255. *Use of Cobalt Catalyst in the Preparation of Borazole and its Derivatives.*[1]

By H. J. Emeléus and G. J. Videla.

Brown and Laubengayer [2] described the preparation of *B*-trichloroborazole by passing boron trichloride vapour with nitrogen over ammonium chloride at 165—175°, or by refluxing chlorobenzene in which ammonium chloride was suspended, while boron trichloride vapour was passed in. Both procedures gave yields of about 35%. In using the first of these methods we found that the yield was only 10—12% when ammonium chloride of A.R. purity was used, whereas the salt of commercial purity gave yields of about 30%. As the latter contained ferric chloride, we were led to study metallic iron, cobalt, and nickel as catalysts for the preparation of *B*-trichloroborazole and *B*-trichloro- and *B*-tribromo-*N*-trimethylborazole. Preliminary results show that the best results were obtained with cobalt,which was examined in some detail.

The catalyst was prepared by reducing cobalt oxide on a pumice support and the product was mixed with ammonium chloride in a 1 : 10 ratio. With ammonium chloride and boron trichloride a smooth reaction occurred at 80—120° when Brown and Laubengayer's general procedure was followed, and the amount of non-volatile product was reduced, probably because of the lower temperature. With methylamine hydrochloride in place of ammonium chloride, reaction was complete at 150° and yields were similar. Even more striking results were obtained in preparing *N*-tribromoborazole from ammonium bromide and boron tribromide. Without catalyst, reaction occurred at 280—290° and the yield was very low, whereas, with catalyst, there was a smooth reaction at 160—180° and a yield of purified product of 40—45%. Results with methylamine hydrobromide were similar. When hydrazine salts were used in place of those of ammonia the reaction temperature was reduced, even without the use of a catalyst. Thus hydrazine hydrochloride reacted with boron trichloride at 80—120° and gave a 35% yield of purified trichloroborazole: with catalyst, the reaction temperature was 80° and the yield about 50%. Results for hydrazine hydrobromide and boron tribromide were similar. With methylhydrazine hydrobromide and boron tribromide reaction was complete at 150° and the yield of purified *B*-tribromo-*N*-trimethylborazole was 45%: without catalyst these values were 160—180° and 6—8% respectively.

Hydrazine salts also give enhanced yields in the preparation of borazole by the method of Schaeffer, Schaeffer, and Schlesinger,[3] who showed that ammonium chloride and lithium borohydride gave yield of borazole of about 30% at 290°, whilst reaction did not occur with sodium borohydride. On use of hydrazine hydrochloride, borazole was formed with lithium or sodium borohydrides at 180° in 40—50% yield. The cobalt catalyst was used in the case of the sodium salt. Further experiments are being made to elucidate the mode of action of the cobalt, which is probably converted superficially into chloride. Though its effect on these reactions is not equally great in each instance, it is sufficiently striking to suggest that its presence facilitates the formation of one of the intermediates in the poorly understood reactions which result in borazole and its derivatives. We hope also to examine other possible catalysts.

Experimental.—Preparations were done in a long combustion tube heated near the inlet end, in which the salt was placed, by a small electric furnace as described by Brown and Laubengayer.[2] The boron halide (8—15 g. per hr.) was passed over the salt mixed with catalyst, which was prepared by damping powdered pumice (30 g.) with saturated cobalt nitrate solution, drying, and calcining at 800—850°. The product was reduced in hydrogen at 300—350°. The catalyst (3—4 g.) was ground with the halide (30 g.) in a dry box.

Preparation of trichloroborazole. Ammonium chloride (30 g.), mixed with catalyst (3—4 g.),

[1] See Emeléus and Videla, *Proc. Chem. Soc.*, 1957, 288.
[2] Brown and Laubengayer, *J. Amer. Chem. Soc.*, 1955, **77**, 3699.
[3] G. Schaeffer, A. Schaeffer, and Schlesinger, *ibid.*, 1951, **73**, 1612.

was placed in the heated zone of the reaction tube and boron trichloride vapour mixed with nitrogen was passed at a controlled rate. Reaction commenced at 80° and was complete below 120°. Crude product was removed from the cold part of the tube in a dry box and purified by vacuum sublimation at 70° (yield 20·5 g., 60% on ammonium chloride taken) (Found: B, 17·6; Cl, 57·9; N, 22·8. Calc. for $B_3N_3H_3Cl_3$: B, 17·7; Cl, 57·6; N, 22·8%); m. p. 84° (sealed tube). The vapour pressures agreed with values reported by Brown and Laubengayer. The infrared spectrum, which will be reported elsewhere, showed no B–H frequency.

Preparation of B-*trichloro*-N-*trimethylborazole*. Dry methylamine hydrochloride (25 g.), mixed with catalyst (2·5 g.), was treated as above. Reaction started at 100° and was complete at 150°. The crude product was sublimed *in vacuo* at 120° (yield 6·8 g., 50% on methylamine hydrochloride taken) (Found: B, 14·3; N, 18·5; C, 15·8; H, 4·2%; *M*, cryoscopic in benzene, 225. Calc. for $C_3H_9B_3N_3Cl_3$: B, 14·4; N, 18·6; C, 16·0; H, 4·0%; *M*, 226).

Preparation of B-*tribromoborazole*. Ammonium bromide (10 g.) was mixed in a dry box with cobalt catalyst (1 g.). Reaction with boron tribromide carried in nitrogen commenced at 160° and was complete at 200°. The crude product was sublimed *in vacuo* at 120° (yield 8·2 g., 42% on ammonium bromide taken) (Found: B, 10·0; Br, 74. Calc. for $B_3N_3H_3Br_3$: B, 10·2; Br, 75·6%); m. p. 128—129° (sealed tube).

