-DL-aspartic acid (1 g.) was dissolved in concentrated hydrochloric acid and the solution evaporated *in vacuo*. The hydrochloride was obtained quantitatively with m. p. 87°.

Reactions of alkylamines or amino-esters with *N*-benzyl-DL-aspartic anhydride hydrochloride were carried out according to one of three procedures for each of which one typical example is given, the remainder being summarized in the Table. That with ethyl DL-α-aminobutyrate, which involves the separation of three isomers, is described in full.

(a) N^2-*Benzyl*-N^1-*ethyl*-DL-*asparagine*. The anhydride (1·2 g.) and ethylamine (0·5 g.) in acetone (10 ml.) were heated under reflux for 30 min., then left at room temperature overnight. The precipitate, recrystallized from ethanol, had m. p. 208° (0·4 g., 32%).

(b) N-*Benzyl*-DL-α-*asparagine*. The anhydride (1·5 g.) was dissolved in 25% aqueous ammonia (10 ml.) at 0° and the solution was evaporated on the water-bath. The residue was freed from ammonium chloride by trituration with cold methanol, then having m. p. 196° (1 g., 71%). The m. p. was erroneously reported as 180° in a previous communication.[6]

(c) (N-*Benzyl*-β-DL-*aspartyl*)*glycine ethyl ester*. The anhydride (2·4 g.) was added to a solution of glycine ethyl ester (2·06 g.) in acetone (15 ml.). Crystallisation started after about 15 min., but the mixture was left at room temperature overnight. The product, washed with acetone and recrystallized from a small quantity of ethanol, had m. p. 201° (1·8 g., 59%).

Preparation of N^2-*benzyl*-DL-*aspartyl amides and peptide esters.*

(Recrystallized from ethanol, if not indicated otherwise.)

Anhydride treated with	Type of deriv.	Yield (%)	M. p.	Method
Ethylamine	β	48	208°	*b*
Allylamine	β	60	211	*a*
*cyclo*Hexylamine	α [a]	17	189	*a*
	β [a]	33	245 [b]	
Benzylamine	β	74	215 [c]	*b*
p-Toluidine	α [a]	16	184 [d]	*a*
	β [a]	70	224 [c]	
α-Naphthylamine	β	35	199 [e]	*a*
DL-α-Alanine Et ester	β	53	197	*c*
β-Alanine ,,	β	50	195	*c*
DL-Valine ,,	β	40 [e]	170 [f]	*c*

[a] The isomers were separated by fractional crystallization from ethanol. [b] Owing to insolubility the substance was purified by dissolution in alkali, precipitation with hydrochloric acid, and washing with water and hot ethanol. [c] Recryst. from water. [d] New (Found: C, 69·0; H, 6·5; N, 8·9. $C_{18}H_{20}O_3N_2$ requires C, 69·2; H, 6·4; N, 8·9%). Hydrogenolysis yielded N-*tolyl*-DL-α-*asparagine*, m. p. 235° (from water) (Found: C, 59·2; H, 6·3; N, 12·2. $C_{11}H_{14}O_3N_2$ requires C, 59·4; H, 6·3; N, 12·6%). [e] The mixture was kept at 0° for 2 weeks. [f] Recryst. from a very small volume of ethanol.

Ethyl (N-*benzyl*-α- *and* -β-DL-*aspartyl*)-DL-α-*aminobutyrate*. The anhydride (2·4 g.) was added to a solution of ethyl DL-α-aminobutyrate (2·6 g.) in acetone (20 ml.) and left at room

[3] Liwschitz, Edlitz-Pfeffermann, and Lapidoth, *J. Amer. Chem. Soc.*, 1956, **78**, 3069.
[4] Frankel, Liwschitz, and Amiel, *ibid.*, 1953, **75**, 330.
[5] Liwschitz and Zilkha, *ibid.*, 1955, **77**, 1265.
[6] *Idem, ibid.*, 1954, **76**, 3698.
[7] Desnuelle and Bonjour, *Biochim. Biophys. Acta*, 1952, **9**, 356.
[8] LeQuesne and Young, *J.*, 1952, 24.

temperature overnight. After cooling in an ice-bath, the precipitate consisting of a mixture of two stereoisomeric racemic β-derivatives and ethyl DL-α-aminobutyrate hydrochloride was collected. Trituration with a small volume of water resulted in the practical removal of the ester hydrochloride. After recrystallization from ethanol, ethyl (*N*-benzyl-β-DL-aspartyl)-α-aminobutyrate, m. p. 183° (0·9 g., 27%), was obtained.[2] The m. p. was raised to 186° by a second recrystallization from ethanol. The ethanolic mother-liquor was evaporated and the residue recrystallized from water, yielding the second racemic modification of the β-dipeptide derivative, m. p. 161° (0·5 g., 15%).[2] To the original filtrate of the mixture (acetone) ether was added until the appearance of cloudiness and the whole was left at 0° for 7 days. Ethyl (*N*-benzyl-α-DL-aspartyl)-DL-α-aminobutyrate which crystallized was recrystallized from water, then having m. p. 85° (1 g., 30%).

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883. NN′-*Dialkyl*-DL-*asparagines*.

By Y. LIWSCHITZ, YOLAN EDLITZ-PFEFFERMANN, and Y. SHORR.

FEW *NN′*-dialkylasparagines, $NHR'\cdot CH(CO_2H)\cdot CH_2\cdot CO\cdot NHR$, have been reported,[1] apart from such dialkyl derivatives in which R′ is benzyl and which served as an intermediate masking group.[2] However, any desired compound of this class may be prepared by condensation of the appropriate alkylmaleamic acid with an amine, the alkyl radical of which becomes the *N*-substituent (R′). Preparation of alkylmaleamic acids [2] is nearly always quantitative and the subsequent addition of amines to the double bond gives satisfactory yields in most cases. Although for steric reasons β-aspartylamides are produced predominantly, formation of α-isomers has been established in all cases so far encountered, except *NN′*-di-*n*-hexyl-DL-asparagine, by a positive biuret reaction.[3] These derivatives of α-asparagine, however, are soluble in the reaction solvent (pyridine), whereas the β-asparagines are precipitated. In a few cases, when the yield of the α-isomers formed seemed appreciable, their isolation was performed.

