774. 7-(2 : 3-*Dihydroxypropyl*)*theophylline.*

By David B. Ishay.

This substance [1] is best prepared as follows :

Theophylline (180 g.; dehydrated) is dissolved in N-potassium hydroxide, the solution evaporated to dryness on a water-bath, and the residual potassium salt dried *in vacuo*. It is added portionwise, with stirring, to α-chlorohydrin (122 g.) at 115° during 40—60 min. The mixture is then heated at 120—125° for 1 hr., and methanol (500 c.c.) is dropped in with stirring. The precipitated potassium chloride is filtered off and washed with methanol (50 c.c.). Cooling the filtrate and washings in ice–salt causes crystallisation of 7-(2 : 3-dihydroxypropyl)theophylline which was washed with acetone–methanol (1 : 1; 2 × 50 c.c.). The product (198 g., 78%) then has m. p. 155—158°.

Hillel Remedy Factory Ltd.,
Haifa Bay, Israel.

[*Received, February 2nd*, 1956.]

[1] Maney, Jones, and Korns, *J. Amer. Pharm. Assoc.*, 1946, **35**, 266; U.S.P. 2,575,344.

775. *Effect of Added Hydroxy-compounds on the Association of Benzoic Acid.*

By Winifred G. Wright.

Previously it had been shown [1] that very small concentrations of water in benzene increase the association of benzoic acid in that solvent. The three alcohols, di-*p*-*tert*.-butylphenyl- and di-*p*-methoxyphenyl-methanol and 1-β-naphthylethanol, have now been found to exert a similar effect, the increase in association produced by the alcohol being comparable to that obtained by a similar concentration of water and becoming greater with increase of alcohol concentration.

The experimental methods were as described previously.[1] Plots of degree of association against concentration of solute at constant concentration of alcohol had the same shape as that recorded earlier for the association of benzoic acid in benzene in the presence of water and tended to become parallel to the concentration axis; rounded values of M/M_0 at 0·10 mole of solute/1000 g. of solvent are recorded in the Table.

Solute	Concn. of added alcohol (moles/1000 g. of solvent)	M/M_0
Nil	—	1·6
Water	0·0158	1·9
Di-*p*-*tert*.-butylphenylmethanol	0·0155	1·9
Di-*p*-methoxyphenylmethanol	0·0158	1·9
1-β-Naphthylethanol	0·0139	1·8
,, ,,	0·0239	1·9

University of Natal, Durban.

[*Received, March 27th*, 1956.]

[1] Wright, *J.*, 1949, 683.

776. *The Preparation of* [2 : 4 : 7 : 9-$^{14}C_1$]-1 : 10-*Phenanthroline and* [4 : 4′ : 6 : 6′-$^{14}C_1$]-2 : 2′-*Dipyridyl.*

By Peter Ellis, R. G. Wilkins, and M. J. G. Williams.

In continuation of our studies [1] of exchange reactions of complex ions by using labelled ligands we have synthesized [^{14}C]-1 : 10-phenanthroline in yields better than those of reported preparations [2,3] of the inactive material.

[1] Popplewell and Wilkins, *J.*, 1955, 4098.
[2] Halcrow and Kermack, *J.*, 1946, 155.
[3] Breckenridge and Singer, *Canad. J. Res.*, 1947, **25**, *B*, 583.

1 : 10-Phenanthroline is usually prepared by a Skraup reaction [4] between *o*-phenylenediamine and glycerol in the presence of sulphuric and arsenic acids. Carbon-14 can therefore be introduced into the phenanthroline molecule *via* either (*a*) labelled diamine or (*b*) labelled glycerol. We chose the latter for two reasons: first [1-^{14}C]glycerol is readily available (The Radiochemical Centre, Amersham), whereas *o*-phenylenediamine would need to be prepared from [*ar*-$^{14}C_1$]aniline. Secondly, the subsequent conversion of [^{14}C]-1 : 10-phenanthroline into [^{14}C]-2 : 2′-dipyridyl would involve a loss of one-third of the radioactive carbon if the former originated from uniformly labelled aniline but not if it was prepared from [1-^{14}C]glycerol.

Unfortunately, a three- or four-fold excess of glycerol is usually employed in the Skraup reaction.[4] In a modification of the original procedure,[2] we were able to improve the reported yield (45%) by strict control of the conditions and substantially reduced the amount of glycerol without loss of yield, which amounted to 70% based on diamine and 44% based on glycerol.

[^{14}C]Phenanthroline was converted into [^{14}C]-2 : 2′-dipyridyl in 55% yield by oxidation [5] to [^{14}C]dipyridyl-3 : 3′-dicarboxylic acid and decarboxylation of the latter with copper powder in diphenyl at 200°.

Experimental.—A series of Skraup reactions essentially following Halcrow and Kermack's method [2] were carried out with *o*-phenylenediamine (2 g.). Different temperatures, times of reaction, and amounts of glycerol were tried with results shown in the Table. These results represent the mean of several experiments. In general, stirring improved the yield. There appeared to be an increase in yield of crude product as the amount of glycerol was reduced, but this may have been fortuitous.

Temp.	Time (min.)	Glycerol (g.)	Yield † (%)	Temp.	Time (min.)	Glycerol (g.)	Yield † (%)
130—140°	120	10·8 *	6	140—145°	60	6·0	32
150—160	60	10·8	9	140—145	60	4·6	50
140—145	60	10·8	15	140—145	60	3·5	tar, difficult
140—145	75	10·7	14	140—145	60	1·8	to solidify
140—145	90	8·0	23				

* 3 moles. † Based on glycerol.

