NOTES.

Dissociation Constants of the Dihydrolysergic Acids.

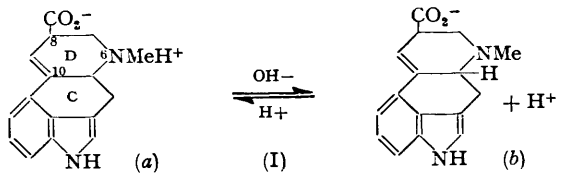
By J. B. STENLAKE.

[Reprint Order No. 5812.]

FOR reasons detailed elsewhere (*Chem. and Ind.*, 1953, 1089) and contrary to Cookson (*ibid.*, p. 337), Stenlake deduced from the $pK'_{a,2}$ values of lysergic (7·68, 7·96) and *iso*-lysergic acid (I) (8·31, 8·60) (see Craig, Shedlovsky, Gould, and Jacobs, *J. Biol. Chem.*, 1938, **125**, 289) that the former acid, being the weaker, has the conformation in which the carboxyl group and $N_{(6)}$ are remote from each other; it is here assumed that in both acids ring D has the semi-chair structure (cf. Raphael and Stenlake, *Chem. and Ind.*, 1953, 1286; Barton, Cookson, Klyne, and Shoppee, *ibid.*, 1954, 21); the carboxyl group would then be axial in *iso*lysergic and equatorial in lysergic acid. This interpretation is supported by comparable assignments of structure to the isomeric cytidylic and adenylic acids (Cavalieri, *J. Amer. Chem. Soc.*, 1953, **75**, 5268) based on dissociation constants, this being confirmed by independent chemical and physical evidence (Brown, Fasman, Magrath, Todd, Cochran, and Woolfson, *Nature*, 1953, **172**, 1184; Michelson and Todd, *J.*, 1954, 34).

Cookson (*loc. cit.*) showed by conformational analysis, based on the relative stabilities of the dihydrolysergic acids, that the carboxyl group is equatorial in dihydrolysergic acid I and dihydro*iso*lysergic acid II and axial in dihydro*iso*lysergic acid I. Thus on the

assumption that the now saturated ring D adopts the more stable chair conformation as in other piperidine derivatives (Sparke, *Chem. and Ind.*, 1953, 759; Bose and Chaudhuri, *Nature*, 1953, **171**, 652) the carboxyl group will be more remote from $N_{(6)}$ in dihydrolysergic

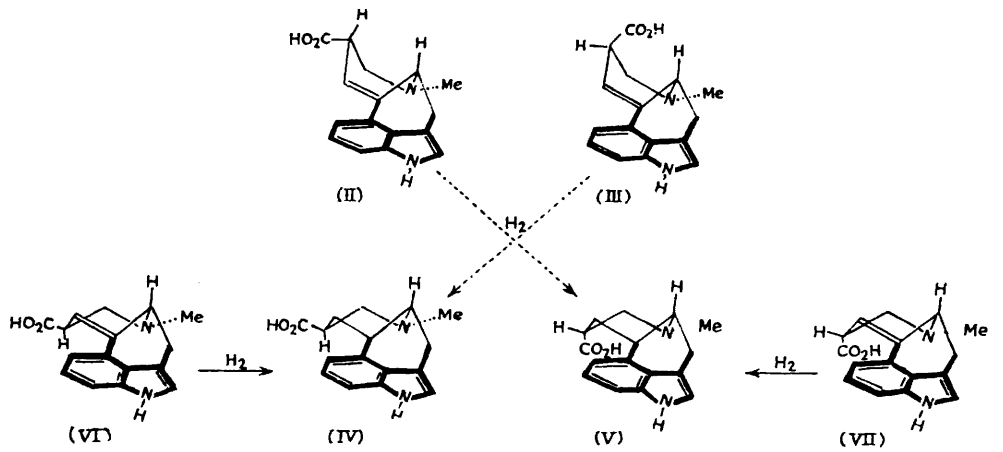


acid I and dihydro*iso*lysergic acid II than in dihydro*iso*lysergic acid I. Thus dihydro*iso*-lysergic acid I should be a stronger base (weaker base-conjugate acid) than the other two isomers. This has now been shown to be correct by measurement of the pK'_a of these three dihydro-acids (see Table). Dissociation constants for dihydrolysergic acid I and

	pK'_a at 20° (present work)	pK'_a at 24° (Craig *et al.*)
Dihydrolysergic acid I	8·50, 8·46	8·45
Dihydro*iso*lysergic acid I	8·88, 8·94	—
Dihydro*iso*lysergic acid II	8·52	8·57, 8·64

dihydro*iso*lysergic acid II measured by Craig *et al.* (*loc. cit.*; they did not give a figure for dihydro*iso*lysergic acid I) agree with ours. The similar values for dihydrolysergic acid I and dihydro*iso*lysergic acid II confirm the similar orientation of the carboxyl group in these acids. The influence of the carboxyl group on the ionisation of the dihydrolysergic acids ($\Delta pK'_{a,2}$ 0·43) is somewhat less than that (0·63) observed by Craig *et al.* for the corresponding lysergic acids and accords with the greater intensity of the direct effect to be expected in the more strongly basic dihydro-derivatives, since with increasing basicity the ionised form becomes more favoured.

Cookson (*loc. cit.*) suggested that ring D in lysergic acid and *iso*lysergic acids has a boat structure. Structures (II) and (III) of this type would, however, lead to the dihydro-acids (V) and (IV) respectively, in each of which the orientation of the carboxyl with



respect to $N_{(6)}$ is the reverse of that in the parent acid. The fact that lysergic and dihydrolysergic acid I are each stronger acids (weaker bases) than their corresponding *iso*-acid (ΔpK values are of the same sign and order of magnitude in each series) implies that the orientation of the carboxyl group relative to $N_{(6)}$ is not significantly altered by hydrogenation of the 9 : 10-double bond. Such a condition is satisfied only if all four acids have identical conformations of ring D (*i.e.*, all either chair or semi-chair) as already postulated (Stenlake, *loc. cit.*). This follows irrespectively of configuration at the new asymmetric centre, $C_{(10)}$. Lysergic and *iso*lysergic acid therefore, have the structures (VI) and (VII) respectively, in which ring D adopts a semi-chair conformation.

[*Added*, December 29th, 1954.]—After submission of this manuscript, Stoll, Petrzilka, Rutschmann, Hofmann, and Günthard (*Helv. Chim. Acta*, 1954, **37**, 2039) reported pK and other evidence leading to similar conclusions with regard to the stereochemistry of lysergic acid and its derivatives.