TABLE 1. *Preparation of* NN′-*dialkyl*-DL-*asparagines*.

R	R′	Yield (%)	M. p.	Reflux time (min.)	Formula	C (%) Found	C (%) Reqd.	H (%) Found	H (%) Reqd.	N (%) Found	N (%) Reqd.
Pr^n	Bu^n	48	228°	75	$C_{11}H_{22}O_3N_2$	58·0	57·4	9·8	9·6	12·1	12·2
	n-Pentyl	55	229	60	$C_{12}H_{24}O_3N_2$	58·8	59·0	9·4	9·9	11·3	11·4
	*iso*Pentyl	54	216	60	$C_{12}H_{24}O_3N_2$	59·1	59·0	9·6	9·9	11·2	11·4
	n-Hexyl	45	226	60	$C_{13}H_{26}O_3N_2$	60·8	60·4	9·8	10·1	10·6	10·9
Bu^n	*n*-Hexyl	68	214—217	75	$C_{14}H_{28}O_3N_2$	61·3	61·7	10·2	10·4	10·1	10·3
n-Hexyl	Pr^n	47	226	65	$C_{13}H_{26}O_3N_2$	60·1	60·4	9·9	10·1	10·8	10·9
	Pr^i	20	192	150	$C_{13}H_{26}O_3N_2$	61·2	60·4	9·9	10·1	10·7	10·9
	Bu^n	51	220	40	$C_{14}H_{28}O_3N_2$	61·6	61·7	10·2	10·4	10·2	10·3
	n-Pentyl	40	221	120	$C_{15}H_{30}O_3N_2$	63·6	62·9	10·8	10·6	9·5	9·8
	*iso*Pentyl	35	212	120	$C_{15}H_{30}O_3N_2$	63·0	62·9	10·1	10·6	9·7	9·8
	*cyclo*Hexyl	24	197	150	$C_{16}H_{30}O_3N_2$	64·5	64·4	10·2	10·1	9·1	9·4

Experimental.—M. p.s were determined in a Fisher–Johns apparatus.

Preparation of NN′-*dialkyl*-DL-*asparagines*. The *N*-alkylmaleamic acid (0·02 mole) and the

[1] McMillan and Albertson, *J. Amer. Chem. Soc.*, 1948, **70**, 3778.
[2] Liwschitz, Edlitz-Pfeffermann, and Lapidoth, *ibid.*, 1956, **78**, 3069.
[3] Liwschitz and Zilkha, *ibid.*, 1954, **76**, 3698.

amine (0·02 mole) were heated in pyridine (20 ml.) under reflux (for reaction times, etc., see Tables 1 and 2), the product being precipitated. This was washed with acetone and generally recrystallized from aqueous ethanol.

TABLE 2. *Preparation of* NN'-*dialkyl*-DL-*asparagines.*

R = R'	Yield (%)	M. p.	Reflux time (min.)	Formula	C (%) Found	C (%) Reqd.	H (%) Found	H (%) Reqd.	N (%) Found	N (%) Reqd.
Pr^n	87	238°	60	$C_{10}H_{20}O_3N_2$	55·6	55·5	9·0	9·3	12·9	12·9
n-Hexyl	84	221	45	$C_{16}H_{32}O_3N_2$	63·8	63·9	10·5	10·7	9·1	9·3
p-C_6H_4·OMe [a] ...	8	225	60	$C_{18}H_{20}O_5N_2$	61·7	62·6	5·1	5·8	7·9	8·1

[a] N-p-*Methoxyphenylmaleamic acid*, m. p. 200° (Found: C, 59·0; H, 5·0; N, 6·3. $C_{11}H_{11}O_4N$ requires C, 59·6; H, 5·0; N, 6·3%).

TABLE 3. *Isolation of* NN'-*dialkyl*-DL-α-*asparagines.*

R	R'	Yield (%)	M. p.	Reflux time (min.)	Formula	C (%) Found	C (%) Reqd.	H (%) Found	H (%) Reqd.	N (%) Found	N (%) Reqd.
Pr^n	*n*-Hexyl	34	108°	60	$C_{13}H_{26}O_3N_2$	60·0	60·4	9·9	10·1	10·3	10·9
Bu^n	*n*-Hexyl	14	103	75	$C_{14}H_{28}O_3N_2$	61·8	61·7	10·4	10·4	10·2	10·3
n-Hexyl	*iso*Pentyl	16	142	120	$C_{15}H_{30}O_3N_2$	62·2	62·9	10·5	10·6	9·0	9·8

Isolation of NN'-*dialkyl*-DL-α-*asparagines.* The pyridine mother-liquor was evaporated and the residue triturated with acetone. Recrystallization from ethyl acetate resulted in complete separation from small amounts of β-isomer, since the latter, being insoluble in that solvent, could be eliminated by filtration. Results are summarized in Table 3.

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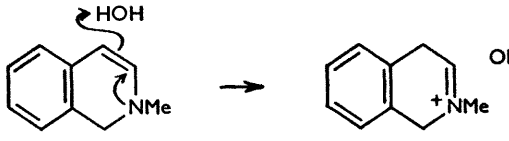
884. *Reduction of Quaternized* iso*Quinoline Derivatives with Sodium Borohydride.*

By R. MIRZA.

*iso*QUINOLINE METHIODIDE is reduced by sodium borohydride in aqueous methanol almost quantitatively to 1 : 2 : 3 : 4-tetrahydro-2-methyl*iso*quinoline (Torossian [1] reports an 85% yield by use of potassium borohydride). Similarly, berberine, which can be regarded as a quaternized *iso*quinoline derivative, is reduced to its tetrahydro-derivative, (±)-canadine, and the methiodide of papaverine gave (±)-laudanosine, both in excellent yields.* However, reduction in dry methanol gave only tars.