[^{14}C]*Phenanthroline.* [1-^{14}C]glycerol (0·05 mc; 4·5 mg.; supplied by The Radiochemical Centre, Amersham), inactive glycerol (4·6 g.), *o*-phenylenediamine (2·0 g.), sulphuric acid (44 c.c.; 69%) and arsenic acid (10 c.c.; 80%) were heated for 60 min. at 140—145°. After cooling, water was added (60 c.c.) and then ammonia solution (120 c.c.; *d*, 0·88), and the mixture was set aside overnight. The tar was filtered off and dried. The filtrate was extracted with several portions of hot benzene; the tar was boiled for about 50 hr. with benzene. Evaporation of the solvent from the combined extracts left a brown granular solid (2·7 g.). The identity of this crude product (*A*) was established as follows (similarly prepared inactive material being used): (*a*) Spectrophotometric analysis as the deeply coloured ferrous complex [6] indicated that material (*A*) contained about 90% phenanthroline; possible impurities (*e.g.*, *o*-phenylenediamine, 8-aminoquinoline) are not likely to form strongly coloured ferrous complexes. (*b*) Distillation of (*A*) (3·1 g.) at 150—160°/0·1 mm. and subsequent crystallisation from water (charcoal) gave 1 : 10-phenanthroline hydrate (2·7 g.) (Found: C, 72·5; H, 5·05; N, 14·3. Calc. for $C_{12}H_{10}ON_2$: C, 72·7; H, 5·0; N, 14·2%). (*c*) Hydrated nickel nitrate (1 mole) and material (*A*) (3·5 moles) heated in aqueous solution gave a brown solution. This was extracted with ether and the remaining cherry-red aqueous solution evaporated slowly almost to dryness. The crystalline product was washed with a very small amount of cold water, alcohol, and finally chloroform (which removed a small amount of brown material). The spectrum of this dried product, obtained in very good yields, agreed exactly with that of authentic triphenanthrolinenickel(II) nitrate.

[^{14}C]-2 : 2′-*Dipyridyl.* Crude phenanthroline (2·3 g.) was converted into impure 2 : 2′-[^{14}C]-dipyridyl-3 : 3′-dicarboxylic acid by alkaline permanganate as described by Smith and Inglett.[5] We were not able to reproduce, consistently, the yields (80%) reported by these authors but our

[4] " Organic Reactions," Chapman and Hall Ltd., London, 1953, Vol. VII, p. 59.
[5] Smith and Inglett, *J. Amer. Chem. Soc.*, 1950, **72**, 842.
[6] Kolthoff, Leussing, and Lee, *ibid.*, p. 2173.

preparation was carried out on a similar scale. The product (1·8 g.) was not further purified but was well mixed with diphenyl (6·0 g.) and precipitated copper (1·0 g.; Hopkin and Williams), and the mixture heated at 190—210° until evolution of carbon dioxide ceased (about 20 min.). The cooled melt was removed from the reaction flask with cold methylated spirit, and after copper had been filtered off the solvent was removed. Dipyridyl was extracted from the residue by hot 2N-hydrochloric acid (about 100 c.c.) and the solution was boiled with animal charcoal. Sodium hydroxide was added to the filtered solution until crude dipyridyl (0·85 g.) was precipitated. A further 0·12 g. was obtained by extraction of the mother liquor with benzene. Light petroleum was added to this product, a small amount of insoluble impurity removed, and the filtrate evaporated almost to dryness. The crystalline residue (0·8 g.), m. p. 69—70° (Found: C, 75·5; H, 5·3; N, 17·7. Calc. for $C_{10}H_8N_2$: C, 76·9; H, 5·1; N, 17·9%), was shown to be pure 2 : 2′-dipyridyl by its ultraviolet spectra in methanol [7] and from the infrared spectra of the solid trisdipyridylnickel(II) nitrate when compared with samples obtained from "AnalaR" dipyridyl (m. p. 69—70°).

The radiochemical yield (92%) was determined by quantitative oxidation of the diluted glycerol and of the final pure complex to carbon dioxide, which was counted as "infinitely" thick barium carbonate samples.

We are grateful to the Department of Scientific and Industrial Research for a Maintenance Allowance (to M. J. G. W.) and to the University of Sheffield for an Alfred Tongue Scholarship (to P. E.).

THE UNIVERSITY, SHEFFIELD. [*Received, March 28th*, 1956.]

[7] Gillam, Hey, and Lambert, *J.*, 1941, 364.

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777. *Experiments with* 1 : 2 : 3 : 4-*Tetrahydro*-3-*methylquinazoline and Related Compounds.*

By A. R. OSBORN and K. SCHOFIELD.

DI- or TETRA-HYDRO-1- AND -3-METHYLQUINAZOLINE appeared to be promising starting materials for synthesis of 1- and 3-methylquinazolinium salts. Mirza [1] reported that 3-methyl-4-quinazolone, on reduction with lithium aluminium hydride, gave either 1 : 2-dihydro-3-methyl-4-quinazolone or 1 : 2 : 3 : 4-tetrahydro-3-methylquinazoline as the main product, depending upon the conditions. The tetrahydro-compound, for which no properties were reported but of which the picrate (m. p. 156°) and methiodide were described, was synthesised from 2-aminobenzylmethylamine, but details of the synthesis were not given.

In the present work we found that 3-methyl-4-quinazolone, with an equimolecular amount of lithium aluminium hydride gave, not 3 : 4-dihydro-4-hydroxy-3-methylquinazoline, but a 60% yield of crystalline 1 : 2 : 3 : 4-tetrahydro-3-methylquinazoline. With excess of the reagent a better yield of the same product was obtained. The structure of this compound was confirmed by synthesis, of which we give details.

With lead tetra-acetate the tetrahydro-compound gave 3 : 4-dihydro-3-methylquinazoline (identical with a specimen prepared by the method of Gabriel and Colman [2]) or 3-methyl-4-quinazolone, depending on the conditions. Potassium ferricyanide produced only the latter product. Iodine in ethanol has been used to oxidise tetrahydro*iso*quinolines to quaternary salts,[3] but 1 : 2 : 3 : 4-tetrahydro-3-methylquinazoline consumed only one equivalent of this reagent, producing an equimolecular mixture of 3 : 4-dihydro-3-methylquinazoline and starting material. The same oxidising agent in the presence of silver acetate gave an inseparable mixture, whilst in large excess it produced 3-methyl-4-quinazolone.