Preparation of B-*tribromo*-N-*trimethylborazole*. Methylamine hydrobromide (18 g.) was mixed with catalyst (1·8 g.). Reaction with boron tribromide carried in nitrogen started at 190° and was complete at 220°. The crude product was sublimed at 120° (yield 5·6 g., 40% on methylamine hydrobromide taken) (Found: B, 8·95; N, 11·3; Br, 66·4; C, 9·7%; *M*, cryoscopic in benzene, 358. Calc. for $C_3H_9B_3N_3Br_3$: B, 9·05; N, 11·6; Br, 66·75; C, 10·0%; *M*, 359).

Preparation of B-*trichloroborazole from hydrazine hydrochloride*. The procedure was the same as with ammonium chloride. Hydrazine hydrochloride (25 g., dried *in vacuo* over P_2O_5) was placed in the heated tube and boron trichloride (38 g., 19 g. per hour) was passed in at 120°. The crude product was sublimed in *vacuo* at 70° (yield 6·90 g., 35% on hydrazine hydrochloride taken). The same quantities of reactants being used with the addition of 10% of catalyst, reaction was complete at 120° (yield of sublimed trichloroborazole, 9·7 g., 50%). In both cases, and in the experiments described below, the purity of the product was controlled by analysis, m. p., and infrared spectrum.

Preparation of B-*trichloro*-N-*trimethylborazole with methylhydrazine hydrochloride*. The hydrazine hydrochloride (25 g.) was treated as above with boron trichloride (26 g., 13 g./hr.). Reaction started at 120° and the temperature was raised to 140° for the last 20 min. The yield of sublimed *B*-trichloro-*N*-trimethylborazole was 5·72 g. (30%). With the same quantities and procedure, but with 10% of cobalt catalyst, reaction occurred at 110°, the yield of pure product was 7·1 g. (45%).

Preparation of B-*tribromoborazole with hydrazine hydrobromide*. Hydrazine hydrobromide (11·6 g.) was treated as above with boron tribromide (16 g. in 2 hr.). Reaction was complete at 180°. The yield of pure product was 1·9 g. (30%). With the same quantities but with the addition of 10% of cobalt catalyst, the yield was 2·5 g. (40%).

Preparation of B-*tribromo*-N-*trimethylborazole with methylhydrazine hydrobromide*. Methylhydrazine hydrobromide (12·3 g.) was treated with boron tribromide (16 g. in 2 hr.) at 160—180°. The yield of pure sublimed product was 0·6 g. (8%). With the same quantities, but with the addition of 10% of cobalt catalyst, reaction was complete in 2 hr. at 140—150°. The yield of sublimed product was 2·52 g. (45%).

Preparation of borazole by use of lithium and sodium borohydride. In a typical experiment hydrazine hydrochloride (10·5 g.) (dried in *vacuo* over P_2O_5) was mixed with crushed Pyrex glass (30 g.) in a dry box and transferred to the reaction flask, which was swept out with dry nitrogen. Lithium borohydride (4·35 g.) was added and the contents were mixed. The flask was attached to cooled traps and the usual vacuum fractionation apparatus and heated at 175—180° until hydrogen evolution ceased (1½ hr.). The volatile products were collected and fractionated. The borazole (3·8 g., 50%) was characterised by vapour-pressure measurements and by its m. p. and infrared spectrum. By the same procedure but with sodium borohydride (11·3 g.), hydrazine hydrochloride (10·5 g.), and cobalt catalyst (1·2 g.) the yield of pure borazole was 3·18 g. (40%).

One of the authors (G. J. V.) thanks the Argentine Atomic Commission for Study Leave.

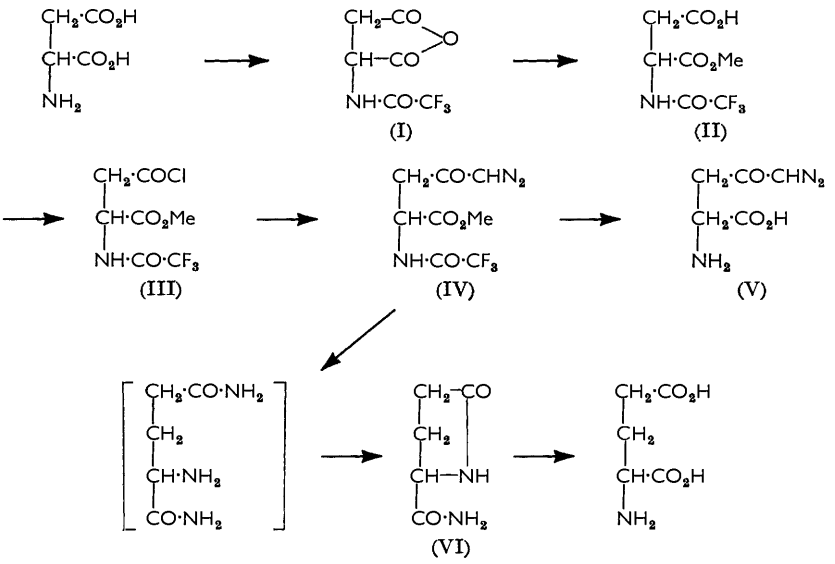
UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, August 27th*, 1958.]

256. *Synthesis of 5-Diazo-4-oxo-L-norvaline.*

By Y. Liwschitz, R. D. Irsay, and A. I. Vincze.