A possible mechanism involves preliminary reduction of the metho-salt to 1 : 2-dihydro-2-methyl*iso*quinoline,[3, 4] which in presence of water could be converted into 1 : 4-dihydro*iso*quinolinium hydroxide (I); the latter should be easily reducible to the tetrahydro*iso*quinoline. In absence of water, it is not possible for the 1 : 2-dihydro-2-methyl derivative to go through the process indicated and in view of the labile nature of the 1 : 2-dihydro*iso*quinolines a tarry product is not surprising.



(I)

* Our work was independent of that of Witkop.[2]

[1] Torossian, *Compt. rend.*, 1952, **235**, 1312.
[2] Witkop, *J. Amer. Chem. Soc.*, 1953, **75**, 4474.
[3] Whaley and Robinson, *J. Amer. Chem. Soc.*, 1953, **75**, 2008.
[4] Panouse, *Compt. rend.*, 1951, **233**, 260.

It is known [5] that lithium aluminium hydride reduces *iso*quinoline methiodide to 1 : 2-dihydro-2-methyl*iso*quinoline, berberine to dihydroberberine, and papaverine methiodide to 1 : 2-dihydro-*N*-methylpapaverine. These results are easily understood in view of the mechanism of reduction now proposed. Reductions by lithium aluminium hydride occur in complete absence of water and thus the carbon–carbon double bond in the 1 : 2-dihydro-compound is not thus reducible. Dihydroberberine is readily reduced to (±)-canadine in aqueous methanol by sodium borohydride.

It has been reported that borohydride reduces pyridine methiodide to 1 : 2 : 3 : 6-tetrahydro-1-methylpyridine,[4] methyl nicotinate methiodide to arecoline,[6] methylsempervirine chloride to hexahydromethylsempervirine,[7] and harman methobromide to tetrahydro-*Py*-*N*-methylharman.[8] These compounds have a close relationship to *iso*quinoline salts and a similar mechanism explains their reduction. The necessity for the presence of water has previously not been realised, and may apply in these cases.

Experimental.—Reduction of iso*quinoline methiodide.* Sodium borohydride (500 mg.) and *iso*quinoline methiodide (540 mg.) in methanol (10 ml.) and water (1 ml.) were refluxed for 10 min. After addition of more water (50 ml.) the mixture was extracted with chloroform. Evaporation of chloroform gave a liquid residue which in methanol (10 ml.) gave 1 : 2 : 3 : 4-tetrahydro-2-methyl*iso*quinoline picrate (720 mg.), m. p. and mixed m. p. 147—148°.

Other reductions. Berberine hydrochloride (1·0 g.) on reduction gave (±)-canadine (720 mg.), m. p. 177—178°; papaverine methiodide (1·0 g.; anhyd.) gave (±)-laudanosine (690 mg.), m. p. 113—114°; dihydroberberine (50 mg.) gave (±)-canadine (20 mg.). In all these reductions an equal weight of sodium borohydride was used. The products were purified by sublimation and their identities established by mixed m. p.

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[*Received, May 30th*, 1957.]

[5] Karrer and Schmid, *Helv. Chim. Acta*, 1949, **32**, 960.
[6] Panouse, *Compt. rend.*, 1951, **233**, 1200.
[7] Witkop, *J. Amer. Chem. Soc.*, 1953, **75**, 3361.
[8] Gray, Spinner, and Cavallito, *ibid.*, 1954, **76**, 2793.

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885. *The Chemistry of Gum Labdanum. Part III.* A Proof of the β-Configuration of the* $C_{(9)}$ *Side-chain of Labdanolic Acid.*

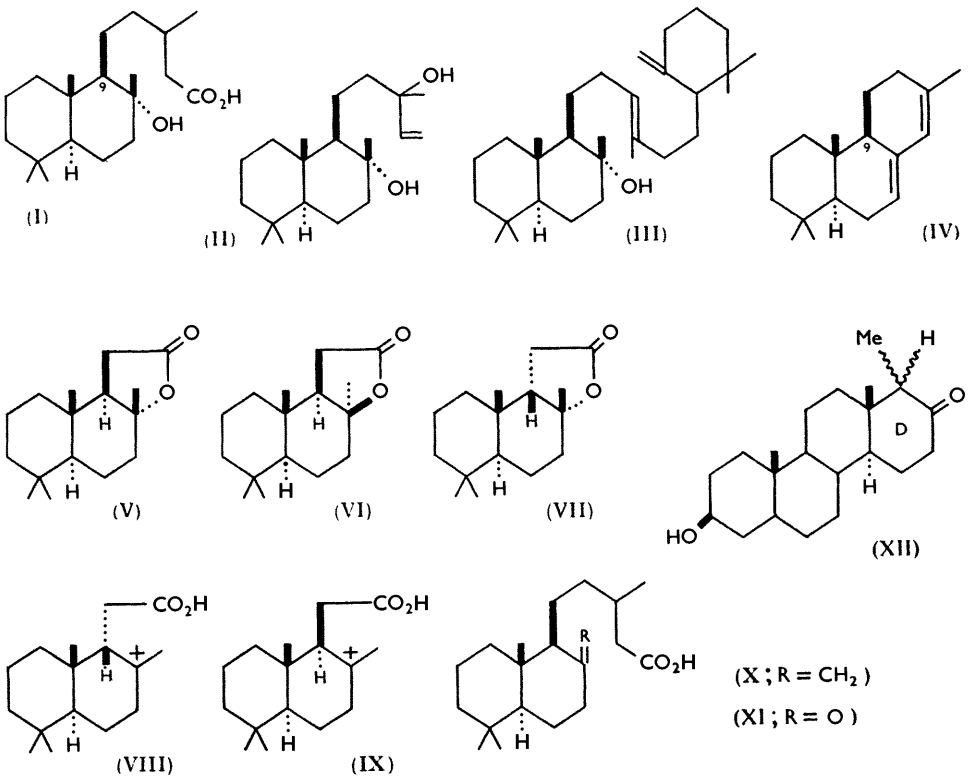
By J. D. COCKER and T. G. HALSALL.