With palladium–charcoal in boiling ethanol 3 : 4-dihydro-3-methylquinazoline gave none of the desired product, and potassium ferricyanide produced 3-methyl-4-quinazolone.

[1] Mirza, *Sci. and Cult.*, 1952, **17**, 530.
[2] Gabriel and Colman, *Ber.*, 1904, **37**, 3646.
[3] Haworth, *J.*, 1924, 1675.

In the only successful experiment a poor yield of 3-methylquinazolinium hydroxide was obtained from the dihydro-compound by the action of excess of iodine in boiling butanol. It was later noticed that 3 : 4-dihydro-3-methylquinazoline was completely converted into 3-methyl-4-quinazolone when boiled in light petroleum, an observation according with the ready oxidation of 3-*p*-fluorophenyl-3 : 4-dihydroquinazoline recorded by Farrar.[4]

The more difficultly accessible 1-methyl-4-quinazolone [5] was reduced by lithium aluminium hydride to 1 : 2 : 3 : 4-tetrahydro-1-methylquinazoline, characterised as its picrate.

Experimental.—*2-Aminobenzylmethylamine.* When methyl-2-nitrobenzylamine [6] (4·66 g.), methanol (250 ml.), and 5% palladium–charcoal (2·5 g.) were shaken with hydrogen, reduction was complete in ½ hr. The filtered solution was evaporated under reduced pressure and the residue was distilled, giving the amine (3·0 g.), b. p. 114—118°/10 mm., as a very pale yellow oil. With alcoholic hydrochloric acid this gave the dihydrochloride, m. p. 218°. Busch [7] gave m. p. 217°.

1 : 2 : 3 : 4-*Tetrahydro-3-methylquinazoline.* The above diamine (0·3 g.), potassium hydroxide (0·2 g.), formaldehyde (excess of a 40% aqueous solution), and methanol (5 c.c.) were warmed for ¼ hr. on the steam-bath. The cooled mixture was extracted with ether, and the dried (Na_2SO_4) extract was concentrated. The residue, on recrystallisation from light petroleum (b. p. 40—60°), gave colourless needles of 1 : 2 : 3 : 4-*tetrahydro-3-methylquinazoline,* m. p. 83—83·5 (Found : C, 73·2; H, 8·4. $C_9H_{12}N_2$ requires C, 72·9; H, 8·2%), identical with the compound described below. The *picrate,* m. p. 134° (Found : C, 47·6; H, 3·8. $C_9H_{12}N_2,C_6H_3O_7N_3$ requires C, 47·8; H, 4·0%), formed orange-yellow needles from ethanol.

Reduction of 3-methyl-4-quinazolone. (*a*) 3-Methyl-4-quinazolone (2 g.) in ether (100 c.c.) was added slowly to lithium aluminium hydride (1 mol.) in refluxing ether (50 c.c.) under nitrogen. A yellow solid was precipitated, and refluxing was continued for 4 hr. Water was added and the mixture was poured into excess of 2N-sulphuric acid. The organic layer was removed and combined with an ether extract of the acid layer. The sticky residue (0·025 g.) obtained from the ether was extracted with boiling light petroleum (b. p. 40—60°), leaving undissolved a white solid which formed colourless crystals, m. p. *ca.* 111°, from benzene–light petroleum. Sublimation (85°/0·1 mm.) raised the m. p. to 111—114°. The substance was probably 1 : 2-dihydro-3-methyl-4-quinazolone for which Mirza reported m. p. 115°. The original aqueous acid layer was neutralised with barium hydroxide solution, filtered, and extracted with ether. The dried (Na_2SO_4) extract provided a cream-coloured solid (0·87 g.) which from light petroleum (b. p. 40—60°) gave needles of 1 : 2 : 3 : 4-tetrahydro-3-methylquinazoline, m. p. 83°, identical with that above. Strong basification of the aqueous mother-liquor with potassium hydroxide, and continuous extraction with benzene, gave more (0·48 g.) of this compound.

(*b*) The reduction was repeated with the quinazolone (1·48 g.) and a two-fold excess of lithium aluminium hydride in ether (100 c.c.). The initial yellow precipitate slowly dissolved. After being refluxed for 6 hr. the solution was decomposed with water and dilute sulphuric acid. Basification of the acid layer and extraction with ether afforded the tetrahydro-compound (1·08 g.).

Oxidation of 1 : 2 : 3 : 4-*tetrahydro-3-methylquinazoline.* (*a*) The tetrahydro-compound (0·2 g.) in acetic acid (10 c.c.) at 70° was treated with lead tetra-acetate (1·22 g.), in portions during 5 min. The deep red solution formed initially became gradually lighter. It was set aside at room temperature for 2 hr. and then heated for 15 min. on the steam-bath. The mixture was poured into water (50 c.c.), and the basified solution was extracted continuously with benzene. Evaporation of the dried (Na_2SO_4) extract gave a pale yellow oil (0·095 g.) which crystallised. With picric acid this gave 3 : 4-dihydro-3-methylquinazoline picrate which from ethanol formed bright yellow prisms, m. p. 197—199° (Found : C, 48·4; H, 3·5. Calc. for $C_9H_{10}N_2,C_6H_3O_7N_3$: C, 48·0; H, 3·5%), alone and mixed with a specimen obtained by the method of Gabriel and Colman.[2]

(*b*) A similar experiment with the tetrahydro-compound (0·2 g.) and lead tetra-acetate (2·5 g.) gave 3-methyl-4-quinazolone (0·04 g.), identified as its picrate (yellow needles from ethanol), m. p. and mixed m. p. 214°.