Experimental.—An alk-acid glass electrode in conjunction with a Pye direct reading pH meter was used for pK determinations. As only 2—3 mg. of material were available the method of Craig *et al.* (*loc. cit.*) was adopted, in which the pK was determined from individual pH measurements at 20° of an 0·002M-solution of the substance, which had been neutralised by the calculated amount of carbonate-free 0·1N-sodium hydroxide. Addition of alkali and dilution to volume were carried out by weight. Control experiments with glycine gave consistent values of pK'_{a_2} 9·80 (Orthner and Hein, *Biochem. Z.*, 1933, **262**, 461, give 9·75; Albert, *Biochem. J.*, 1950, **47**, 531, gives 9·86). The purity of the samples used was confirmed as far as possible by means of their physical constants.

The author thanks Professor A. Stoll for the gift of dihydrolysergic acids, and Dr. A. L. Glenn for helpful discussions and suggestions in the preparation of the manuscript.

THE SCHOOL OF PHARMACY, THE ROYAL TECHNICAL COLLEGE,
GLASGOW. [*Received, October 21st*, 1954.]

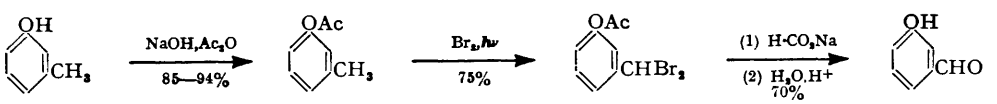
Photobromination Studies. Part II. A Convenient Synthesis of* m-*Hydroxybenzaldehyde.*

By ERNEST L. ELIEL and KENNETH W. NELSON.

[Reprint Order No. 5986.]

IT has recently been found that hydroxybenzaldehydes bearing an electron-withdrawing substituent, such as a nitro-, carboxy-, or methoxycarbonyl group, can be readily synthesized from the corresponding substituted cresols by dibromination of the side-chain followed by hydrolysis (Segesser and Calvin, *J. Amer. Chem. Soc.*, 1942, **64**, 825; Eliel and Rivard, Part I;* Eliel, Rivard, and Burgstahler, *J. Org. Chem.*, 1953, **18**, 1679). To prevent ring-bromination it is necessary only to reduce the activating influence of the phenolic group by acetylation.

We have now studied the extension of this reaction to the synthesis of *m*-hydroxybenzaldehyde, *i.e.*, an aldehyde bearing no deactivating group in the ring. Hitherto, this compound has usually been synthesized by nitration of benzaldehyde followed by reduction and diazotization (Woodward, *Org. Synth.*, 1945, **25**, 55; Icke, Redeman, Wisegarver, and Allen, *ibid.*, 1949, **29**, 72, 6, 63; Kranz, U.S. Pat. 1,715,417; *Chem. Abs.*, 1929, **23**, 3717; G.P. 18,016; Friedlander, 1877—1887, **1**, 586). The yields in this series of reactions are low and the procedure is tedious, especially since the intermediate *m*-aminobenzaldehyde must be handled either as an acetal or as a tin chloride complex. Other preparations of *m*-hydroxybenzaldehyde, *e.g.*, by oxidation of *m*-tolyl sulphonates with manganese dioxide (G.P. 162,322; Friedlander, 1905—1907, **8**, 154) and through side-chain chlorination of *m*-tolyl carbonate or benzoate (Raschig, G.P. 233,631; Friedlander, 1910—1912, **10**, 163; cf. Copisarow, *J.*, 1929, 588), have been reported in the patent literature but appear to be of little value as laboratory preparations. We have now found that *m*-hydroxybenzaldehyde can be obtained from *m*-cresol in about 50% overall yield by the very convenient sequence indicated below:



m-Tolyl acetate, obtained by Chattaway's procedure (*J.*, 1931, 2495) in 85—94% yield, is readily dibrominated photochemically in 75% yield. The hydrolysis of the crude

* Presented before the Division of Organic Chemistry at the 124th Meeting of the American Chemical Society at Chicago, Illinois, September 10th, 1953. Part I, *J. Org. Chem.*, 1952, **17**, 1252.

dibromo-compound was best effected by means of sodium formate (Levene and Walti, *Org. Synth.*, Coll. Vol. II, 1943, 5; Bachmann and Ramirez, *J. Amer. Chem. Soc.*, 1950, **72**, 2525), the yield of aldehyde being 70%.

Some extensions of this reaction to other carbonyl compounds were investigated. The synthesis of *m*-hydroxyacetophenone from the readily available *m*-ethylphenol failed because bromination of the side-chain did not proceed beyond the monosubstitution stage. *p*-Nitrotoluene was dibrominated, and the crude dibromination product hydrolyzed by means of concentrated sulphuric acid (sodium formate was ineffective in this case) to give *p*-nitrobenzaldehyde in rather poor overall yield; a detailed study of this reaction has not been made, however, and it is believed that the yield is susceptible to improvement. *o*-Nitrobenzaldehyde could not be prepared in this manner.

Experimental.—m-*Tolyl acetate*. From 32·4 g. of *m*-cresol, essentially by Chattaway's method (*loc. cit.*), this acetate, b. p. 96·5°/13 mm., was obtained in 85—94% yield (38—42·6 g.).

Photodibromination of m-*tolyl acetate*. A solution of the ester (30 g., 0·2 mole) in carbon tetrachloride (150 ml.), in a two-necked flask equipped with a reflux condenser and dropping-funnel, was illuminated with a 500-w unfrosted tungsten projector bulb. The solution was heated to gentle boiling by means of a small flame, and a solution of bromine (64 g., 0·4 mole) in carbon tetrachloride (225 ml.) was added at such a rate (1¾ hr.) that no permanent red bromine colour appeared in the solution. The solution was then cooled, washed with water, dilute aqueous sodium hydrogen carbonate and again water, dried (Na_2SO_4), and concentrated. Distillation of the residue from a small Claisen flask gave 46 g. (75%) of the crude *m*-acetoxybenzylidene bromide, b. p. 138—147°/1 mm., 165—169°/11 mm. Material so obtained was suitable for the next step.

m-*Hydroxybenzaldehyde*. The following procedure was the best of several studied. To a solution of crude *m*-acetoxybenzylidene bromide (30·8 g., 0·1 mole) in 95% ethanol (150 ml.) was added sodium formate (16·4 g., 0·24 mole); the suspension was then heated to boiling, and enough water (*ca.* 30 ml.) was added to produce a homogeneous mixture. Boiling under reflux was continued for 48 hr. Concentrated hydrochloric acid (*ca.* 5 ml.) was added just before the end of the reflux period. Most of the ethanol was then removed by distillation at reduced pressure, and water was added to bring the total volume to about 50 ml. Upon chilling of the solution in an ice-bath, *m*-hydroxybenzaldehyde was precipitated, and was collected, washed with a little cold water, dried, and recrystallized from ether–light petroleum (b. p. 60—90°). The product so purified (8·5 g., 70%) had m. p. 103—104° (lit. 106°) undepressed by an authentic specimen.