THE structure of labdanolic acid has already been shown to be (I), it being assumed that the $C_{(9)}$ side-chain of sclareol (II) and ambrein (III), with which labdanolic acid has been related, has the β-configuration.[1] Although there is strong circumstantial evidence in favour of this configuration it has not yet been proved. Rotational evidence [2-4] concerning certain degradation products of sclareol (and manoöl) (*e.g.*, IV) shows that these have the carbon chain β at $C_{(9)}$. If it is assumed that inversion does not occur during the preparation of the degradation products then the $C_{(9)}$ side-chain of sclareol must have the β-configuration. Klyne [4] has also pointed out that the isomerisation with ethanolic

* Part II, *J.*, 1956, 4262.

[1] Cocker and Halsall, *J.*, 1956, 4262.
[2] Ruzicka, Zwicky, and Jeger, *Helv. Chim. Acta*, 1948, **31**, 2143.
[3] Barton, *Quart. Rev.*, 1949, **3**, 61.
[4] Klyne, *J.*, 1953, 3072.

hydrogen bromide of the lactone (V), obtained by oxidation from sclareol [5,6] and ambrein,[7] to a second lactone (VI) is most satisfactorily explained by assuming that the isomerisation involves the rearrangement of a *trans*-fused lactone system (cf. V) to a *cis*-fused system (cf. VI). It is conceivable, however, that the lactone (VI) could arise from the *cis*-lactone (VII) which would correspond to the side-chain of sclareol having the α-configuration. The mechanism of such a change could involve O–alkyl fission of the lactone (VII) under acidic conditions,[cf. 8] giving the ion (VIII). This could then rearrange by loss and addition of a proton at $C_{(9)}$ to the ion (IX) which would cyclise to the lactone (VI). This type of



isomerisation of lactones through an unsaturated intermediate has been suggested to explain some of the rearrangements of the desmotroposantonins.[9,10]

Evidence has now been obtained that the side-chain of labdanolic acid, and hence of sclareol and ambrein, has the stable β-configuration. Labd-8(20)-en-15-oic acid (X) was ozonised in ethyl acetate at −70° and the ozonide decomposed with zinc dust and acetic acid at 10° to the keto-acid (XI). These conditions are regarded as sufficiently mild to preclude epimerisation at $C_{(9)}$ as Jones, Lewis, Shoppee, and Summers [11] were able to prepare coprostan-6-one by oxidation of the corresponding alcohol in acetic acid at room

[5] Ruzicka and Janot, *Helv. Chim. Acta*, 1931, **14**, 645.
[6] Ruzicka, Seidel, and Engel, *ibid.*, 1942, **25**, 621.
[7] Lederer and Mercier, *Experientia*, 1947, **3**, 188.
[8] Stimson, *J.*, 1955, 2673.
[9] Huang-Minlon, *J. Amer. Chem. Soc.*, 1948, **70**, 611.
[10] Barton, *J. Org. Chem.*, 1950, **15**, 466.
[11] Jones, Lewis, Shoppee, and Summers, *J.*, 1955, 2876.

temperature for 18 hr. Coprostan-6-one is very labile, being converted into cholestan-6-one by acid and alkali. After treatment with alkali the keto-acid (XI) was unchanged. If the side-chain had had the α-configuration epimerisation would have been expected corresponding to the change from an axial to an equatorial conformation. Ramirez and Stafiej have shown that in the presence of alkali the analogous epimeric 17*a*-methyl-17-oxo-D-homosteroid (XII), with the $C_{(17a)}$ methyl group α-orientated, equilibrates to a mixture in which the 17*a*-β-methyl epimer predominates.

Experimental.—M. p.s were determined on a Kofler block and are corrected.

Ozonolysis of labd-8(20)-en-15-oic acid (X). The acid (5·03 g.) in ethyl acetate (200 c.c.) was treated with ozonised oxygen at −70° until a faint blue colour persisted. The excess of ozone was removed by passing a stream of nitrogen through the solution for 10 min. The mixture was then stirred at 10° with acetic acid (80 c.c.) and zinc dust (30 g.) until it no longer coloured starch–iodide paper. The zinc dust was removed and washed with ethyl acetate. Ether (100 c.c.) was added to the filtrate and washings. The solution was then washed with water, dried, and evaporated to give a gum which afforded 20-nor-8-oxolabdan-15-oic acid as needles (from methanol–water), m. p. 110°, identical with the product (m. p. 110·5—111°; $[\alpha]_D$ −40°) [12] obtained by hydrolysis of methyl 20-nor-8-oxolabdan-15-oate.

Attempted isomerisation of 20-nor-8-oxolabdan-15-oic acid. The acid (0·24 g.) was heated under reflux for 1 hr. with methanolic potassium hydroxide (20%; 10 c.c.). After being kept at 20° for 1 hr. the mixture was poured into water, and dilute hydrochloric acid was added. Ethereal extraction of the solution afforded needles (from methanol–water), m. p. 109—111°. which were identified as starting material by m. p., mixed m. p., and rotation.

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THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, May 31st*, 1957.]

[12] Ramirez and Stafiej, *J. Amer. Chem. Soc.*, 1955, **77**, 134; *Chem. and Ind.*, 1955, 1180.

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886. *Some 4-Alkylaminoquinolines.*

By ALFRED CAMPBELL and (MRS.) S. D. CAVALLA.

IT having been found that 4-heptylamino-6-methoxyquinaldine had considerable antitubercular activity *in vitro*, a series of related aminoquinolines was prepared. As can be seen from the Table, peak activity was found in 7-chloro-4-heptylaminoquinoline (No. 9) but tests *in vivo* in mice were negative.