[4] Farrar, *J.*, 1954, 3253.
[5] Morley and Simpson, *J.*, 1949, 1354.
[6] Holmes and Ingold, *J.*, 1925, 1814.
[7] Busch, *J. prakt. Chem.*, 1895, **51**, 131.

(*c*) The tetrahydro-compound (0·295 g.) in absolute ethanol (15 c.c.) was heated on the steam-bath and treated dropwise with ethanolic iodine (2·55 g. in 50 c.c.) until the colour was no longer discharged (5 c.c. of the iodine solution were needed). The pale yellow solution deposited colourless crystals (0·195 g.; m. p. *ca.* 260°, giving a deep red melt) which were combined with the partly crystalline ether-insoluble residue (0·325 g.) obtained by evaporating the mother-liquor, dissolved in water, and strongly basified with 50% potassium hydroxide solution at 0°. Extraction with ether recovered a deliquescent solid (0·260 g.) which was treated with picric acid in ethanol. Fractional crystallisation of the product from methanol gave 3 : 4-dihydro-3-methylquinazoline picrate (0·21 g.), m. p. 197—199°, and 1 : 2 : 3 : 4-tetrahydro-3-methylquinazoline picrate (0·21 g.), m. p. 134°.

From an experiment carried out similarly, except that 4 equivs. of iodine were used, a poor recovery of a white solid (0·05 g.) was obtained. From this, boiling light petroleum removed 3-methyl-4-quinazolone (0·02 g.), identified as its picrate, and left undissolved a colourless solid (0·03 g.), m. p. 120—160°, which gave a neutral solution in water (3-methylquinazolinium hydroxide gives a strongly alkaline solution).

Oxidation of 3 : 4-*dihydro*-3-*methylquinazoline*. (*a*) The dihydro-compound (0·15 g.) in boiling butanol (10 c.c.) was treated with iodine (0·255 g.) in ethanol. The ethanol was boiled off and the butanol solution was refluxed for 3 hr., cooled, and poured into water. The mixture was basified with potassium hydroxide solution at 0° and extracted with ether. The solvent was removed from the dried ($CaSO_4$) extract *in vacuo* at 20° and the brown crystalline residue (0·1 g.) was boiled with ethyl acetate. A colourless solid (5 mg.; m. p. 195—220°) remained undissolved, and crystallisation of the ethyl acetate-soluble material from benzene gave colourless rhombs of 3-methylquinazolinium hydroxide (10 mg.), m. p. 163—165°, alone and mixed with a specimen prepared by the method of Schöpf and Oechler.[8]

(*b*) The dihydro-compound (0·18 g.) in water (2 c.c.) was added to 50% potassium hydroxide solution (1 c.c.) and then treated at −5° with potassium ferricyanide (0·3 g.) in water (2 c.c.). The mixture was shaken at −5° for 10 min. and filtered. The residue was washed with water, and the combined aqueous solution was repeatedly extracted with ether. Evaporation of the dried (Na_2SO_4) extract gave a solid (0·13 g.) which on recrystallisation from water gave 3-methyl-4-quinazolone m. p. 106°.

Three recrystallisations, from boiling light petroleum (b. p. 60—80°), of 3 : 4-dihydro-3-methylquinazoline resulted in the latter's complete conversion into 3-methyl-4-quinazolone.

1 : 2 : 3 : 4-*Tetrahydro*-1-*methylquinazoline*. 1-Methyl-4-quinazolone[5] (0·18 g.) was added by means of a Soxhlet apparatus to an excess of lithium aluminium hydride in ether (100 c.c.). The mixture was refluxed for 6 hr. and worked up by ether-extraction of the basified liquid in the usual way. The resulting brown oil did not crystallise and was converted into a picrate. Recrystallisation from ethanol gave orange-yellow crystals of 1 : 2 : 3 : 4-*tetrahydro*-1-*methylquinazoline picrate*, m. p. 161° (decomp.) (forming a red melt) (Found : C, 48·4; H, 3·9; N, 18·4. $C_9H_{12}N_2,C_6H_3O_7N_3$ requires C, 47·8; H, 4·0; N, 18·6%).

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[*Received, April 25th,* 1956.]

[8] Schöpf and Oechler, *Annalen*, 1936, **523**, 1.

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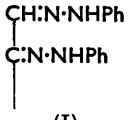
778. *The Ultraviolet Light Absorption of* 3-O-*Methylglycerosazone.*

By J. C. P. SCHWARZ and (in part) MAUREEN FINNEGAN.

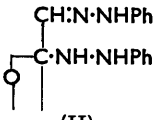
BARRY, MCCORMICK, and MITCHELL [1] have recently confirmed and extended earlier semi-quantitative observations [2] that sugar osazones have very similar ultraviolet light absorption spectra. It has been suggested that these compounds have acyclic structures containing the chromophore (I), which may be chelated,[3] rather than cyclic structures containing the chromophore (II), which would necessitate the presence of 2 : 3- and 2 : 4-epoxide rings in glycerosazone and erythrosazone, respectively. However, the spectra of the sugar osazones differ appreciably from those of the bisphenylhydrazones of glyoxal and

[1] Barry, McCormick, and Mitchell, *J.*, 1955, 222.
[2] Engel, *J. Amer. Chem. Soc.*, 1935, **57**, 2419.
[3] Mester, *ibid.*, 1955, **77**, 4301.

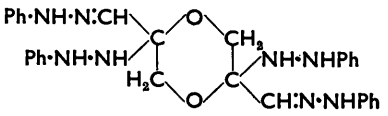
methylglyoxal [1] (see Table), which contain the chromophore (I). Furthermore, glycerosazone may have the cyclic structure (III) which contains the chromophore (II), and erythrosazone may be represented by a 1 : 4-epoxide ring structure. In view of recent conflicting evidence regarding the structure of the osazones,[4] we have examined the spectrum of 3-*O*-methylglycerosazone, in which epoxide ring formation is impossible.