p-*Nitrobenzylidene bromide*. The photobromination of *p*-nitrotoluene (13·74 g., 0·1 mole) in carbon tetrachloride (150 ml.) by bromine (32 g., 0·2 mole) in carbon tetrachloride (150 ml.) appeared to be complete after 3½ hr. The mixture was chilled in ice, diluted with 200 ml. of light petroleum (b. p. 60—90°), and further cooled with carbon dioxide–acetone. The precipitated crude *m*-nitrobenzylidene bromide was collected and washed with a small amount of light petroleum; it weighed 21 g. but was apparently contaminated with the monobromo-compound as shown by the low m. p., 60—65°. Two recrystallizations from ethanol raised the m. p. to 76—78° (Wachendorf, *Annalen*, 1877, **185**, 268, reports m. p. 82°).

p-*Nitrobenzaldehyde*. A well-stirred suspension of *p*-nitrobenzylidene bromide (3·8 g.; m. p. 76—78°) in 45% sulphuric acid (100 ml.) was kept at the b. p. under reflux for 3 hr. It was then exhaustively steam-distilled (about 200 ml. of distillate were collected) and the distillate was warmed to 80°. This dissolved the *p*-nitrobenzaldehyde but left unhydrolyzed dibromo-compound (0·5 g., 11%) as an oil (which crystallized). The hot aqueous phase was decanted and chilled, and the product collected (0·8 g., 42%; m. p. 97·5—100°). Recrystallization from ether–light petroleum did not raise the m. p. above 100—102° (lit., 106·5°), but purification through the bisulphite compound gave material of m. p. 104—106° in 65% yield. The 2 : 4-dinitrophenylhydrazone had m. p. 318° (lit., 320°).

UNIVERSITY OF NOTRE DAME, NOTRE DAME, INDIANA, U.S.A. [*Received, December 20th*, 1954.]

" *Diazoperbromides.*"

By M. Aroney and R. J. W. Le Fèvre.

[Reprint Order No. 6008.]

Substances corresponding to formulæ RN_2Br_3 were first isolated by Griess (*Annalen*, 1864, **137**, 50; *Phil. Trans.*, 1864, 673; *J.*, 1867, **20**, 36) by the addition of excess of bromine water containing hydrobromic acid to aqueous benzenediazonium nitrate. Subsequent work showed that chlorine, bromine, or iodine could form analogous compounds, and Hantzsch (*Ber.*, 1895, **28**, 2754) prepared trihalides containing nine out of the ten possible combinations of these three halogens.

Griess (*loc. cit.*, 1867, p. 44) remarked " The constitution of the perbromide of diazobenzol appears to be the same as that of periodide of tetraethylammonium and similar compounds of other bases." Chattaway (*J.*, 1909, **95**, 862; 1915, **107**, 105) considered the " diazoperbromides " to be tri-*N*-bromoarylhydrazines ($Ar{\cdot}NBr{\cdot}NBr_2$) because they could be obtained by the direct action of bromine on arylhydrazines. Hantzsch, noting the parallelism between diazoperhalides and perhalides of the alkali metals, concluded (*Ber.*, 1915, **48**, 1344) with Forster (*J.*, 1915, **107**, 260) that the former were true diazonium salts.

Of obvious relevance to this question is the recent observation that a vibration frequency around 2260 cm.$^{-1}$ is characteristic of the $R{\cdot}N_2^+$ cation (Aroney, Le Fèvre, and Werner, *J.*, 1955, 276). We have, therefore, prepared the " diazoperbromides " from *p*-toluidine, *p*-chloroaniline, and β-naphthylamine, and recorded their absorption spectra over the range 3250—1350 cm.$^{-1}$. Results were as tabulated.

Main infrared absorption bands between 3250 *and* 1350 *cm.*$^{-1}$

p-$C_6H_4Me{\cdot}N_2Br_3$	3048	2248	1575	1557		
p-$C_6H_4Cl{\cdot}N_2Br_3$	3072	2250		1555	1465	1410
β-$C_{10}H_7{\cdot}N_2Br_3$	3055	2242	1611			

Reading horizontally, the second feature in each case appeared slightly more intense than the first or third. Two roughly common frequencies are seen, at 3048—3072 and 2240—2250 cm.$^{-1}$. The former, presumably due to C–H stretching vibrations, requires no comment. The latter is well within the limits, *viz.*, 2230—2310 cm.$^{-1}$, found by Aroney *et al.* (*loc. cit.*) to include the " triple bond " absorptions of 21 diazonium salts. We conclude therefore that the perbromides contain the $R{\cdot}N_2^+$ group.

Chattaway (*loc. cit.*) had observed that the oils separating during the preparation of perbromides may hold no fewer than 9 atoms of bromine, although these could only be retained by preventing the escape of bromine vapour. In order to remove the possibility that such higher polybromides contributed to the spectra, and to substantiate that, at the time of recording, the substances were in reality tribromides, bromine estimations were made.

The perbromide (*ca.* 0·3 g.) was dissolved by gentle heat in a solution of sodium sulphite in dilute sulphuric acid, and the mixture refluxed for 10 min. to reduce the bromine to bromide. After cooling, aqueous silver nitrate (0·1N; 50 c.c.) was added with stirring together with nitric acid (6N; 10 c.c.) and ferric alum indicator. Back-titration with standard potassium thiocyanate solution followed. Bromine contents between 1 and 1·5% lower than those calculated for $R{\cdot}N_2Br_3$ were obtained. An estimation without initial reduction indicated an almost total absence of Br^- in the perbromide solution; heating the compounds in dilute acid liberated bromine.

The Br_3^- anion, by analogy with $(ICl_2)^-$ and $(IBr_2)^-$ in salts of the alkali metals, has a rectilinear structure (Mooney, *Z. Krist.*, 1935, **90**, 143; 1938, **98**, 377, cf. Zelezny and Baenziger, *J. Amer. Chem. Soc.*, 1952, **74**, 6151) with the central atom having a *p-d* valency configuration (Kimball, *J. Chem. Phys.*, 1940, **8**, 194). Since $(R{\cdot}N{\vdots}N)^+$ should also be extended, the relative stability of solid diazonium perbromides may, on a simple view, be due to the shapes of their cations and anions which permit a close mutual approach where electrostatic are reinforced by van der Waals forces, thus favouring the stability of an ion-pair arrangement.