Experimental.—With the exception of compounds 1 and 7, a modification of Holcomb and Hamilton's method [1] was used in the preparation of these materials, *viz.*:

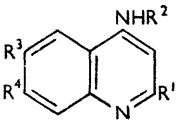
The substituted 4-chloroquinoline (0·1 mole) and the base (0·2 mole) were refluxed for 4 hr. (No. 2 required 17 hr. at 140°). The warm viscous mixture was dissolved in methanol (25 ml.) and poured into an excess of 2N-sodium hydroxide, and the precipitate extracted with ether (2 × 200 ml.). After being dried (K_2CO_3), the ether was removed and the base (Nos. 3, 4, 9) crystallised from acetone. Low-melting bases (Nos. 2, 5, 6, 8) were converted into the hydrochlorides which were crystallised from absolute methanol–ether.

4-Heptylaminoquinoline. A solution of 7-chloro-4-heptylaminoquinoline (10 g.) in ethanol (250 ml.) containing N-sodium hydroxide (38 ml.) was shaken with palladised charcoal in hydrogen (924 ml. of hydrogen were absorbed). The filtered solution was concentrated under

[1] Holcomb and Hamilton, *J. Amer. Chem. Soc.*, 1942, **64**, 1309.

reduced pressure and the product crystallised once from ethanol; pure 4-*heptylaminoquinoline* (7·5 g.; 82%) formed rhombohedra, m. p. 107—108°.

4-*Amino*-6-*methoxyquinaldine*. Phenylhydrazine (5·4 g.), 4-chloro-6-methoxyquinaldine (10·4 g.), and medicinal paraffin (50 ml.) were heated at 200° for 1 hr. The yellow solid was



No.	R^1	R^2	R^3	R^4	M. p.	Activity *
1	CH_3	H	OCH_3	H	207—208°	20
2	CH_3	n-C_4H_9	OCH_3	H	217—218	20
3	CH_3	n-C_6H_{13}	OCH_3	H	134—135	2·5
4	CH_3	n-C_7H_{15}	OCH_3	H	132—133	1·25
5	CH_3	n-$C_{10}H_{21}$	OCH_3	H	158—160	4
6	CH_3	n-$C_{16}H_{33}$	OCH_3	H	159—161	5
7	H	n-C_7H_{15}	H	H	107—108	5
8	H	n-C_7H_{15}	OCH_3	H	208—210 (decomp.)	20
9	H	n-C_7H_{15}	H	Cl	114—115	0·62

	Found, %				Required, %		
No.	C	H	N	Formulæ	C	H	N
1	70·0	6·5	15·0	$C_{11}H_{12}ON_2$	70·2	6·4	14·9
2	60·0	7·7	9·2	$C_{15}H_{20}ON_2,HCl,H_2O$	60·2	7·8	9·3
3	75·1	9·0	10·4	$C_{17}H_{24}ON_2$	75·0	8·9	10·3
4	75·3	8·9	9·7	$C_{18}H_{26}ON_2$	75·5	9·1	9·8
5	68·7	9·2	7·8	$C_{21}H_{31}ON_2,HCl$	69·1	9·1	7·7
6	72·0	10·2	6·2	$C_{27}H_{44}ON_2$	72·2	10·1	6·2
7	79·1	9·2	11·6	$C_{16}H_{22}N_2$	79·3	9·2	11·6
8	66·0	8·2	9·2	$C_{17}H_{24}ON_2,HCl$	66·1	8·2	9·1
9	69·3	7·6	9·9	$C_{16}H_{21}N_2Cl$	69·4	7·7	10·1

* In μg./ml.; causing complete inhibition of growth in *M. tuberculosis* H37Rv. Compounds No. 1, 3, 4, and 9 crystallised as needles from acetone; compound No. 7 formed rhombohedra from ethyl alcohol; and compounds No. 2, 5, 6, and 8 needles from methyl alcohol–ether.

collected and rinsed with ether before being suspended in concentrated hydrochloric acid (100 ml.). Zinc dust was then added gradually to the boiling suspension until the yellow solid had completely dissolved. The cooled solution was made alkaline with 28% aqueous ammonia and the product extracted with ethyl acetate. Crystallisation from benzene or acetone gave 4-*amino*-6-*methoxyquinaldine* (2·5 g.; 26%) as needles, m. p. 207—208°.

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887. *Ultraviolet Absorption Spectra and Paper Chromatography of 2-Thiohydantoins.*

By D. T. ELMORE and J. R. OGLE.

SINCE several methods of stepwise degradation of peptides involve the liberation and identification of either the *C*- or the *N*-terminal amino-acid as the corresponding 2-thiohydantoin,[1-4] we investigated methods for the recognition and quantitative determination of these compounds by chromatography and absorption spectrophotometry, and have extended the range of earlier chromatographic studies [1,3] to include a number of compounds described recently.[5] Of the solvents already described for the paper chromatography of

[1] Edward and Nielson, *Chem. and Ind.*, 1953, 197.
[2] Kenner, Khorana, and Stedman, *J.*, 1953, 673.
[3] Dautrevaux and Biserte, *Compt. rend.*, 1955, **240**, 1153.
[4] Elmore and Toseland, *J.*, 1954, 4533.
[5] Elmore, Ogle, and Toseland, *J.*, 1956, 192.

2-thiohydantoins, butan-1-ol saturated with water [1] was satisfactory (Table 1), but propionic acid–light petroleum (b. p. 100—120°) [2] did not give discrete spots. The system of Dautrevaux and Biserte [3] as well as a new solvent (C, Table 1) occasionally gave rise to multiple spots. The reason for this is not certain, but we believe that with solvent C,

TABLE 1.