(I)



(II)



(III)

Attempts to prepare 3-*O*-methylglycerosazone from 2 : 3-di-*O*-methylglyceraldehyde diethyl acetal [5] gave unpromising results, but the osazone was readily obtained from 1-hydroxy-3-methoxypropanone, prepared by oxidation of 1-*O*-methylglycerol with bromine in the presence of sodium carbonate.[6] Its ultraviolet light absorption spectrum (see Table) was found to be very similar to those of the osazones examined by Barry, McCormick,

3-*O*-Methylglycerosazone		Glycerosazone		Methylglyoxal bisphenylhydrazone (from ref. 1)	
$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ)	ε
396	21,800	395	20,600	364	46,250
308—310	9,900	308—310	9,800	302—304	11,950
256—257	20,300	256	18,900	—	—

and Mitchell.[1] This suggests that the difference in spectrum between the sugar osazones and methylglyoxal bisphenylhydrazone should be ascribed to the $C_{(3)}$-oxygen function in the former compounds, rather than to epoxide-ring formation.

Barry, McCormick, and Mitchell [1] have shown that the molecular extinction coefficients of the sugar osazones at the maximum in the region 395—399 mμ lie within a narrow range ($\varepsilon_{max.}$ = 20,100—20,700) and they have used this fact to determine molecular weights. 3-*O*-Methylglycerosazone was found to absorb slightly more strongly in this region; redetermination of the spectrum of glycerosazone gave good agreement with the results of the above authors. Spectrophotometric determination of molecular weights may therefore be less accurate with 3-*O*-substituted osazones.

During the course of this work it was noted that alcoholic solutions of glycerosazone and 3-*O*-methylglycerosazone showed considerable changes in spectrum after exposure to daylight for 5 hours. These changes, which include displacement of the maxima at 395—396 mμ towards shorter wavelengths, occur more slowly in the dark.

Experimental.—Glycerosazone was prepared from glyceraldehyde diethylacetal and crystallised from benzene.

3-O-*Methylglycerosazone*. 1-*O*-Methylglycerol [7] (11 g.) and anhydrous sodium carbonate (13 g.) in water (60 c.c.) were treated at 10° with bromine (4·8 c.c.), added in one portion with shaking. After 2 hr. the solution was acidified and the excess of bromine was destroyed with sulphur dioxide. The solution was then brought to pH 4 and treated with an aqueous solution of phenylhydrazine hydrochloride (5 g.) and sodium acetate (7 g.). After 24 hr. at 35°, the resulting tarry solid was separated by filtration. Crystallisation from benzene yielded 3-O-*methylglycerosazone* (0·85 g.); more (0·3 g.) was obtained by chromatography of the benzene mother-liquor on alumina. Three crystallisations from methanol yielded needles, m. p. 140—142° (Found: C, 68·2; H, 6·3; N, 19·5; OMe, 10·8. $C_{16}H_{18}ON_4$ requires C, 68·1; H, 6·4; N, 19·9; OMe, 11·0%). The m. p. and spectrum were unchanged by further crystallisation.

Light-absorption measurements. These were made on a Unicam SP 500 spectrophotometer with 1 cm. quartz cells and freshly prepared solutions of the osazones in 95% aqueous ethanol. The maxima were determined before the remainder of the spectrum.

[4] Aspinall and Schwarz, *Ann. Reports*, 1955, **52**, 255.
[5] Rothstein, *J.*, 1940, 1560.
[6] Neuberg, *Biochem. Z.*, 1931, **238**, 459.
[7] Grün and Bockisch, *Ber.*, 1908, **41**, 3465.

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DEPARTMENT OF CHEMISTRY, THE UNIVERSITY, EDINBURGH, 9. [*Received, May 18th,* 1956.]

779. *Reduction of Amides by Lithium Borohydride.*

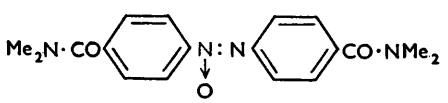
By M. DAVIS.

AMIDES are readily reduced to amines by lithium aluminium hydride, but not by sodium or potassium borohydride; lithium borohydride has not been extensively investigated in this connection.

Bailey [1] found that 2-acetamidoethanol gave only 1·5% of 2-ethylaminoethanol when treated with lithium borohydride in boiling tetrahydrofuran for 3 hours, and concluded that there was little risk of amide reduction with sparingly soluble peptides. On the other hand, Crawhall and Elliott [2] have demonstrated that certain peptides can undergo cleavage under similar conditions, with formation of the corresponding alcohol and amine. Wittig and Hornberger [3] found that some tertiary *N*-carbazolyl-amides of cinnamic acid and its vinylogues when treated with a limited amount (0·25 mol.) of lithium borohydride in boiling ether, gave some of the corresponding aldehyde, but that *NN*-dimethyl-, *NN*-methylphenyl-, and *NN*-diphenyl-amides were usually unaffected.

I have examined the behaviour of benzamide, *N*-methylbenzamide, and *NN*-dimethylbenzamide towards excess of lithium borohydride (1·1 mol.; prepared *in situ* from potassium borohydride and lithium chloride [4, 5]) in boiling tetrahydrofuran. The primary and secondary amides were recovered, but the tertiary amide was completely reduced to a mixture of *NN*-dimethylbenzylamine (33%) and benzyl alcohol (58%). The preparation of benzyl alcohol from *NN*-diethylbenzamide by using lithium aluminium hydride has been recorded by Nystrom and Brown,[6] but this reduction was carried out under conditions which favoured the formation of aldehyde rather than of amine.[7]

Previous workers have shown that the nitro-group does not normally interfere in the reduction of other groups by lithium borohydride, although Nystrom, Chaikin, and Brown [8] found that nitrobenzene gave 22% of aniline, 30% of unidentified oil, and 30% of unchanged material with the reagent in boiling ether–tetrahydrofuran, whilst Brown, Mead, and Subba Rao [5] reported that a vigorous reaction occurred with nitrobenzene in diethylene glycol dimethyl ether at 100°, but they made no attempt to characterise the products.