6-Diazo-5-oxo-L-norleucine (DON) has antibiotic and tumour-inhibitory properties.[1] Since, moreover, Mickelson and Flippen [2] showed that hydrolysates of tumorous mouse tissue (Sarcoma 180) contained significantly less aspartic acid than that of healthy animals, it appeared of interest to prepare the lower homologue, 5-diazo-4-oxo-L-norvaline, related to aspartic acid.

Our synthesis [3] of this substance (summarised in the scheme) is based on the α-methyl ester of *N*-trifluoroacetyl-L-aspartic acid. Weygand and his co-workers independently prepared 5-diazo-4-oxo-*N*-trifluoroacetyl-L-norvaline ethyl ester by the same route [4] but failed to remove the protecting groups in this particular instance, although they succeeded in synthesising two higher homologues, *i.e.*, 6-diazo-5-oxo-L-norleucine and L-2-amino-7-diazo-6-oxoœnanthic acid.[5] Our previous attempts to prepare the substance by catalytic hydrogenation of *N*-benzyloxycarbonyl-5-diazo-4-oxo-L-norvaline benzyl ester were unsuccessful, since the diazo-group was affected, in accordance with the findings of others.[6]



Removal of the trifluoroacetyl and methyl ester groups proved indeed difficult and using sodium or barium hydroxide gave only sufficient materials for spectral and elementary analysis. We now find that use of tetraethylammonium hydroxide (a quaternary amine has to be used to prevent aminolysis of the ester) gives a 20% yield in the hydrolysis step and affords the crystalline amino-acid (V).

So far, tumour-inhibitory properties of the substance have been investigated only against Sarcoma 37 in mice: administration of 8—10 mg./kg. reduced tumour sizes by 26·4% (average), and the substance is thus " intermediate " in the nomenclature of the American Association for Cancer Research.

[1] Dion, Fusari, Jakubowski, Zora, and Bartz, *J. Amer. Chem. Soc.*, 1956, **78**, 3075.
[2] Mickelson and Flippen, *Archiv. Biochem. Biophys.*, 1956, **64**, 246.
[3] For a preliminary announcement to the Israel Chemical Society, April, 1957, see Liwschitz and Irsay, *Bull. Res. Council Israel*, 1957, **6**, 292.
[4] Weygand, Klinke, and Eigen, *Chem. Ber.*, 1957, **90**, 1896.
[5] Weygand, Bestmann, and Klieger, *ibid.*, 1958, **91**, 1037.
[6] Wienhaus and Ziehl, *Ber.*, 1932, **65**, 1461; Birkofer, *Chem. Ber.*, 1947, **80**, 83.

Experimental.—M. p.s were determined in a Fisher–Johns apparatus. Biological tests were carried out by Dr. M. Schlesinger of the Dept. of Experimental Pathology (Cancer Research Laboratories), The Hebrew University, Hadassah Medical School, Jerusalem, whose help is greatly appreciated.

α-*Methyl hydrogen* N-*trifluoroacetyl*-L-*aspartate* (II). *N*-Trifluoracetyl-L-aspartic anhydride [4] (13 g.) was heated under reflux with absolute methanol (50 ml.) for 4 hr. After removal of the solvent *in vacuo*, the residue solidified overnight to a pasty mass. Recrystallisation from a small volume of chloroform and prolonged cooling yielded prisms, m. p. 114—115° (11·5 g., 77%), of the *ester* (Found: C, 35·0; H, 3·5; N, 5·8. $C_7H_8O_5NF_3$ requires C, 34·6; H, 3·3; N, 5·8%), $[\alpha]_D^{21}$ −13·6° (*c* 0·22 in ethyl acetate).

L-β-*Methoxycarbonyl*-β-*trifluoroacetamidopropionyl chloride* (III). The ester (II) (7 g.) and thionyl chloride (2·5 ml.) were refluxed in benzene (30 ml.) for 30 min. After removal of the solvent and excess of reagent *in vacuo*, the residue solidified. Recrystallisation from benzene gave the *chloride* as needles, m. p. 127° (7·1 g., 94%). Further recrystallisation from benzene raised the m. p. to 128° (Found: N, 5·2; Cl, 13·3. $C_7H_7O_4NClF_3$ requires N, 5·3; Cl, 13·6%). $[\alpha]_D^{24}$ was −17·4° (*c* 0·23 in ethyl acetate).

5-*Diazo*-4-*oxo*-N-*trifluoroacetyl*-L-*norvaline methyl ester* (IV). Freshly prepared chloride (III) (6·5 g.) in dry ether (20 ml.) was added with stirring to ethereal diazomethane (large excess) at 0°. After 10 min. the mixture was freed from a small amount of solid, and excess of reagent and solvent were removed *in vacuo*. The residual *ester* recrystallised from benzene as long yellow needles, m. p. 113—114° (5 g., 76%) (Found: C, 36·3; H, 3·3; N, 14·0. $C_8H_8O_4N_3F_3$ requires C, 36·0; H, 3·0; N, 15·7%. Nitrogen determinations of aliphatic diazo-compounds tend to be low), $[\alpha]_D^{15}$ −11·3° (*c* 0·167 in methanol).

Glutamic acid by Wolff rearrangement and hydrolysis of the ester (IV). The ester (0·5 g.) in dioxan (10 ml.) was slowly added to a mixture of sodium carbonate (0·125 g.), silver oxide (0·05 g.) and sodium thiosulphate (0·075 g.) in 5 ml. of water at 50—60°. After 90 min., during which the temperature was gradually raised to 100°, part of the yellow diazoketone still remained. The mixture was refluxed for 3 hr., then evaporated *in vacuo*. The residue was heated under reflux with 20% hydrochloric acid (15 ml.) for 5 hr. After filtration, the solution was concentrated to a third of its volume. Ascending paper chromatography (phenol–water) of this solution, together with an authentic sample of L-glutamic acid, gave identical R_F values.