University of Sydney, N.S.W., Australia. [*Received, January 4th*, 1955.]

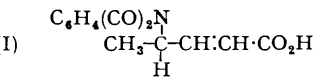
Configuration of (+)-γ-Aminovaleric Acid. Conversion of L-Alanine into its Vinylogue.

By K. Balenović and D. Cerar.

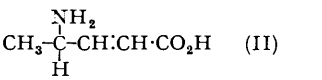
[Reprint Order No. 6018.]

γ-Aminovaleric acid was first prepared and resolved into its optical antipodes by Fischer and Groh (*Annalen*, 1911, **383**, 363) by a very tedious procedure; the (+)- and the (−)-form showed $[\alpha]_D$ +12° and $[\alpha]_D$ −12° in water respectively.

We applied the Doebner condensation (*Ber.*, 1900, **33**, 2140; 1902, **35**, 1137) to L-α-phthaloylimidopropaldehyde, prepared from L-alanine (cf. Balenović, Bregant, Cerar, Fleš, and Jambrešić, *J. Org. Chem.*, 1953, **18**, 297), and obtained the pent-2-enoic acid (I), which after hydrogenation and hydrolysis gave (+)-γ-aminovaleric acid, $[\alpha]_D$ +14°, in an overall yield of 32% (based on L-alanine). (+)-γ-Aminovaleric acid is therefore related to the L-amino-acid series.



(I)



(II)

According to the procedure for the preparation of the vinylogue of glycine (Balenović, Jambrešić, and Urbas, *ibid.*, 1954, **19**, 1589), hydrazinolysis of (+)-4-phthalimidopent-2-enoic (I) at room temperature gave poor yields of (−)-4-aminopent-2-enoic acid (II), the vinylogue of L-alanine.

Experimental.—Proof of configuration of L-α-phthalimidopropaldehyde. To a solution of this aldehyde prepared according to Balenović *et al.* (*loc. cit.*) (1 g.; $[\alpha]_D$ −28°) in acetone (10 c.c.), Jones's chromic acid reagent (1·44 c.c.) (Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39) was gradually added at room temperature. The mixture was left for 1 hr. at room temperature, diluted with two volumes of water, and extracted with ether. From the extracts crude *N*-phthaloyl-L-alanine was isolated (1·1 g., 99%), having m. p. 150°, $[\alpha]_D^{19}$ −10·5° ± 0·2° (*c*, 2·0 in EtOH). [Fischer (*Ber.*, 1907, **40**, 489) reported m. p. 150—152° and $[\alpha]_D^{18}$ −17·5°.] It was recrystallized from water for analysis (Found: C, 60·3; H, 4·0. Calc. for $C_{11}H_9O_4N$: C, 60·3; H, 4·1%).

(+)-4-*Phthalimidopent-2-enoic acid* (I). A suspension of the finely powdered aldehyde (2 g., 0·01 mole; $[\alpha]_D$ −28°) and malonic acid (2 g., 0·02 mole) in pyridine (5 g.) was heated for 8 hr. at 70—75° (bath-temp.). The cooled mixture was diluted with five volumes of water, acidified with 10% sulphuric acid to pH 6, and left over-night at 0°. The crystalline *acid* precipitated was collected, washed with 10% sulphuric acid and water, and dried (yield, 2·4 g., 100%). Recrystallization from ethanol gave the pure product (85%), m. p. 163°, $[\alpha]_D^{17}$ +10·5° ± 0·8° (*c*, 1·13 in EtOH) (Found: C, 63·3; H, 4·6. $C_{13}H_{11}O_4N$ requires C, 63·6; H, 4·5%).

(+)-γ-*Phthalimidovaleric acid.* The acid (I) (3 g., 0·01 mole; $[\alpha]_D$ +10°) in ethanol (45 c.c.) was hydrogenated over Adams platinum oxide (100 mg.), 1 mol. being absorbed in 5 hr. The (+)-γ-*phthalimidovaleric acid* precipitated during the hydrogenation was separated by dissolution in hot ethanol (30 c.c.). Evaporation and recrystallization from ethanol gave the pure product (2·9 g., 95%), m. p. 146°, $[\alpha]_D^{17}$ +37·5° ± 0·9° (*c*, 0·3 in EtOH) (Found: C, 63·1; H, 5·4. $C_{13}H_{13}O_4N$ requires C, 63·2; H, 5·3%).

(+)-γ-*Aminovaleric acid.* γ-Phthalimidovaleric acid (2·5 g., 0·01 mole) was heated under reflux during 7 hr. with acetic acid (7 c.c.) and 47% hydriodic acid (8 c.c.), and the mixture left at 0° overnight. Next morning the precipitated phthalic acid was removed, and the filtrate evaporated to dryness under reduced pressure. The residue was again dissolved in water, recovered by evaporation, dissolved in water, and passed through a column containing Amberlite IR-4B (17 g.; 20—50 mesh) at a flow rate of 30 c.c./hr., yielding (+)-γ-aminovaleric acid (1·0 g., 95%), m. p. 202°, $[\alpha]_D$ +9·3°. Recrystallization from water–methanol (1 : 8) gave white prisms of the pure product (0·8 g., 76%), m. p. 208°, $[\alpha]_D^{22}$ +13·9° ± 0·2° (*c*, 0·8 in H_2O). Fischer and Groh (*loc. cit.*) reported m. p. 208°. Paper chromatography on Whatman No. 1 paper, at 19°, with phenol–water as mobile phase and ninhydrin as reagent, gave a violet spot, R_F 0·89 (Found: N, 11·9. Calc. for $C_5H_{11}O_2N$: N, 12·0%).