(I)

Treatment of *NN*-dimethyl-*p*-nitrobenzamide with lithium borohydride in boiling tetrahydrofuran gives the corresponding azoxy-compound (I) (41%) together with a neutral oil which is largely *p*-nitrobenzyl alcohol (52%). The structure assigned to (I) has been confirmed by further reduction with stannous chloride to *p*-amino-*NN*-dimethylbenzamide, and by independent synthesis from the known *pp'*-dicarboxyazoxybenzene.

Experimental.—Reduction of NN-*dimethylbenzamide.* Lithium chloride (4·66 g.; dried at 120°) was added to a stirred mixture of *NN*-dimethylbenzamide (14·9 g.) and potassium borohydride (5·94 g.) in anhydrous tetrahydrofuran (60 ml.). The mixture was refluxed for 20 hr., then cooled, diluted with water, and extracted with ether (3 × 150 ml.). The ether solution

[1] Bailey, *Biochem. J.*, 1955, **60**, 170.
[2] Crawhall and Elliott, *Nature*, 1955, **175**, 299.
[3] Wittig and Hornberger, *Annalen*, 1952, **577**, 11.
[4] Paul and Joseph, *Bull. Soc. chim. France*, 1952, 550; Kollonitsch, Fuchs, and Gabor, *Nature*, 1954, **173**, 125.
[5] Brown, Mead, and Subba Rao, *J. Amer. Chem. Soc.*, 1955, **77**, 6209.
[6] Nystrom and Brown, *ibid.*, 1948, **70**, 3738.
[7] Brown, *Organic Reactions*, 1951, **6**, 479.
[8] Nystrom, Chaikin, and Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 3245.

was washed with 2N-hydrochloric acid (2 × 50 ml.) and water, dried, and evaporated. The residue (6·3 g.) was benzyl alcohol, identified (mixed m. p.) as the *p*-nitrobenzoate, m. p. 84—86° (lit.,[9] m. p. 85°). The acid extract was basified and extracted with ether (2 × 100 ml.), and the washed and dried extract was evaporated, giving *NN*-dimethylbenzylamine (4·5 g.), identified (mixed m. p.) as the picrate, m. p. 95·5—96·5° (lit.,[10] 96°), and the methiodide, m. p. 179—181° (lit.,[11] 179°).

Reduction of NN-*dimethyl*-p-*nitrobenzamide*. Dry lithium chloride (2·26 g.) was added to a stirred mixture of *NN*-dimethyl-*p*-nitrobenzamide (9·4 g.) and potassium borohydride (2·88 g.) in anhydrous tetrahydrofuran (60 ml.). The mixture was refluxed for 20 hr., cooled, diluted with water, and filtered from pp'-*di*(*dimethylcarbamoyl*)*azoxybenzene* (3·35 g.; m. p. 211—216°), which separated from ethanol in orange plates, m. p. 214—216° [Found: C, 63·7; H, 6·05; N, 16·4%; *M*, 310 (in acetone). $C_{18}H_{22}O_3N_2$ requires C, 63·5; H, 5·9; N, 16·5%; *M*, 340]. [$\lambda_{max.}$ in EtOH: 272 (ε 10,700) and 332 mμ (ε 19,800); shoulder at 300 mμ (ε 14,100)]. Extraction of the original filtrate with ether gave a neutral oil (3·8 g.) which was largely *p*-nitrobenzyl alcohol and was identified (mixed m. p.) as the *p*-nitrobenzoate, m. p. 169—170° (lit.,[12] m. p. 168—168·5°). Further reduction of this azoxy-compound (1 g.) with stannous chloride dihydrate (4 g.) in concentrated hydrochloric acid (8 ml.) gave *p*-amino-*NN*-dimethylbenzamide, m. p. 152—153°, not depressed by an authentic specimen (lit.,[13] m. p. 153°). The *picrate* had m. p. 207—209°, not depressed by an authentic specimen, m. p. 208—210° (Found: C, 45·8; H, 4·15; N, 17·5. $C_9H_{12}ON_2,C_6H_3O_7N_3$ requires C, 45·8; H, 3·8; N, 17·8%).

Synthesis of pp'-*di*(*dimethylcarbamoyl*)*azoxybenzene*. *pp'*-Dicarboxyazoxybenzene, prepared as described by Bacharach and Weinstein [14] and recrystallised from dimethylformamide, did not melt <360°. A mixture of this acid (1 g.) and thionyl chloride (25 ml.) was refluxed for 7 hr., the filtered solution was evaporated, and the residue was warmed for 15 min. at 100° with aqueous dimethylamine (25%; 20 ml.). Recrystallisation of the product from ethanol gave the dimethylamide, m. p. 215—217°, mixed m. p. 215—216·5° (Found: C, 63·8; H, 6·35; N, 16·4%).

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THE RESEARCH LABORATORIES, MAY & BAKER LTD.,
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[*Received, May 28th,* 1956.]

[9] Meisenheimer and Schmidt, *Annalen*, 1929, **475**, 175.
[10] Von Braun, Kühn, and Goll, *Ber.*, 1926, **59**, 2335.
[11] Emde, *Arch. Pharm.*, 1909, **247**, 353.
[12] Lyons and Reid, *J. Amer. Chem. Soc.*, 1917, **39**, 1735.
[13] Wenker, *ibid.*, 1938, **60**, 1081.
[14] Bacharach and Weinstein, *Rec. Trav. chim.*, 1935, **54**, 931.