5-*Diazo*-4-*oxo*-L-*norvaline* (V). The ester (IV) (2 g.) was dissolved in 0·1N-tetraethylammonium hydroxide (200 ml.) and left for 30 min. The solution darkened, but much less than when treated with alkali hydroxide of the same concentration, as in previous experiments. The pH was then adjusted to 6·2 by addition of trifluoroacetic acid (Beckman Model G pH meter). By freeze-drying the mixture a dark brown material was obtained which was triturated with dry methanol and filtered. Recrystallisation from 75% methanol (it must be filtered hot to free it from dark impurities) gave orange needles, forming spherical aggregates which decomposed explosively at about 140° (0·235 g., 20%) (Found: C, 37·7; H, 4·8; N, 24·8; diazo-N, 18·0. $C_5H_7O_3N_3$ requires C, 38·2; H, 4·5; N, 26·8; diazo-N, 17·9%). Accurate polarimetric determinations could not be made because the substance is strongly coloured, thus allowing measurements only at very low concentrations. 5-Diazo-4-oxo-L-norvaline (V) has an infrared spectrum which is very similar to that of DON,[1] possessing strong absorption bands at 2·90, 3·20, 3·31, 3·80, 4·20, 4·70, 6·10, 2·29, 6·67, 6·90, 7·18, 7·40, 7·58, 7·70, 8·0, 8·68, and 8·81 μ. Its ultraviolet absorption spectrum also conforms to that of DON,[1] having max. at 274 mμ ($E_{1\,cm.}^{1\%}$ 600) and at 244 mμ ($E_{1\,cm.}^{1\%}$ 310).

N-*Benzyloxycarbonyl*-5-*diazo*-4-*oxo*-L-*norvaline benzyl ester*. α-Benzyl hydrogen *N*-benzyloxycarbonyl-L-aspartate [7] (2 g.) was dissolved in dry ether (30 ml.) and cooled in an ice-bath. Phosphorus pentachloride (1·25 g.) was added and the mixture shaken for 15 min. at 0° and for an additional 15 min. at room temperature. After filtration, the solvent was evaporated *in vacuo*. The residue was redissolved in dry ether and added to ethereal diazomethane (large excess). The mixture was left for a few hours, then filtered, and evaporated *in vacuo*. The residual *ester*, recrystallised from propan-1-ol, had m. p. 78—79° (0·9 g., 41%) (Found: C, 62·6; H, 5·1; N, 9·4. $C_{20}H_{19}O_5N_3$ requires C, 62·9; H, 5·0; N, 11·0%).

Department of Organic Chemistry,
The Hebrew University, Jerusalem, Israel. [*Received, October 6th*, 1958.]

[7] Bergmann, Zervas, and Salzmann, *Ber.*, 1933, **66**, 1288.

257. *Alkaline Hydrolysis of Ethyl 1-Naphthoates. Steric Inhibition of Mesomerism involving the 4-Dimethylamino-substituent.*

By A. FISCHER, HELEN M. FOUNTAIN, and J. VAUGHAN.

RATES of alkaline hydrolysis, in 85% (w/w) ethanol–water, of several substituted ethyl 1-naphthoates have previously been communicated.[1,2] For 3- and 4-substituents an excellent fit to the Hammett equation was obtained, except with the 4-nitro-group. It was suggested that deviation for this substituent is the result of steric inhibition of mesomerism; the *peri*-hydrogen atom (at position 5) prevents coplanarity of the nitro-group and the naphthalene ring. We have now measured similar rate constants for ethyl 4-fluoro-, 4-methoxy-, and 4-dimethylamino-1-naphthoate at 50°: these substituents sometimes show deviations from a Hammett plot. The dimethylamino-substituent in particular was expected to show a deviation more marked than that of the 4-nitro-group, because the resonance component of the Hammett substituent constant (σ) is greater for the amino- than for the nitro-group. Thus Taft [3] has estimated for p-NO_2 a resonance component (σ_R) of +0·15 and an inductive component (σ_I) of +0·64. For p-NH_2, σ_R is −0·76 and σ_I +0·1: the M-effect is proportionately much greater for the amino-group and a similar conclusion should hold when the amino-group is methylated.

Experimental.—Esters. These were prepared from the acids by the Fischer–Speier method. Physical constants and relevant analyses were as follows: *ethyl 4-fluoro-*, b. p. 123°/2·5 mm. (Found: C, 71·6; H, 4·8; F, 8·3. $C_{11}H_7O_2F$ requires C, 71·6; H, 5·0; F, 8·7%), *4-methoxy-*, m. p. 65·5° (Found: C, 73·1; H, 6·0. $C_{14}H_{14}O_3$ requires C, 73·1; H, 6·1%), and *4-dimethylamino-1-naphthoate*, b. p. 152°/1 mm. (Found: N, 5·9. $C_{15}H_{17}O_2N$ requires N, 5·8%). 4-Dimethylamino-1-naphthoic acid, m. 161°, was obtained in 20% yield from 4-bromo-*NN*-dimethyl-1-naphthylamine by carboxylation of the lithium compound formed by refluxing the amine (0·04 mole) and butyl-lithium (0·054 mole) in ether (50 ml.) for 13 hr.