(−)-4-*Aminopent-2-enoic acid* (II). A solution of (+)-4-phthalimidopent-2-enoic acid (I) (4·2 g., 0·016 mole) in ethanol (24 c.c.) and ethanolic M-hydrazine hydrate (33·6 c.c., 0·016 mole) was stirred at 25° for two weeks. After a few hours separation of phthaloylhydrazine began, which was complete after two weeks. The entire mixture was evaporated to dryness under reduced pressure, and the residue treated with water (45 c.c.) and acidified to pH 5·5 with acetic acid. After 24 hours' stirring at room temperature the phthaloylhydrazine was filtered off (2·1 g., 100%). The filtrate was evaporated to dryness, and a yellow oil remained (2·1 g.) which partly crystallized. This was triturated with water (1 c.c.) and precipitated with ethanol (10 c.c.); white crystals of (−)-4-*aminopent-2-enoic acid* separated [0·23 g., 12%; m. p. 198° (decomp.)]. Recrystallized from water–ethanol, this had unchanged m. p., $[\alpha]_D^{20}$ −4·8° ± 0·9° (*c*, 1·03 in H_2O) (Found: C, 51·7; H, 7·9; N, 12·0. $C_5H_9O_2N$ requires C, 52·2; H, 7·9; N, 12·2%). Paper chromatography of (−)-4-aminopent-2-enoic acid on Whatman No. 1 paper, at 20°, with butanol–water as mobile phase, gave a yellow spot with a ninhydrin solution, becoming violet on standing (R_F 0·08). Phenol–water as mobile phase gave R_F 0·74. An aqueous solution of (−)-4-aminopent-2-enoic acid gave a strong reaction with ninhydrin. The colour was first yellow, then brown, and, on further heating, deep purple.

Preparation of (+)-*γ-aminovaleric acid from* (−)-4-*aminopent-2-enoic acid.* Hydrogenation over Adams platinum oxide (30 mg.) was carried out with a suspension of (−)-4-aminopent-2-enoic acid (86 mg.) in 10% aqueous acetic acid (15 c.c.) at atmospheric pressure and room temperature. After absorption of 1 mol. of hydrogen the catalyst was filtered off, and the filtrate evaporated to dryness under reduced pressure. Partly racemized (+)-γ-aminovaleric acid remained (90 mg., 100%), $[\alpha]_D^{20}$ +5·7° ± 0·6° (*c*, 1·76 in H_2O), the constitution being confirmed by m. p., mixed m. p., and analysis.

UNIVERSITY CHEMICAL LABORATORY, STROSMAYEROV TRG 14,
ZAGREB, YUGOSLAVIA.

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Some α-Methylamino-acids.

By K. T. POTTS.

[Reprint Order No. 6019.]

WHEN this research was started structural analogues of the naturally occurring α-amino-acids were being investigated as a source of compounds capable of the inhibition of growth of micro-organisms and it was of interest to study analogues of the amino-acids in which the hydrogen atom on the α-carbon atom had been replaced by a methyl group. A renewed activity in this field has been shown recently (Bergel and Stock, *J.*, 1954, 2409; Jönsson, *Acta Chem. Scand.*, 1954, **8**, 1203, 1211) and our results are now reported.

Experimental.—α-Amino-α-methylglutaric acid (α-methyl-DL-glutamic acid) was synthesised by a method similar to that published recently by Gal, Avakian, and Martin (*J. Amer. Chem. Soc.*, 1954, **76**, 4181) except that inorganic ions were removed from solution by Cocker and Lapworth's method (*J.*, 1931, 1391). It crystallised from water as glistening, white needles, m. p. 175° [Gal *et al.*, *loc. cit.*, report m. p. 168—170° (decomp.)] (Found: N, 8·8. Calc. for $C_6H_{11}O_4N$: N, 8·7%). The *phthaloyl* derivative (method: Billman and Harting, *J. Amer. Chem. Soc.*, 1948, **70**, 1473) formed white platelets (from water), m. p. 203° (Found: C, 57·9; H, 4·5. $C_{14}H_{13}O_6N$ requires C, 57·8; H, 4·5%).

α-Amino*iso*butyric acid (α-methyl-DL-alanine) was prepared by the alkaline hydrolysis of 5 : 5-dimethylhydantoin (Bucherer, *J. pr. Chem.*, 1934, **141**, 28). It crystallised from water as white needles and sublimed at 280° without melting (Found: C, 46·5; H, 8·6. Calc. for $C_4H_9O_2N$: C, 46·6; H, 8·8%). Urech (*Annalen*, 1872, **164**, 268) also reported that it sublimed at 280° without melting.

α-*Methyl*-DL-*phenylalanine.* 5-Benzyl-5-methylhydantoin (30 g.; Bucherer, *loc. cit.*), barium hydroxide (150 g.), and water (750 c.c.) were boiled under reflux for 30 hr. After removal of barium ions as barium carbonate and concentration of the mother-liquor, α-methyl-DL-phenylalanine (14 g., 53%) separated as white needles, m. p. 294—295° (decomp.) (Herbst

and Johnson, *J. Amer. Chem. Soc.*, 1932, **54**, 2463, report m. p. 293—294° with charring) (Found : C, 67·1; H, 7·2; N, 7·8. Calc. for $C_{10}H_{13}O_2N$: C, 67·0; H, 7·3; N, 7·8%).

*α-Methyl-*DL*-methionine.* (*a*) 5-Methyl-5-(methylthioethyl)hydantoin. Methyl 3-oxobutyl sulphide (8·0 g.) (Gill, James, Lions, and Potts, *ibid.*, 1952, **74**, 4927) in 50% alcohol (60 c.c.), potassium cyanide (6·4 g.), and ammonium carbonate (20 g.) were heated together at 65—70° for 3 hr. The solution was evaporated to dryness (reduced pressure, water-bath) and the residue extracted several times with hot benzene. The *hydantoin* (3·5 g., 28%) crystallised from the benzene solution. It was soluble in alcohol, acetone, water, and hot benzene and crystallised from benzene as white, irregular prisms, m. p. 108° (Found : C, 44·9; H, 6·7; N, 14·8. $C_7H_{12}O_2N_2S$ requires C, 44·7; H, 6·4; N, 14·9%). (*b*) α-Methyl-DL-methionine. 5-Methyl-5-(methylthioethyl)hydantoin (3·2 g), barium hydroxide (20 g.), and water (100 c.c.) were refluxed together for 36 hr. and the mother-liquor treated as in the previous hydrolyses. After several days, *α-methyl-*DL*-methionine* (0·9 g., 32%) separated as white needles, m. p. 134°, and crystallised from water as white needles without rise in m. p. (Found : S, 19·4. $C_6H_{13}O_2NS$ requires S, 19·6%).