No.	Compound	R_F values with standard deviation in parentheses		
		Sol. A	Sol. B	Sol. C [a]
1	2-Thiohydantoin	0·45 (0·04)	0·14 (0·02)	0·08 (0·02)
2	5-Methyl-2-thiohydantoin	0·64 (0·03)	0·33 (0·05)	0·22 (0·05)
3	5-Ethyl-2-thiohydantoin	0·72 (0·03)	0·53 (0·05)	0·42 (0·07)
4	5-*n*-Propyl-2-thiohydantoin	0·78 (0·03)	0·67 (0·06)	0·72 (0·05)
5	5-*iso*Propyl-2-thiohydantoin	0·78 (0·03)	0·68 (0·05)	0·69 (0·04)
6	5-*n*-Butyl-2-thiohydantoin	0·81 (0·04)	0·84 (0·05)	0·98 (0·02)
7	5-*iso*Butyl-2-thiohydantoin	0·82 (0·03)	0·84 (0·05)	1·00
8	5-*sec.*-Butyl-2-thiohydantoin	0·81 (0·03)	0·82 (0·04)	0·99 (0·02)
9	1-Methyl-2-thiohydantoin	0·59 (0·04)	0·31 (0·05)	0·25 (0·04)
10	5-Benzyl-2-thiohydantoin	0·77 (0·04)	0·65 (0·05)	0·55 (0·04)
11	5-*p*-Hydroxybenzyl-2-thiohydantoin	0·72 (0·03)	0·21 (0·04)	0·06 (0·02)
12	5-3′-Indolylmethyl-2-thiohydantoin	0·83 (0·03)	0·76 (0·06)	0·62 (0·04)
13	Pyrrolidino(1′ : 2′-1 : 5)-2-thiohydantoin	0·71 (0·04)	0·50 (0·04)	0·52 (0·04)
14	5-Methylthiomethyl-2-thiohydantoin	0·71 (0·03)	0·40 (0·05)	0·29 (0·07)
15	5-2′-Methylthioethyl-2-thiohydantoin	0·75 (0·04)	0·56 (0·05)	0·42 (0·05)
16	5-2′-Methylsulphonylethyl-2-thiohydantoin	0·48 (0·06) [b]	streaks	0·00
17	5-Carboxymethyl-2-thiohydantoin	0·12 (0·03)	0·10 (0·02)	0·03 (0·01)
18	5-2′-Carboxyethyl-2-thiohydantoin	0·28 (0·05)	0·17 (0·05)	0·05 (0·00)
19	5-Carbamoylmethyl-2-thiohydantoin	0·27 (0·04)	0·07 (0·03)	0·03 (0·00)
20	5-2′-Carbamoylethyl-2-thiohydantoin	0·33 (0·04)	0·10 (0·01)	0·03 (0·00)
21	5-Sulphomethyl-2-thiohydantoin	0·06 (0·02)	0·00	0·00
22	5-3′-Aminopropyl-2-thiohydantoin,HCl,$\frac{1}{2}H_2O$	0·12 (0·03)	0·02 (0·00)	0·00
23	5-4′-Aminobutyl-2-thiohydantoin,HCl	0·12 (0·02)	0·03 (0·00)	0·00
24	5-3′-Guanidinopropyl-2-thiohydantoin,HCl	0·20 (0·04)	0·02 (0·00)	0·00
25	5-4′-Glyoxalinylmethyl-2-thiohydantoin,HCl	streaks	0·02 (0·00)	0·00

[a] The figures in this column refer to the ratio (distance travelled by compound)/(distance travelled by No. 7). [b] Elongated spot.

multiple spots may arise from photochemical decomposition (see below) during equilibration in the light, since chromatograms equilibrated and run in the dark were satisfactory. This modification did not improve the results with the other system.[3] Useful separation of basic and acidic 2-thiohydantoins was obtained on paper electropherograms.

Ultraviolet absorption data for 2-thiohydantoins are recorded in Table 2. The majority of compounds have maximal absorption at 266 ± 1 mμ (ε 18,500 ± 700). An aliphatic group at $C_{(5)}$ has bathochromic and hyperchromic effects as revealed by a comparison of the spectra of 5-alkyl-2-thiohydantoins with that of 2-thiohydantoin. Simultaneous substitution of $N_{(1)}$ and $C_{(5)}$ in pyrrolidino(1′ : 2′-1 : 5)-2-thiohydantoin causes a greater bathochromic effect ($\lambda_{max.}$ 271 mμ), although $\varepsilon_{max.}$ is considerably lower than normal. The latter effect may result from substitution at $N_{(1)}$, since 1-methyl-2-thiohydantoin has an abnormally low extinction coefficient. Absorption spectra of 2-thiohydantoins derived from lysine, ornithine, and arginine are characteristic since both $\lambda_{max.}$ and $\varepsilon_{max.}$ are lower than normal. The absorbance ratio, $A_{270\ m\mu}/A_{260\ m\mu}$, appears to be a useful constant for the characterisation of 2-thiohydantoins; for example, 5-alkyl-2-thiohydantoins have an absorbance ratio of 1·01—1·05, but chain-branching or the introduction of an aryl or a heterocyclic group at $C_{(1')}$ increases this significantly. A higher absorbance ratio also results from the presence of a sulphur atom in the side-chain at $C_{(5)}$.

Solutions of 2-thiohydantoins were rather unstable in light and the characteristic absorption bands disappeared when a solution was kept on the bench for a few days. The mechanism of the photochemical decomposition of 2-thiohydantoins is unknown,

but after irradiation of a solution of 5-*iso*propyl-2-thiohydantoin by a high-pressure mercury arc for 6 days, ammonium sulphate (25% yield) was the only identifiable product.

Improved methods for the preparation of some 2-thiohydantoins are recorded in the Experimental section.

TABLE 2.