Hydrolyses. The method for following kinetics, using stainless steel reaction vessels, has been described.[2] Kinetic results are given in Table 1. The good agreement between the mean value found for ethyl 1-naphthoate ($k_{50} = 2{\cdot}50 \times 10^{-3}$ l. mole^{-1} sec.$^{-1}$) and the earlier reported figure ($2{\cdot}42 \times 10^{-3}$) indicates that the tabulated rate constants for substituted esters should be fully comparable with results of previous studies. It is estimated that mean k values are accurate to 5%.

TABLE 1. *Ethyl X-1-naphthoates in 85% w/w ethanol.*

X	Rate constant $10^{-3}k_{50}$	Mean 10^3k_{50}
H	2·50, 2·48, 2·39, 2·51, 2·61	2·50
4-F	4·86, 4·59, 4·66, 4·58, 4·44	4·63
4-OMe	0·636, 0·612, 0·640, 0·625, 0·639, 0·645	0·633
4-NMe_2	0·747, 0·764, 0·791, 0·764	0·766

Discussion.—A regression line has been fitted to the log k_{50} *versus* σ data for ethyl 1-naphthoate containing the following substituents: H, 3-Cl, 4-Cl, 3-Br, 4-Br, 3-Me, 4-Me, 4-F, 4-OMe. The substituent constants used are those listed by McDaniel and Brown.[4] For hydrolysis of ethyl X-1-naphthoates the slope (ρ) of the best Hammett regression line is 2·21, the calculated log k_0 is −2·585, and the correlation coefficient is 0·997. From the expression $\sigma_n = (\log k_{50} + 2{\cdot}585)/2{\cdot}21$, substituent constant values (σ_n, see ref. 2) applicable to this reaction have been calculated and are given, together with McDaniel and Brown's values (σ), in Table 2. This shows that the largest deviations occur with the 4-F, the 4-NO_2 and, outstandingly, the 4-NMe_2 substituent. No steric inhibition of mesomerism is observed for the methoxy-group, presumably because it can lie in the plane of the naphthalene ring with its methyl group "*trans*" to the *peri*-hydrogen atom. On the other hand, for the substituted amino-group, as for the nitro-substituent, inhibition of mesomerism is to be expected. Of these two groups, the very much greater deviation, from the normal σ value, of the dimethylamino-group is in accord with prediction. Resonance

[1] Fischer, Murdoch, Packer, Topsom, and Vaughan, *J.*, 1957, 4358.
[2] Fischer, Mitchell, Ogilvie, Packer, Packer, and Vaughan, *J.*, 1958, 1426.
[3] Taft, *J. Amer. Chem. Soc.*, 1957, **79**, 1045.
[4] McDaniel and Brown, *J. Org. Chem.*, 1958, **23**, 420.

TABLE 2.

Subst.	H	3-NO_2	3-Cl	4-Cl	3-Br	4-Br
σ_n	−0·013	0·703	0·368	0·242	0·368	0·255
σ	0·000	0·710	0·373	0·227	0·391	0·232
Deviation	−0·013	−0·007	−0·007	+0·015	−0·023	−0·023
Subst.	3-Me	4-Me	4-F	4-OMe	4-NO_2	4-NMe_2
σ_n	−0·075	−0·165	0·115	−0·278	0·721	−0·24
σ	−0·069	−0·170	0·062	−0·268	0·778	−0·83
Deviation	−0·006	+0·005	+0·053	−0·010	−0·057	+0·59

inhibition of this substituent has been observed previously in the alkaline hydrolysis of benzoate esters carrying one [5] or two [6] methyl groups adjacent to it: for one methyl group the substituent constant for the dimethylamino-group is −0·36. Thus the steric inhibition of mesomerism resulting from a single *ortho*-methyl group is quite marked. It has been shown recently [7] that a *peri*-CH group of naphthalene has a slightly greater steric effect than an *ortho*-methyl substituent of a benzene derivative, since the strain in 1-methylnaphthalene is measurably greater than that in *o*-xylene. For comparison with this result, values of substituent constants derived from ester hydrolysis indicate that the *peri*-CH grouping has a steric effect at least equal to that of an *ortho*-methyl group.

We thank Dr. A. D. Campbell, University of Otago, for the microanalyses and the Research Committee of the University of New Zealand for a grant.

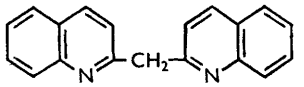
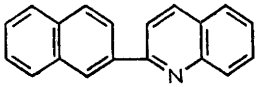
UNIVERSITY OF CANTERBURY,
CHRISTCHURCH, NEW ZEALAND. [*Received, October 6th*, 1958.]

[5] Price and Lincoln, *J. Amer. Chem. Soc.*, 1951, **73**, 5838.
[6] Westheimer and Metcalf, *ibid.*, 1941, **63**, 1339.
[7] Packer, Vaughan, and Wong, *ibid.*, 1958, **80**, 905.

258. *ω-Halogenomethyl-pyridines, -quinolines, and -isoquinolines. Part VIII.* The Formation of 2-β-Naphthylquinoline from Di-2-quinolylmethane.*

By B. R. BROWN, D. LL. HAMMICK, J. NEWBOULD, and A. L. PRICE.

IN the preparation of di-2-quinolylmethane (I) from 2-chloro- or 2-bromo-quinoline and quinaldine, difficulty was experienced in repeating the work of Scheibe and Schmidt.[1,2] When vigorous conditions were used, chromatography of the products on alumina showed that, as well as diquinolylmethane, a small amount of another compound, m. p. 163°, was produced which by comparison with a synthetic specimen was identified as 2-β-naphthylquinoline (II).