*α-Methyl-*DL*-tyrosine.* (*a*) 5-4′-Methoxybenzyl-5-methylhydantoin. *p*-Methoxyphenylacetone (28 g.) (Hoover and Haas, *J. Org. Chem.*, 1947, **12**, 501), potassium cyanide (15 g.), and ammonium carbonate (50 g.) in 50% alcohol (250 c.c.) were heated together at 65—70° for 7 hr. After cooling, the mixture set to a crystalline mass of the *hydantoin* (38·5 g., 97%); a further quantity was isolated from the mother-liquor by the careful addition of hydrochloric acid. It crystallised as fine, white needles, m. p. 198°, from water (Found : C, 61·5; H, 6·2; N, 12·2. $C_{12}H_{14}O_3N_2$ requires C, 61·5; H, 6·0; N, 12·0%). (*b*) 5-4′-Hydroxybenzyl-5-methylhydantoin. The above hydantoin (33·5 g.) and hydriodic acid (150 c.c.; *d* 1·7) were heated together for 30 min. Methyl iodide was rapidly evolved and *5-4′-hydroxybenzyl-5-methylhydantoin* (30 g., 94%) separated from the hot mixture. It crystallised from water as white needles, m. p. 307° (decomp.) (Found : C, 60·0; H, 5·5; N, 12·8. $C_{11}H_{12}O_3N_2$ requires C, 60·0; H, 5·5; N, 12·7%). (*c*) α-Methyl-DL-tyrosine. 5-4′-Hydroxybenzyl-4-methylhydantoin (20 g.) was hydrolysed with barium hydroxide (100 g.) in water (500 c.c.) and the mixture worked up as above. *α-Methyl-*DL*-tyrosine* (6·2 g., 35%) crystallised from water as white, irregular prisms, m. p. 330—332° (decomp.) (Found : C, 61·2; H, 6·7; N, 7·5. $C_{10}H_{13}O_3N$ requires C, 61·6; H, 6·7; N, 7·2%).

*α-Methyl-*DL*-di-iodotyrosine.* A solution of iodine in 4N-potassium iodide (10·4 c.c.) was added slowly and with shaking to a solution of α-methyltyrosine (2·0 g.) in water (20 c.c.) and an excess of 60% aqueous ethylenediamine. After 2 hr. at room temperature the mixture was neutralised with acetic acid and, after a period, pale yellow crystals (3·8 g., 85%) separated. *α-Methyl-*DL*-di-iodotyrosine* crystallised from 50% aqueous acetic acid as fine, white needles, m. p. 215° (decomp.) (Found : C, 27·2; H, 3·0; N, 3·3 $C_{10}H_{11}O_3NI_2$ requires C, 26·9; H, 2·5; N, 3·1%).

*S-Benzyl-α-methyl-*DL*-cysteine.* (*a*) 5-(4-Methylthiobenzyl)-5-methylhydantoin. 1-(Benzylthio)acetone (100 g.) (Wahl, *Ber.*, 1922, **55**, 1449), potassium cyanide (48 g.), and ammonium carbonate (162 g.) in 50% alcohol (400 c.c.) were heated together at 65—70° for 7 hr. The solution was then concentrated (reduced pressure, water-bath) and poured on cracked ice; careful addition of dilute hydrochloric acid caused complete precipitation of the *hydantoin* (128 g., 92%). It crystallised from alcohol as white needles, m. p. 119° (Found : C, 57·7; H, 5·6; N, 10·9. $C_{12}H_{14}O_2N_2S$ requires C, 57·6; H, 5·6; N, 11·2%). (*b*) *S*-Benzyl-α-methyl-DL-cysteine. The above hydantoin (50 g.), barium hydroxide (250 g.), and water (1250 c.c.) were heated under reflux for 30 hr. Barium ions were precipitated as barium carbonate from the solution at 100° and, after cooling, *S-benzyl-α-methyl-*DL*-cysteine* (34·8 g., 71%) crystallised as white needles, m. p. 234°. The m. p. was not raised on further recrystallisation (Found : C, 58·2; H, 6·7; N, 6·4; S, 13·9. $C_{11}H_{15}O_2NS$ requires C, 58·6; H, 6·7; N, 6·2; S, 14·3%).

5-(4-Hydroxy-3 : 5-dinitrobenzyl)-5-methylhydantoin. 5-4′-Hydroxybenzyl-5-methylhydantoin (10 g.) was added in small quantities during 90 min. to a stirred solution of concentrated nitric acid (35 c.c.; *d* 1·42), at 25—32°. During 30 min. a solid separated and the mixture was then poured on cracked ice. The *dinitrohydantoin* (10·5 g., 75%) crystallised from water as yellow needles, m. p. 273° (decomp.) (Found : C, 42·8; H, 3·4; N, 18·1. $C_{11}H_{10}O_7N_4$ requires C, 42·6; H, 3·3; N, 18·1%).

The nitro-compound (5 g.), toluene-*p*-sulphonyl chloride (4·6 g.), and dry pyridine (40 c.c.) were heated under reflux for 30 min. *p*-Methoxyphenol (6·8 g.) was then added and the whole heated for a further 2 hr. The pyridine was removed under reduced pressure, the residual oil dissolved in acetone, and the solution poured on cracked ice. The precipitated solid (4·6 g., 69%)

crystallised first from dilute acetone and then from methanol and 5-(4-p-*methoxyphenoxy*-3 : 5 *dinitrobenzyl*)-5-*methylhydantoin* was obtained as pale yellow needles, m. p. 147° (Found : N, 13·0. $C_{18}H_{16}O_8N_4$ requires N, 13·4%).

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THE UNIVERSITY OF SYDNEY, AUSTRALIA.
[*Present Address :* NATIONAL INSTITUTE OF MEDICAL RESEARCH, LONDON, N.W.7.]

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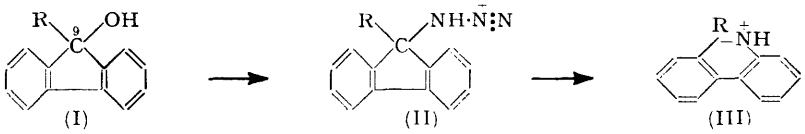
Reactions of Organic Azides. Part IV. The Conversion of 9-Alkylfluoren-9-ols into 9-Alkylphenanthridines.*

By C. L. ARCUS and E. A. LUCKEN.

[Reprint Order No. 6021.]

IT has been found (Parts I and III *) that fluoren-9-ols react with hydrazoic acid in the presence of sulphuric acid to yield phenanthridines. The mechanism of the reaction has been discussed (*locc. cit.*) : the essential step is the rearrangement of a protonated azide (II) to a phenanthridinium ion (III), and it has been shown, from the results with 2- and 3-substituted fluoren-9-ols, that the relative migratory aptitudes of the two rings in such a fluorenol are directly related to the capacities of the rings for electron-release at their point of attachment to $C_{(9)}$.