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780. (+)-β-*Aminobutyric Acid; the Correlation of its Configuration with that of* α-*Amino-acids.*

By K. BALENOVIĆ, N. BREGANT, and D. CERAR.

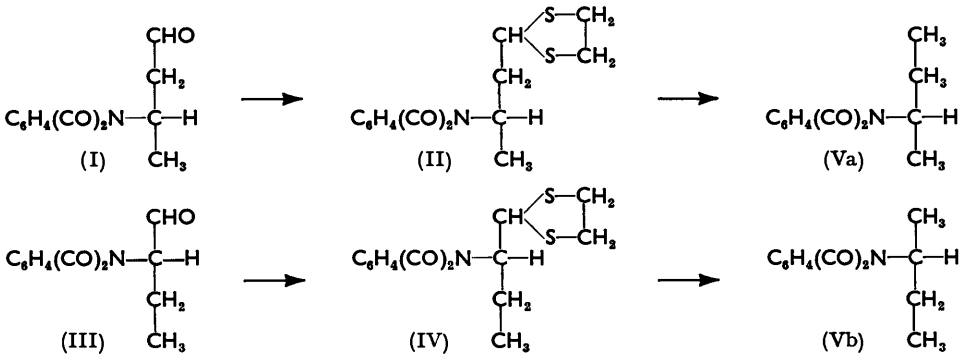
β-AMINOBUTYRIC ACID was first resolved into optical antipodes by Fischer and Scheibler.[1] A few years ago the (+)-antipode was prepared from L-alanine [2] by application of the Arndt–Eistert reaction. Wolff rearrangement of diazo-ketones used in the Arndt–Eistert procedure is known to proceed with retention of configuration when the rearrangement occurs at an asymmetric centre;[3] therefore (+)-β-aminobutyric acid was presumed to be of the L-configuration.*

In the present paper a description is given of the direct chemical correlation of configuration of (+)-β-aminobutyric acid with L-α-aminobutyric acid.

* In this paper, L is used in an extension of the convention for α-amino-acids to β-amino-acids.

[1] Fischer and Scheibler, *Annalen*, 1911, **383**, 337.
[2] Balenović, Cerar, and Fuks, *J.*, 1952, 3316.
[3] Lane, Willenz, Weissberger, and Wallis, *J. Org. Chem.*, 1940, **5**, 276.

(+)-β-Aminobutyric acid was converted into (+)-β-phthalimidobutyraldehyde (I) and its ethylene mercaptal (II). Analogous reactions were applied to the preparations of L-α-phthalimidobutyraldehyde (III) and its ethylene mercaptal (IV) prepared from L-α-aminobutyric acid. Desulphurisation [4] of the mercaptals (II) and (IV) with Raney nickel of low activity, in acetone,[5] gave the hitherto undescribed (+)-2-phthalimidobutane (Va) with $[\alpha]_D$ +34°, and (−)-2-phthalimidobutane (Vb) with $[\alpha]_D$ −32°.



(+)-β-Aminobutyric acid is therefore of the L-configuration, as was expected. Consequently, in the recently suggested terms [6] (+)-2-phthalimidobutane would now be (*S*)-2-phthalimidobutane, and the (−)-antipode would be (*R*)-2-phthalimidobutane.

Catalysts of higher activities than used in earlier similar desulphurisations [7] afforded 2-(hexahydrophthalimido)butanes.

Experimental.—(+)-β-*Phthalimidobutyric acid.* A solution of methyl (+)-β-phthalimidobutyrate [2] (3·2 g.) in acetic acid (18 c.c.) was treated with 48% hydrobromic acid (36 c.c.) and kept at 40—50° during 3 hr., with stirring. After cooling, water was added (100 c.c.) and the mixture extracted with benzene in the usual manner. The extracts were evaporated to dryness, and an oily residue of (+)-β-*phthalimidobutyric acid* (2·4 g., 80%) was obtained, which crystallised on addition of a small quantity of benzene. Recrystallisation from the same solvent gave white needles of the pure compound, m. p. 80° $[\alpha]_D^{19}$ +43 ± 1° (*c*, 1·61 in C_6H_6) (Found: C, 61·7; H, 4·9. $C_{12}H_{11}O_4N$ requires C, 61·8; H, 4·8%).

(+)-β-*Phthalimidobutyryl chloride.* A solution of the acid (2 g.) in thionyl chloride (15 c.c.) was left at room temperature overnight; the excess of thionyl chloride was then removed under reduced pressure and the oily residue of (+)-β-*phthalimidobutyryl chloride* (1·9 g., 88%) dissolved in benzene, from which white needles were obtained by precipitation with light petroleum (b. p 40—60°). Repeated recrystallisation from benzene–light petroleum yielded the pure compound, m. p. 92° and $[\alpha]_D^{20}$ +65° ±2° (*c*, 0·43 in C_6H_6) (Found: C, 57·1; H, 4·0. $C_{12}H_{10}O_3NCl$ requires C, 57·3; H, 4·0%).

(+)-β-*Phthalimidobutyraldehyde* (I). A solution of (+)-β-phthalimidobutyryl chloride (4·6 g., 0·02 mole) in xylene (20 c.c.) was reduced by the Rosenmund–Zetzsche procedure [8] with palladium (5%) on barium sulphate at 110—115°. After 5 hr. 0·70 mol. of hydrogen chloride had been evolved. The catalyst was filtered off, and the mixture evaporated *in vacuo* until crystallisation started (7—8 c.c.). (+)-β-*Phthalimidobutyraldehyde* (1·8 g., 46%), after recrystallisation from benzene–light petroleum or sublimation at 110°/0·016 mm., formed needles, m. p. 113°, $[\alpha]_D^{22}$ +68° ± 2° (*c*, 0·52 in C_6H_6) (Found: C, 65·9; H, 5·1. $C_{12}H_{11}O_3N$ requires C, 66·3; H, 5·1%).