No.	$\lambda_{max.}$ (mμ)	$\lambda_{min.}$ (mμ)	$\lambda_{max.}$ (mμ)	$\varepsilon_{266} \pm 95\%$ confidence limits	Absorbance ratio *
1	263—264	237	222	17,030 ± 270	0·87
2	265—266	238—239	224	18,210 ± 440	1·01
3	266	238—239	224—225	17,760 ± 330	1·03
4	265—266	239	225	18,220 ± 430	1·04
5	266—267	239	225	18,100 ± 350	1·10
6	266	238—239	224—225	18,670 ± 460	1·05
7	266	238—239	224	18,970 ± 390	1·04
8	266	239	225	18,710 ± 300	1·08
9	265—266	243—244	230	15,280 [a]	1·02
10	267	240	223—225 [b]	17,820 ± 420	1·16
11	268	240	225	17,900 ± 120	1·19
12	278	247	219	13,000 ± 390	1·76
13	271	248	233—234	14,260 [a]	1·44
14	267	238	223—224	[c]	1·12
15	267	239	225	19,260 ± 490	1·16
16	267	239	225	18,510 ± 430	1·12
17	266	239	224	19,210 ± 240	1·02
18	266	238	225	18,810 ± 350	1·07
19	265—266	238—239	224	19,010 ± 410	1·02
20	266	239	225	18,370 ± 320	1·08
21	262—263	238—239	225	[d]	0·76
22	262—263	238	225	15,100 ± 260	0·79
23	262	238	224	15,570 ± 300	0·77
24	261—262	238	225	16,470 [a]	0·77 [e]
25	267	239	—	18,170 ± 480	1·15

* $A_{270\ m\mu}/A_{260\ m\mu}$.

[a] The value of ε is a mean of two determinations. [b] Point of inflexion. [c] Insufficient material for more than one determination. [d] Too hygroscopic for determination of ε. [e] Aqueous solutions used for spectral determinations.

ε ± 95% confidence limits at other wavelengths: No. 12, 18,080 ± 450 at 278 mμ; No. 13, 15,640 at 271 mμ; No. 22, 16,180 ± 30 at 262 mμ; No. 23, 16,580 ± 310 at 262 mμ; No. 24, 17,520 at 261 mμ.

Experimental.—The following systems were used for paper chromatography of 2-thiohydantoins: (A) butan-1-ol saturated with water on Whatman No. 11 paper, (B) *cyclo*hexane–butan-1-ol–90% acetic acid (60 : 20 : 20) on Whatman No. 52 paper, and (C) *cyclo*hexane–propan-2-ol–90% acetic acid (65 : 15 : 20) on Whatman No. 52 paper in the dark. System B was run on ascending chromatograms in a constant-temperature room at 25° after equilibration for several hours. Both phases of system C were used for equilibration and chromatograms were irrigated with the upper phase for about 24 hr. (The lower end of the paper was serrated with pinking shears.)

Electrophoresis for 14 hr. on Whatman No. 54 paper (4v/cm.) in a buffer (pH 5·9) consisting of 0·025M-citric acid and 0·05M-disodium hydrogen phosphate (2 : 3) caused the following migrations: compounds (17) and (21), 12 cm. to anode; (18), 9·5 cm. to anode; (22) and (23), 17 cm. to cathode; (24), 15 cm. to cathode; (25), 14 cm. to cathode.

All spectra, except where otherwise indicated in Table 2, were measured on freshly-prepared solutions in 95% ethanol, a Beckman DU ultraviolet absorption spectrophotometer being used. Matched quartz cells (Thermal Syndicate Ltd., Wallsend, Northumberland) with optical path $1 \pm <0{\cdot}001$ cm. were employed. The absorbance was determined at several dilutions, and all compounds obeyed Beer's law over the range $1{\cdot}5—5{\cdot}0 \times 10^{-5}$ molar. The molar extinction coefficient was calculated from the slope of the graph of absorbance against concentration by the least-squares method. Replicate determinations of ε by this method were tested for compatibility by the *t* test, following standard statistical methods, and sufficient measurements were obtained to give a mean value of ε with 95% confidence limits of $< \pm 500$.

1-*Methyl*-2-*thiohydantoin*. *N*-Benzoylthiocarbamoylsarcosine ethyl ester[5] (1 g.) was heated under reflux in ethanol (50 c.c.) and 3N-hydrochloric acid (50 c.c.) for 3 hr. After removal of solvents under reduced pressure, the residue was partitioned between ethyl acetate and saturated sodium hydrogen carbonate, and the upper layer was washed and dried. Addition of light petroleum (b. p. 60—80°) afforded the product (0·21 g.), m. p. 224—226° (decomp.) after recrystallisation from 95% ethanol.

5′-*Oxopyrrolidino*(1′ : 2′-1 : 5)-2-*thiohydantoin*. DL-5-Oxopyrrolidine-2-carboxylic acid (2 g.) and dry ammonium thiocyanate (1·5 g.) were heated for 20 min. at 100° in acetic anhydride (9 c.c.) and glacial acetic acid (1 c.c.). Water (25 c.c.) was added; the product (1·0 g.), m. p. 204—205°, crystallised overnight in the refrigerator.

5-2′-*Carboxyethyl*-2-*thiohydantoin*. A solution of 5′-oxopyrrolidino(1′ : 2′-1 : 5)-2-thiohydantoin (0·78 g.) in 4N-hydrochloric acid (25 c.c.) was evaporated to dryness on the steam-bath. The residual gum crystallised on cooling; the product (0·60 g.) had m. p. 121—122° after recrystallisation from water.

5-4′-*Aminobutyl*-2-*thiohydantoin hydrochloride*. The oil, which resulted from the reaction of ε-*N*-benzyloxycarbonyl-L-lysine (5 g.) with ammonium thiocyanate in acetic anhydride–acetic acid,[5] was shaken with a solution (50% w/v; 30 c.c.) of hydrogen bromide in acetic acid for 30 min. The gum, which resulted from pouring the mixture into ether (600 c.c.), was converted into the thiohydantoin (0·55 g.), m. p. 236—237° (decomp.), by hot 3N-hydrochloric acid as described previously.[5]

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888. *The Reaction of Benzaldehyde with Ammonium Acetate.*

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PINNER[1] in 1889 reported that benzaldehyde, when refluxed with twice its weight of ammonium acetate, gave a compound, m. p. 247°, to which he assigned the formula $C_{42}H_{37}O_2N_3$. It was sparingly soluble in the usual organic solvents and dissolved unchanged in concentrated sulphuric acid. The reaction has now been reinvestigated.