(I)   (II)

We have proved that 2-β-naphthylquinoline results from the reaction of diquinolylmethane with quinaldine hydrobromide in quinaldine at the boiling point. Presumably it is formed by this route during the preparation of diquinolylmethane. Careful purification of the starting materials has shown that in neither preparation does the naphthylquinoline arise from impurities, but at this stage it is not profitable to speculate on the mechanism of this remarkable change in which the nitrogen atom of a quinoline ring is eliminated.

Experimental.—2-β-Naphthylquinoline [3] separated from ethanol as pale yellow plates, m. p. 163° (Found: C, 89·2; H, 5·1; N, 5·5. Calc. for $C_{19}H_{13}N$: C, 89·45; H, 5·1; N, 5·5%). The *picrate* separated from ethanol as yellow plates, m. p. 174° (Found: C, 61·4; H, 3·85; N, 10·5. $C_{25}H_{16}O_7N_4,C_2H_6O$ requires C, 61·1; H, 4·15; N, 10·6%).

Reaction of 2-bromoquinoline with quinaldine. A mixture of 2-bromoquinoline (7·2 g.) and

* Part VII, *J.*, 1957, 5073.

[1] Scheibe, *Ber.*, 1921, **54**, 786.
[2] Scheibe and Schmidt, *Ber.*, 1922, **55**, 3159.
[3] Buu-Hoï and Cagniant, *Rec. Trav. chim.*, 1943, **62**, 713.

quinaldine (15 ml.) was heated to boiling during 20 min. and refluxed gently for 20 min. After extraction with acetone (400 ml.) and steam-distillation, the residual aqueous mixture was extracted with benzene (800 ml.), and the extract concentrated to 50 ml., and chromatographed on alumina (Spence Grade O; 300 g.). Elution with benzene (1 l.) yielded 2-β-naphthylquinoline (20 mg.) which separated from ethanol as pale yellow plates, m. p. and mixed m. p. 163° (Found: C, 89·1, 89·2; H, 5·45, 5·2; N, 5·4, 5·0%). The infrared and ultraviolet spectra were identical with those of an authentic specimen. The picrate separated from ethanol as yellow plates, m. p. and mixed m. p. 174° (Found: C, 61·0; H, 4·1; N, 10·9%).

Further elution with benzene–ether (1 : 1 v/v; 3 l.) yielded di-2-quinolylmethane (1·4 g.) which separated from light petroleum (b. p. 100—120°) as pink needles, m. p. 102°.

A similar experiment with 2-chloroquinoline gave the same products.

Reaction of di-2-quinolylmethane with quinaldine hydrobromide. Diquinolylmethane (3·3 g.), quinaldine (3·8 ml.), and quinaldine hydrobromide (1·25 g.) were brought to boiling during 30 min. and refluxed for 40 min. Extraction and chromatography as above yielded a yellow oil (0·30 g.) and unchanged diquinolylmethane (2·0 g.). Chromatography of the yellow oil yielded 2-β-naphthylquinoline which separated from ethanol as pale yellow plates (3 mg.), m. p. and mixed m. p. 162°. The infrared spectrum was identical with that of the synthetic specimen.

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, October 29th,* 1958.]

259. *Studies of the Coal-tar Bases. Part VIII.* Isolation of 2 : 3 : 6-Trimethylpyridine from the Collidine Fraction.*

By R. F. EVANS.

PREVIOUS Parts described the successful application of fractional distillation to the separation of constituents of the picoline [1,2] and lutidine [3] fractions of coal-tar bases. Fractional distillation of the collidine fraction, either alone or mixed with an azeotrope-forming substance such as phenol,[3] removes minor constituents such as 3-ethylpyridine, but does not bring about worthwhile separation of the two major components, 2 : 3 : 6- and 2 : 4 : 6-trimethylpyridine. This is in accord with the results of earlier investigators [4–7] who combined fractional distillation and fractional precipitation with picric or picrolonic acids to obtain small quantities of purified 2 : 3 : 6-trimethylpyridine from a mixture of coal-tar or petroleum bases. This being laborious, Tsuda *et al.*[8] synthesised 2 : 3 : 6-trimethylpyridine for use in dissociation constant experiments [9] in preference to using a specimen from coal-tar.

Since we were interested in the isolation of 2 : 3 : 6-trimethylpyridine in kilogram quantities, a promising new chemical approach was initiated. A binary mixture of 2 : 3 : 6- and 2 : 4 : 6-trimethylpyridine, produced by precise fractional distillation under reduced pressure of a crude collidine fraction, was converted into the *N*-oxides which were then treated with concentrated nitric and sulphuric acids. 2 : 3 : 6-Trimethylpyridine *N*-oxide, the only pyridine *N*-oxide present with a vacant 4-position, was the only constituent nitrated. 2 : 3 : 6-Trimethyl-4-nitropyridine *N*-oxide, a high-melting solid, separated easily and was easily purified. The nitro-group could be replaced by chlorine by heating with concentrated hydrochloric acid; the temperature (190°) required for this nucleophilic replacement was much higher than that (110°) required for the corresponding transformation in 4-nitropyridine *N*-oxide,[10] and reflected the adverse effect of three methyl groups releasing electrons to the pyridine nucleus. A two-stage reduction of 4-chloro-2 : 3 : 6-trimethylpyridine *N*-oxide afforded pure 2 : 3 : 6-trimethylpyridine.

* Part VII, Coulson and Ditcham, *J.*, 1957, 356.