(+)-β-*Phthalimidobutyraldehyde ethylene mercaptal* (II). The aldehyde (0·8 g.; $[\alpha]_D$ +47°) and ethanedithiol (0·5 c.c.) were dissolved in a 3% solution of anhydrous hydrochloric acid in dioxan (15 c.c.). After 3 days at room temperature, the solvent was removed *in vacuo*. The

[4] Bougault, Cattelain, and Chabrier, *Bull. Soc. chim. France*, 1938, **5**, 1699; 1940, **7**, 780.
[5] Cf. Spero, McIntosh, jun., and Levin, *J. Amer. Chem. Soc.*, 1948, **70**, 1907.
[6] Cahn, Ingold, and Prelog, *Experientia*, 1956, **12**, 81.
[7] Cf., *e.g.*, Mozingo, Wolf, Harris, and Folkers, *J. Amer. Chem. Soc.*, 1943, **65**, 1013; Wolfrom, Lemieux, and Olin, *ibid.*, 1949, **71**, 2870.
[8] Cf., *e.g.*, Mosettig and Mozingo, *Organic Reactions*, 1948, **4**, 368.

oily residue of *mercaptal* was dissolved in benzene (20 c.c.), filtered through alumina (10 g.), and washed with the same quantity of benzene. After evaporation of the combined filtrates *in vacuo*, a clear oil (0·9 g., 80%), $[\alpha]_D$ +41° ± 1° (unchanged after distillation at 130°/0·005 mm.), was obtained (Found: C, 57·6; H, 5·2. $C_{14}H_{15}O_2NS_2$ requires C, 57·3; H, 5·2%).

(+)-2-*Phthalimidobutane* (Va). A solution of the foregoing mercaptal (0·5 g., $[\alpha]_D$ +41°) in acetone [5] (15 c.c.) was heated with Raney nickel (7 g.; W-1 activity; [9] kept under 96% ethanol for 1 month before use) under reflux with stirring during 7 hr., then cooled. The catalyst was filtered off and washed with acetone, and the combined acetone filtrates were evaporated under reduced pressure. (+)-2-*Phthalimidobutane* remained as a colourless oil (0·3 g., 86%) which after two distillations at 60°/0·01 mm. became crystalline and had m. p. 33—35°, $[\alpha]_D^{18}$ +34° ± 1° (*c*, 1·43 in C_6H_6) (Found: C, 70·9; H, 6·7. $C_{12}H_{13}O_2N$ requires C, 70·9; H, 6·5%).

L-α-*Phthalimidobutyric acid*. A mixture of L-α-aminobutyric acid [10] (0·03 mole; $[\alpha]_D$ +20°) and phthalic anhydride (0·033 mole) was heated for 2 hr. at 115—120°, cooled, and dissolved in a small quantity of hot ethanol. Precipitation with water and recrystallisation from aqueous ethanol gave colourless needles of L-α-*phthalimidobutyric acid*, m. p. 73—75°, $[\alpha]_D$ −31° ± 1° (*c*, 1·71 in EtOH) (Found: C, 62·0; H, 5·0. $C_{12}H_{11}O_4N$ requires C, 61·8; H, 4·8%).

L-α-*Phthalimidobutyryl chloride*. L-α-Phthalimidobutyric acid and thionyl chloride were treated in the usual manner, and the *chloride* recrystallised from light petroleum as needles, m. p. 58°, $[\alpha]_D^{20}$ −59° ± 1° (*c*, 1·19 in C_6H_6) (Found: C, 57·5; H, 4·2. $C_{12}H_{10}O_3NCl$ requires C, 57·3; H, 4·0%).

(−)-α-*Phthalimidobutyraldehyde* (III) was prepared in the same manner as the inactive compound,[11] in 35% yield, with m. p. 83—84°, $[\alpha]_D^{20}$ −37° ± 1°) (*c*, 1·41 in C_6H_6) (Found: C, 66·3; H, 5·3. $C_{12}H_{11}O_3N$ requires C, 66·4; H, 5·1%).

This aldehyde (2·9 g.; $[\alpha]_D$ −32°) was converted into the *ethylene mercaptal* in the same manner as the β-compound (yield, 2·35 g., 60%), and after several recrystallisations from ethanol formed prisms, m. p. 121—122°, $[\alpha]_D^{17}$ +34° ± 1° (*c*, 1·61 in EtOH) (Found: C, 57·4; H, 5·2. $C_{14}H_{15}O_2NS_2$ requires C, 57·3; H, 5·2%).

(−)-2-*Phthalimidobutane* (Vb). The preceding mercaptal (0·5 g.; $[\alpha]_D$ +32°) was desulphurized in the same manner as the β-compound. The (−)-2-*phthalimidobutane* (0·3 g., 86%) thus obtained, after distillation at 60°/0·01 mm., had m. p. 33—35°, $[\alpha]_D^{18}$ −32° ± 1° (*c*, 1·81 in C_6H_6) (Found: C, 71·0; H, 6·4. $C_{12}H_{13}O_2N$ requires C, 70·9; H, 6·5%).

A mixture of equal quantities (10 mg.) of pure (+)- and (−)-2-phthalimidobutanes with m. p.s 33—35° was distilled at 60°/0·01 mm. The distillate solidified in long needles, was optically inactive, and had m. p. 24—25°, as described earlier [12] for racemic 2-phthalimidobutane.

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[9] Adkins and Covert, *J. Amer. Chem. Soc.*, 1932, **54**, 4116.
[10] Birnbaum, Levintow, Kingsley, and Greenstein, *J. Biol. Chem.*, 1952, **194**, 455.
[11] Balenović, Bregant, Galijan, Štefanac, and Škarić, *J. Org. Chem.*, 1956, **21**, 115.
[12] Mumm and Richter, *Ber.*, 1940, **73**, 843.