The effect on the course of the reaction of electron-release at $C_{(9)}$ by the group R (in I) (*i.e.*, release other than by the migrating rings) has now been investigated. 9-Ethyl-, 9-*iso*propyl-, and 9-*tert.*-butyl-fluoren-9-ol have been converted into the corresponding 9-alkylphenanthridines; the yields (at 25°, total reaction time 2¼ hours) are recorded in the Table. Inductive electron-release increases, and release by hyperconjugation decreases,

Phenanthridine :		9-Ethyl-	9-*iso*Propyl-	9-*tert.*-Butyl- *
Yield (%)	Expt. (i)	84	79	66
	Expt. (ii)	89	88	61

* 9-Azido-9-*tert.*-butylfluorene, (i) 19, (ii) 21%, also isolated.

in the series ethyl, *iso*propyl, *tert.*-butyl. The yield of 9-methylphenanthridine from 9-methylfluoren-9-ol has been found (Part III) to be 47% under similar conditions (time : 2 hours); however, this value cannot properly be compared with those in the Table, because methylfluorenylmethylphenanthridine was also formed, in 27% yield, a side-reaction not encountered with the other 9-alkylfluoren-9-ols.

From the reaction with 9-*tert.*-butylfluoren-9-ol, as from that with unsubstituted fluoren-9-ol (Part I), the intermediate azide was isolated. It is inferred, at least for these two fluorenols, that the last of the following reactions is rate-controlling :

$$R'OH + 2H_2SO_4 \longrightarrow R'^+ + H_3O^+ + 2HSO_4^-$$

$$R'^+ + HN_3 \longrightarrow R'\cdot\overset{+}{N}_3H$$

$$R'\cdot\overset{+}{N}_3H \longrightarrow R'\overset{+}{N}H + N_2$$

The comparatively low yield of 9-*tert.*-butylphenanthridine is therefore ascribed to the relatively slow decomposition of the protonated azide. Decomposition results in the

* Part I, *J.*, 1953, 178; Part III, *J.*, 1954, 4319.

formation of the $RC{=}\overset{+}{N}H$ double bond (which may alternatively be regarded as the aromatisation of the central ring), a process which would be expected to be facilitated by hyperconjugation with R; hyperconjugation is possible with ethyl and *iso*propyl, but not with *tert.*-butyl. A result relating to the effect of conjugation by R has been recorded in Part III: 9-phenylfluoren-9-ol, on reaction as above, but for 2 hours, gave 9-phenylphenanthridine in 94% yield; the phenyl group is presumed to conjugate with the heterocyclic ring as the latter is formed.

It is concluded that a capacity for hyperconjugation or conjugation by the group R facilitates, but is not essential to, the rearrangement of the protonated azide to the phenanthridinium ion.

Experimental.—A solution of fluorenone (11·2 g.) in benzene–ether (25 ml. each) was added to ethylmagnesium bromide [from magnesium (1·92 g.), ethyl bromide (5·8 ml.), and ether (70 ml.)] during 1 hr.; the whole was heated under reflux for a further hour, and, when cold, was added to a mixture of ice and ammonium chloride. Benzene (200 ml.) was added, the whole was shaken, and the organic layer separated. The latter was washed with water and then dried (Na_2SO_4), and the solvents were distilled; the product, on recrystallisation from light petroleum (b. p. 60—80°), yielded 9-ethylfluoren-9-ol (7·4 g.), m. p. 99—100°, and m. p. 101° on further recrystallisation. Ullmann and von Wurstemberger (*Ber.*, 1905, **38**, 4107) record m. p. 101°.

A similar preparation with fluorenone (10·8 g.) and *iso*propylmagnesium bromide [from magnesium (2·10 g.) and *iso*propyl bromide (7·4 ml.)] yielded 9-*iso*propylfluoren-9-ol (6·1 g.), m. p. 119—121°, and m. p. 127° after repeated recrystallisation from light petroleum (b. p. 100—120°). Schlenk and Bergmann (*Annalen*, 1928, **463**, 214) record m. p. 124°.

A similar preparation with fluorenone (18·0 g.) and *tert.*-butylmagnesium chloride [from magnesium (4·6 g.) and *tert.*-butyl chloride (21·8 ml.)] gave 9-tert.-*butylfluoren*-9-*ol* [4·0 g., from light petroleum (b. p. 100—120°)], m. p. 80—90°, which formed prisms, m. p. 96°, on repeated recrystallisation from light petroleum (b. p. 40—60°) (Found: C, 86·1; H, 7·9. $C_{17}H_{18}O$ requires C, 85·7; H, 7·6%).

To a suspension of sodium azide (2·0 g.) in chloroform (20 ml.), cooled in ice, sulphuric acid (97%; 8 ml.) was added with stirring during ½ hr. The ice was replaced by a water-bath at 25°, and a solution of 9-ethylfluoren-9-ol (4·20 g.) in chloroform (10 ml.) was added during 1¼ hr.; stirring was continued for 1 hr. The mixture was poured into cold water (300 ml.); the chloroform layer was extracted with dilute hydrochloric acid, and the extract added to the main acidic solution. The combined aqueous solutions were made alkaline with sodium hydroxide solution, and the precipitated base was extracted with ether. The extract was dried (Na_2SO_4) and the ether was distilled; there was obtained 9-ethylphenanthridine (3·58 g.), m. p. 50—53°. In a similar experiment the fluorenol (2·10 g.) yielded the base (1·84 g.). 9-Ethylphenanthridine, recrystallised from acetone, had m. p. 55·5°, and formed a *picrate*, golden needles (from dioxan), m. p. 211° (decomp.) (Found: N, 12·6. $C_{21}H_{16}O_7N_4$ requires N, 12·85%); Pictet and Hubert (*Ber.*, 1896, **29**, 1186) record m. p. 54—55° for the base.

By the same procedure 9-*iso*propylfluoren-9-ol [4·48 g., added in solution in chloroform (25 ml.)] gave 9-iso*propylphenanthridine* (3·47 g.), m. p. 50—53°. In a similar experiment the fluorenol (2·24 g.) yielded the base (1·98 g.). After recrystallisation from aqueous ethanol, 9-*iso*propylphenanthridine formed needles, m. p. 55° (Found: C, 86·9; H, 6·9; N, 6·35. $C_{16}H_{15}N$ requires C, 86·8; H, 6·85; N, 6·35%) [*picrate*, yellow prisms (from dioxan), m. p. 206° (decomp.) (Found: N, 12·3. $C_{22}H_{18}O_7N_4$ requires N, 12·45%)].