When benzaldehyde is refluxed with ammonium acetate or ammonium propionate for 3—4 hr. a highly crystalline neutral compound, $C_{28}H_{24}ON_2$, m. p. 259°, is obtained in 60% yield. It shows infrared absorption at 3·05(w), 6·09(s), and 6·5 μ(s), suggesting the presence of a secondary amide group, and brief treatment with 70% sulphuric acid gives benzaldehyde and a base, $C_{21}H_{20}ON_2$, which from its infrared spectrum is also a secondary amide. Further hydrolysis of this with 70% sulphuric acid gives benzoic acid and *meso*-1 : 2-diphenylethylenediamine. The base is therefore *N*-benzoyl*meso*-1 : 2-diphenylethylenediamine and the original compound *N*-benzoyl-*N*′-benzylidene*meso*-1 : 2-diphenylethylenediamine.

The formation of a 1 : 2-diphenylethylenediamine derivative under such mild conditions probably involves a benzoin-type condensation. This view is supported by the effect of substituents on the course of the reaction. Products analogous to that from benzaldehyde are formed rapidly from *p*-chloro- and *m*-nitro-benzaldehyde but under the same conditions *p*-tolualdehyde and anisaldehyde give no comparable compounds. *p*-Nitrobenzaldehyde reacts rapidly but not as expected.

Experimental.—Reaction of benzaldehyde with ammonium acetate. Benzaldehyde (30 g.) was refluxed with ammonium acetate (60 g.) for 3 hr., the mixture cooled and the product filtered

[1] Pinner, *Ber.*, 1889, **22**, 1598.

and washed repeatedly with ethanol. Recrystallisation from butan-1-ol gave N-*benzoyl*-N'-*benzylidene*meso-1 : 2-*diphenylethylenediamine* (60%), m. p. 258—259° (Found: C, 83·1; H, 5·95; N, 7·05. $C_{28}H_{24}ON_2$ requires C, 83·1; H, 5·9; N, 6·9%).

The above product (5 g.) was refluxed with 70% sulphuric acid (60 ml.) for 20 min. and the solution poured on ice. The resulting suspension was extracted with ether and then made alkaline with 2N-sodium hydroxide. Filtration of the precipitate and crystallisation from aqueous ethanol gave N-*benzoyl*meso-1 : 2-*diphenylethylenediamine*, m. p. 204—205° (Found: C, 79·5; H, 6·25; N, 8·95. $C_{21}H_{20}ON_2$ requires C, 79·65; H, 6·3; N, 8·85%). The *picrate* (from alcohol) had m. p. 204° (decomp.) (Found: N, 12·6. $C_{27}H_{23}O_8N_5$ requires N, 12·85%). Refluxing with acetic anhydride for 0·5 hr. gave the acetate, m. p. (from nitrobenzene) 316° (lit.[2] m. p. 316°) (Found: C, 77·1; H, 6·2; N, 7·9. Calc. for $C_{23}H_{22}O_2N_2$: C, 77·1; H, 6·2; N, 7·8%).

Hydrolysis of the original benzylidene-benzoate or further hydrolysis of the benzoate with 70% sulphuric acid under reflux for 1 hr. gave as the basic product of hydrolysis *meso*-1 : 2-diphenylethylenediamine, m. p. (from ether at 0°) 120·5—121·5° (Found: C, 79·5; H, 7·5; N, 13·5. Calc. for $C_{14}H_{16}N_2$: C, 79·25; H, 7·6; N, 13·2%).

meso-1 : 2-*Di*-p-*chlorophenylethylenediamine*. *p*-Chlorobenzaldehyde (10 g.) was refluxed with ammonium acetate (20 g.) for 3 hr. and the product crystallised from butan-1-ol to give N-p-*chlorobenzoyl*-N'-p-*chlorobenzylidene*meso-1 : 2-*di*-p-*chlorophenylethylenediamine* (65%), m. p. 249° (Found: C, 62·0; H, 3·7; N, 5·15. $C_{28}H_{20}ON_2Cl_4$ requires C, 62·0; H, 3·7; N, 5·2%). Hydrolysis of this with 70% sulphuric acid under reflux for 1 hr. gave meso-1 : 2-*di*-p-*chlorophenylethylenediamine*, m. p. (from ether) 137—138° (Found: C, 60·0; H, 5·0; N, 9·5. $C_{14}H_{14}N_2Cl_4$ requires C, 59·8; H, 5·0; N, 9·95%). Refluxing with acetic anhydride–acetic acid gave the *diacetate*, m. p. (from acetic acid) 360° (Found: C, 59·4; H, 5·0. $C_{18}H_{18}O_2N_2Cl_2$ requires C, 59·15; H, 5·0%).

meso-1 : 2-*Di*-m-*nitrophenylethylenediamine*. *m*-Nitrobenzaldehyde (10 g.) was refluxed with ammonium acetate (20 g.) for 3 hr. The product (7·5 g.) was very insoluble in the usual solvents and could not be recrystallised. Hydrolysis with 70% sulphuric acid under reflux for 1 hr. gave meso-1 : 2-*di*-m-*nitrophenylethylenediamine*, m. p. (from butan-1-ol) 189—190° (Found: C, 55·9; H, 4·9; N, 18·5. $C_{14}H_{14}O_4N_4$ requires C, 55·6; H, 4·7; N, 18·5%). Refluxing with acetic anhydride–acetic acid gave the *diacetate*, m. p. (from acetic acid) 354—355° (Found: C, 56·2; H, 4·8; N, 15·0. $C_{18}H_{18}O_6N_4$ requires C, 56·0; H, 4·7; N, 14·5%).

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[2] Japp and Moir, *J.*, 1900, **77**, 611.