[1] Coulson and Jones, *J. Soc. Chem. Ind.*, 1946, **65**, 169.
[2] Jones, *ibid.*, 1950, **69**, 99.
[3] Coulson, Hales, Holt, and Ditcham, *J. Appl. Chem.*, 1952, **2**, 71.
[4] Eckert and Loria, *Monatsh.*, 1917, **38**, 225.
[5] Hackmann, Wibaut, and Gitsels, *Rec. Trav. chim.*, 1943, **62**, 229.
[6] Matsumoto and Ihara, *Coal Tar (J. Japan Tar Ind. Assoc.)*, 1951, **3**, 224; *Chem. Abs.*, 1952, **46**, 7741.
[7] Fushizaki, *Technol. Repts. Osaka Univ.*, 1951, **1**, 309; *Chem. Abs.*, 1592, **46**, 7746.
[8] Tsuda, Ikekawa, Iino, Furukawa, and Hattori, *Pharm. Bull. (Japan)*, 1953, **1**, 126.
[9] Ikekawa, Sato, and Maeda, *ibid.*, 1954, **2**, 205.
[10] Den Hertog and Combé, *Rec. Trav. chim.*, 1951, **70**, 581.

Experimental.—Microanalyses and infrared spectral measurements were carried out by Miss M. Corner and Mr. W. Kynaston respectively of this laboratory. M. p.s are corrected.

Oxidation of collidines. The starting material was a fraction, b. p. 107—108°/100 mm., which was obtained by the refractionation through a 50-plate column of a crude collidine fraction kindly supplied by Messrs. Yorkshire Tar Distillers Ltd. Infrared analysis revealed that this fraction was a binary mixture of 2 : 3 : 6-trimethylpyridine (*ca.* 65% w/w) and its 2 : 4 : 6-isomer.

This binary mixture (121 g.) was quantitatively converted into the *N*-oxides with glacial acetic acid (600 ml.) and hydrogen peroxide (198 ml., 30%) according to Ochiai's procedure.[11]

2 : 3 : 6-*Trimethyl*-4-*nitropyridine* N-*oxide*. The mixed *N*-oxides (68·5 g., 0·5 mole), concentrated sulphuric acid (200 ml., *d* 1·98) and concentrated nitric acid (50 ml., *d* 1·42) were heated on the steam-bath under reflux for 7½ hr. The cold mixture was poured into 2 l. of water and the solution was made slightly alkaline with sodium hydroxide solution. After cooling, the solid yellow nitro-compound (21 g.) was filtered off. Chloroform extraction of the filtrate led to the recovery of additional nitro-compound (3·5 g.) giving a total yield of 40% based on the amount of 2 : 3 : 6-trimethylpyridine present in the starting material. After two crystallisations from alcohol, 2 : 3 : 6-*trimethyl*-4-*nitropyridine* N-*oxide* had m. p. 115·5—117° [Found: C, 52·7; H, 5·7; N, 15·2. $C_8H_{10}O_3N_2$ requires C, 52·7; H, 5·5; N, 15·4%].

4-*Chloro*-2 : 3 : 6-*trimethylpyridine* N-*oxide*. Nitro-compound (20·2 g.) and hydrochloric acid (95 ml. of 24%) were heated at 190—200° in a sealed tube for 24 hr. The mixture was evaporated at 100°/20 mm., the residue was dissolved in water and titrated with aqueous sodium hydroxide to a phenolphthalein end-point. The solution was again evaporated to dryness at 100°/20 mm. and the solid residue was extracted four times with boiling alcohol. Evaporation of the alcoholic extract furnished 4-*chloro*-2 : 3 : 6-*trimethylpyridine* N-*oxide* (16 g., 92%) which crystallised from acetone in white needles, m. p. 135—137·5° [Found: C, 56·2; H, 6·2; N, 7·9; Cl, 20·7. $C_8H_{10}ONCl$ requires C, 56·0; H, 5·9; N, 8·2; Cl, 20·7%).

4-*Chloro*-2 : 3 : 6-*trimethylpyridine*. 4-Chloro-2 : 3 : 6-trimethylpyridine *N*-oxide (7·25 g.), iron powder (4 g.), and glacial acetic acid (40 ml.) were heated on the steam-bath under reflux for 2 hr. The mixture was made alkaline with aqueous sodium hydroxide and steam-distilled for 2 hr. The aqueous distillate being cooled in ice, 4-*chloro*-2 : 3 : 6-*trimethylpyridine* (6·0 g.), m. p. 33·5—34·5°, separated (Found: C, 61·8; H, 6·5; N, 8·6. $C_8H_{10}ONCl$ requires C, 61·8; H, 6·5; N, 9·0%). Ether-extraction of the filtrate gave additional material (0·9 g.) which brought the total yield of chloro-compound almost to 100%. The *picrate* crystallised in yellow needles, m. p. 139·5—141·5°, from alcohol [Found: C, 43·6; H, 3·5; N, 14·6. $C_{14}H_{13}O_7N_4Cl$ requires C, 43·7; H, 3·4; N, 14·6%).

2 : 3 : 6-*Trimethylpyridine*. In a typical experiment, 4-chloro-2 : 3 : 6-trimethylpyridine (6·6 g.), potassium acetate (5 g.), methanol (25 ml.), and palladium chloride (1 g.) were shaken with hydrogen at room temperature and atmospheric pressure until no more hydrogen was absorbed (4½ hr.). The mixture was filtered and the filtrate evaporated on the steam-bath. Water was added to the residue, which was made alkaline with aqueous sodium hydroxide and twice extracted with ether. The ether extract was dried (Na_2SO_4) and distilled to give 2 : 3 : 6-trimethylpyridine (2·5 g., 49%), b. p. 172°. The infrared spectrum of this material revealed the absence of 2 : 4 : 6-trimethylpyridine. The picrate crystallised as yellow needles, m. p. 146—148° (lit., m. p. 144·5—145·5°,[8] 148—149° [5]), from alcohol (Found: C, 48·45; H, 4·4; N, 15·3. Calc. for $C_{14}H_{14}O_7N_4$: C, 48·0; H, 4·0; N, 15·9%).