Finely powdered 9-*tert.*-butylfluoren-9-ol [(i), (ii) 2·40 g.] was added with stirring during ¾ hr. to a hydrazoic–sulphuric acid solution [prepared as above from sodium azide (1·0 g.), chloroform (15 ml.), and sulphuric acid (4 ml.)] kept at 25°; stirring was continued for 1½ hr. The chloroform layer was decanted and extracted with 10N-sulphuric acid. The extract was added to the sulphuric acid layer, which had been diluted with 150 ml. of water; the whole was then made alkaline and extracted as described above. The base so obtained [(i) 1·58, (ii) 1·45 g.] was an oil which on distillation (b. p. > 250°/5 mm.) yielded 9-tert.-*butylphenanthridine* (Found: C, 86·9; H, 6·85; N, 5·7. $C_{17}H_{17}N$ requires C, 86·8; H, 7·3; N, 5·95%); it separated from ethanol as buff prisms, m. p. 74° [*picrate*, yellow prisms (from dioxan), m. p. 212° (decomp.) (Found: N, 12·0. $C_{23}H_{20}O_7N_4$ requires N, 12·1%)]. Evaporation of the chloroform solution gave 9-*azido*-9-tert.-*butylfluorene* [(i) 0·50, (ii) 0·57 g.], m. p. 66—68°, which on recrystallisation from acetone

formed prisms, m. p. 69° (Found : C, 77·6; H, 6·5; N, 16·3. $C_{17}H_{17}N_3$ requires C, 77·6; H, 6·45; N, 16·0%).

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The Decomposition of Cystine in Acid Solution in the Presence of Indoles.

By J. T. EDWARD and E. F. MARTLEW.

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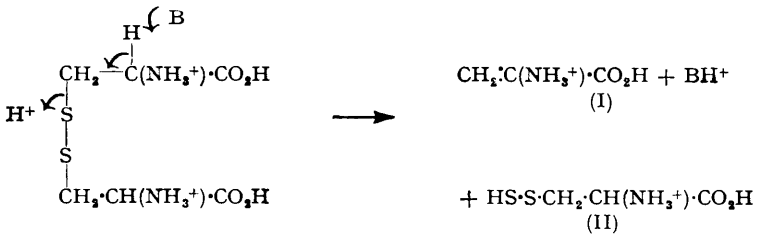
OLCOTT AND FRAENKEL-CONRAT (*J. Biol. Chem.*, 1947, **171**, 583) found that cystine in 7N-hydrochloric acid containing tryptophan at 110° afforded cysteine in about 25% yield. The other naturally occurring amino-acids were without effect. This reaction is of some importance in the hydrolysis of proteins, such as chymotrypsinogen (Brand and Kassel, *J. Gen. Physiol.*, 1941, **25**, 167) and lysozyme (Olcott and Fraenkel-Conrat, *loc. cit.*), which contain large amounts of tryptophan.

We have found that the formation of cysteine is catalysed by other indoles besides tryptophan, and by xanthhydrol, but not by diphenylamine. Examination of the reaction products by paper chromatography showed several other ninhydrin-positive compounds to be formed with cysteine; two of them appeared to be serine and alanine, from their R_F values in three different solvent systems.

Alanine and serine, along with ammonia, pyruvic acid, cysteic acid, hydrogen sulphide, and sulphur, are formed by the decomposition of cystine in phosphoric acid at 100° (Andrews and Bruce, *Arch. Biochem. Biophys.*, 1951, **33**, 427).

It is likely that these decompositions are acid–base-catalysed reactions as shown, the intermediate (I) leading to serine, alanine, or pyruvic acid and ammonia by hydration, reduction, or hydrolysis respectively, and the intermediate (II) to cysteine, sulphur,



cysteic acid, or hydrogen sulphide. The base (B) would be the indole-nitrogen or the $H_2PO_4^-$ or HPO_4^{2-} ions. This would explain why acids stronger than phosphoric are ineffective, the anions derived from them being too weak as bases; and why bases stronger than indole are ineffective in 7N-hydrochloric acid, being completely protonated in acid of this strength. Tarbell and Harnish (*Chem. Rev.*, 1951, **49**, 1) have advanced a similar mechanism for the hydrolysis of cystine to cysteine and other products by aqueous alkali.

Experimental.—Chromatographic identification of cysteine. *N*-Phenylmaleinimide, like *N*-ethylmaleinimide (Hanes, Hird, and Isherwood, *Nature*, 1950, **166**, 288), reacted within a few minutes with cysteine to give a compound (CYS–NPM) which travelled as a compact spot on paper chromatograms, the R_F values for three different solvents being shown in the Table. When phenol–water was used as the developing solvent, the compound failed to give a ninhydrin-positive spot on the chromatogram. The preparation of *N*-phenylmaleinimide (Anschutz and Wirtz. *Annalen*, 1887, **239**, 137) is considerably easier than that of the *N*-ethyl analogue.

Chromatographic analysis of products from cystine. Cystine (10 mg.) and the indole or other base (10 mg.) were heated to 100° in 7N-hydrochloric acid (1 ml.) for 18 hr. in a sealed tube. The mixture was taken to dryness and dissolved in a little water, and the process repeated twice to remove hydrochloric acid as completely as possible. The residue was dissolved in 75% aqueous ethanol (1 ml.) containing 50 micromoles of *N*-phenylmaleinimide, and portions (3 and 6 μl.) were spotted on Whatman No. 1 filter-paper chromatograms. Development was carried out by the ascending technique using as solvents: (A) butanol–acetic acid–water (4 : 1 : 5 v/v); (B) propanol–water (7 : 3 v/v); (C) butanol saturated with water. The R_F values of the ninhydrin-positive spots ("Prod.") given by the reaction of cystine in the presence of 2-methylindole are tabulated below, together with the R_F values of known amino-acids ("Std.") run as standards on the same chromatogram.

	Solvent A		Solvent B		Solvent C	
	Std.	Prod.	Std.	Prod.	Std.	Prod.
Cystine	0·04	0·03	0·08	0·11	0·00	0·00
Serine	0·09	0·10	0·26	0·29	0·02	0·03
Alanine	0·18	0·20	0·32	0·33	0·04	
CYS·NPM	0·41	0·39	0·51	0·52	0·17	0·15
Unidentified	—	0·25, 0·47	—	0·41	—	0·23
	—	0·52, 0·58	—	0·63	—	0·34

Cystine was decomposed to the same products when heated in the presence of tryptophan or xanthhydrol. However, indole and 1 : 2 : 3 : 4-tetrahydrocarbazole did not catalyse the decomposition in 7N-hydrochloric acid, although they did in a mixture of 11N-hydrochloric acid (0·7 ml.) and acetic acid (0·4 ml.); this may be due to their negligible solubility in the first medium or to the greater acidity of the second. The catalytic activity of skatole, 2-methylindole, and tryptophan, but not of diphenylamine, was demonstrated in the second medium.

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CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EGDBASTON, BIRMINGHAM, 15.

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