NATIONAL CHEMICAL LABORATORY, D.S.I.R., TEDDINGTON. [*Received, November 10th*, 1958.]

[11] Ochiai, *J. Org. Chem.*, 1953, **18**, 534.

---

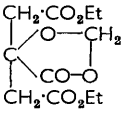
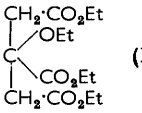
260. *Hydrolysis of "Ethyl Methylenecitrate" [5 : 5-Di(ethoxycarbonylmethyl)-1 : 3-dioxolan-4-one], and an Attempted Synthesis of Agaric Acid.*

By D. W. S. EVANS.

ONE optical form of agaric acid (α-hexadecylcitric acid) occurs in the Basidiomycete, *Polyporus officinalis*, Vill. In an attempt to synthesise this acid two preliminary investigations were undertaken. First, it was confirmed that an ester containing an α-CH_2 group could be monoalkylated by the Hudson and Hauser technique,[1] although

[1] Hudson and Hauser, *J. Amer. Chem. Soc.*, 1940, **62**, 2457; 1941, **63**, 3156.

the yield was poor (13·2% for ethyl α-methylbutyrate). Secondly, it was found as the result of a large number of experiments, in which conditions (nature and amount of hydrolysing agent, duration of reaction, and temperature) were varied widely, that compound (I) could be converted in high yield (about 80%) into citric acid by hydrolysis with cold aqueous sodium hydroxide followed by aqueous ammonia under pressure to effect ring opening. An alternative method (catalytic hydrogenation) did not open the methylene ring. [Several attempts to regenerate citric acid from " methylenecitric acid " or its ester (I) have been reported.[2-4]]

(I)   (II)

When the ester (I) was converted into its α-hexadecyl derivative by Hudson and Hauser's method [1] and the product hydrolysed, the only significant substance isolated was a small amount of stearic acid: von Thoms and Vogelsang [5] showed that stearic acid is a product of alkaline decomposition of agaric acid. The instability of the latter is well known,[6] and it appears that in the attempted synthesis the conditions necessary for removal of the protecting ring structure were too rigorous to allow the survival of the desired product. An attempt to prepare agaric acid by monoalkylation of the ethyl ether (II) was also abortive.

Experimental.—" *Ethyl methylenecitrate* " [5 : 5-*di*(*ethoxycarbonylmethyl*)-1 : 3-*dioxolan*-4-*one*] (I). This was obtained by the following modification of the method of Bayer & Co.[4] " Methylenecitric acid " [3] (131 g.) was heated for 5 hr. under reflux with absolute alcohol (505 ml.), and sulphuric acid (17·2 ml.), then cooled and poured into ice-cold water (1 l.). The crystals were separated, washed three times by stirring with cold water, collected, and dried. They melted at 47°, and did not lose weight on storage as a powder for three days *in vacuo* over phosphoric anhydride. However, when the ester was dissolved in benzene, water equivalent to about 30% of the weight of ester separated. The water was run off, more benzene added, and the solution dried in a Dean and Starke apparatus. After removal of excess of solvent it deposited the ester (65 g., 39%), m. p. 54°, unchanged on further crystallisation from benzene (Bayer & Co.[4] gave m. p. 55°) (Found: C, 50·9; H, 6·4. Calc. for $C_{11}H_{16}O_7$: C, 50·8; H, 6·2%).

Optimum conversion into citric acid. The ester (I) (5 g.) was shaken vigorously for 90 hr. at room temperature with 2N-sodium hydroxide (25 ml.). 2N-Ammonia (38 ml.) was added to the faintly yellow solution, and the mixture was transferred to five 30 ml. soft-glass tubes with well-collapsed bottom seals. These were closed and kept at 100° for 20 hr., the usual precautions being taken. The combined dark orange liquors were acidified (with 6N-hydrochloric acid, 14 ml.), mostly decolorised with carbon, and diluted to 1500 ml. A 10 ml. aliquot part then contained 24·6 mg. (78·3%) of citric acid (assayed absorptiometrically [7]). The remainder was concentrated and again treated with carbon, and the acid obtained through its barium salt as colourless hygroscopic crystals of m. p. 153° (after drying at 120°) [Found: equiv., 63·9. Calc. for $C_3H_5O(CO_2H)_3$: equiv., 64·0]. Its *p*-bromophenacyl ester had m. p. and mixed m. p. 146·8° (three crystallisations from 65% ethanol). The *p*-nitrobenzyl ester after one similar recrystallisation had m. p. and mixed m. p. 103°.

I thank the Ministry of Education for a grant.

THE UNIVERSITY, NOTTINGHAM. [*Received, November 17th*, 1958.]

[2] de Bruyn and van Ekenstein, *Rec. Trav. chim.*, 1901, **20**, 231; Chem. Farb. Schering., Friedlander's " Fortschritte," 1901, Vol. VI, p. 1222.
[3] Sternberg, *Pharm. Ztg.*, 1901, **46**, 1004.
[4] Bayer & Co., Friedlander's " Fortschritte," 1908, Vol. IX, p. 899 (see, however, Hanzlik, *J. Urol.*, 1920, **4**, 145).
[5] von Thoms and Vogelsang, *Annalen*, 1907, **357**, 145.
[6] Schmieder, *Arch. Pharm.*, 1886, **224**, 661.
[7] Hunter and Leloir, *J. Biol. Chem.*, 1945, **159**, 295.