169. *Acetyl Chloride as a Polar Solvent. Part V.*[1] *Titrations in Acetyl Chloride.*

By JASWANT SINGH, RAM CHAND PAUL, and SARJIT SINGH SANDHU.

FOLLOWING studies of the polar behaviour of acetyl chloride[1] we have attempted acid–base titrations in that solvent in the presence of indicators. Crystal Violet and benzanthrone were used as indicators which are not reacted upon irreversibly by acetyl chloride.

Crystal Violet has been used in the study of acid–base neutralizations in thionyl chloride,[2] but results were unsatisfactory as the indicator is unstable therein. In acetyl chloride, however, its colour changes are reversible and the dye is sufficiently stable. The colours of Crystal Violet and benzanthrone in acetyl chloride and in the solutions of solvoacids and solvobases in acetyl chloride are recorded in Table 1.

TABLE 1. *Colours in acetyl chloride and in acetyl chloride solutions of various solutes.*

Indicator	Concn.	None	$TiCl_4$	$SnCl_4$	quinoline	α-picoline	$Ph{\cdot}NMe_2$
Crystal Violet	moderate	blue	deep yellow	yellow	violet	violet	pink
	high	—	orange yellow	orange yellow	purple	purple	blue
Benzanthrone	moderate	yellow	deep red	red	yellow	yellow	light yellow
	high	—	blood red	deep red	deep yellow	deep yellow	light yellow

The colour changes of Crystal Violet are therefore in the same order in the presence of acids and bases in acetyl chloride as in water, for in aqueous solutions Crystal Violet is yellow, green, and violet at pH 0·1, 1·5, and 3·2, respectively.[3] Similar colour changes in acetic acid have also been reported.[4] The blue colour of Crystal Violet in acetyl chloride serves as a test for the latter's purity for if traces of hydrochloric acid and acetic acid are present the solutions become green and finally yellow. In concentrated sulphuric acid benzanthrone yields a red colour which changes to yellow on large dilution or in the presence of alkalis.

In these acid–base neutralizations in acetyl chloride, precipitation makes detection of colour change near the end point difficult. This has been surmounted by adding the solution dropwise and, on appearance of any colour change, allowing the precipitate to settle before the colour of the supernatant liquid is noted. To examine the reversibility of the indicator, in one set of experiments acid solutions were titrated and in the other the base. Each titration was in duplicate. Results are presented in Table 2.

The colour of Crystal Violet at the neutralization point depends on the individual acid–base pair and the difference is presumably related to the relative strength of the acids and bases in acetyl chloride.[5] For instance, the yellow colour at the neutralization point of dimethylaniline with both acids indicates that dimethylaniline is a weaker base than quinoline and this observation is supported by the colour of Crystal Violet in solutions of quinoline and dimethylaniline in acetyl chloride (Table 1). The values of specific conductivity[3] of these solvobases in acetyl chloride support this observation. The absence of green colour at the neutralization point of dimethylaniline recalls the neutralization of a weak base such as ammonia with hydrochloric acid or sulphuric acid in aqueous solution. The acid colour of the indicator at the neutralization point is explained by hydrolysis of the salts of weak bases and strong acids in aqueous solutions; presumably the yellow colour at the neutralization point of dimethylaniline with stannic chloride is related to the former's weakly basic character.

[1] Part IV, *J.*, 1959, 325.
[2] Garber, Pease, and Luder, *Analyt. Chem.*, 1953, **25**, 581.
[3] Rice, Zuffanti, and Luder, *ibid.*, 1952, **24**, 1022.
[4] Seaman and Allen, *ibid.*, 1951, **23**, 592.
[5] Hawke and Steigman, *ibid.*, 1954, **26**, 1989.

TABLE 2.

Titrant	Reagent	[Titrant]	Vol. of titrant (ml.) (Used)	Vol. of titrant (ml.) (Calc.)	Colour at end point
		Crystal Violet			
Quinoline	Stannic chloride	0·1345	2·30	2·41	Green
	Titanium tetrachloride	0·1298	1·21	1·37	Green
α-Picoline	Stannic chloride	0·1142	18·40	18·24	Greenish yellow
	Titanium tetrachloride	0·2094	5·70	5·70	Greenish yellow
Dimethylaniline	Stannic chloride	0·1352	1·40	1·37	Pale yellow
	Titanium tetrachloride	1·3352	5·20	4·59	Pale yellow
Stannic chloride	Quinoline	0·0788	16·10	16·07	Greenish yellow
	α-Picoline	0·0883	7·85	7·73	Yellow
	Dimethylaniline	0·6277	8·40	8·61	Yellow
Titanium tetrachloride	Quinoline	0·0597	5·00	4·55	Greenish yellow
	α-Picoline	0·0342	8·50	8·49	Yellow
	Dimethylaniline	0·0442	4·80	4·91	Yellow
		Benzanthrone			
Quinoline	Stannic chloride	0·0885	2·90	2·59	Yellow
	Titanium tetrachloride	0·0885	6·00	6·10	Yellow
α-Picoline	Stannic chloride	0·1478	6·10	6·09	Yellow
	Titanium tetrachloride	0·1478	16·40	16·31	Yellow
Dimethylaniline	Stannic chloride	0·0836	3·60	3·72	Pale yellow
	Titanium tetrachloride	1·2180	4·20	4·32	Yellow
Stannic chloride	Quinoline	0·0806	5·05	5·10	Orange red
	α-Picoline	0·1086	2·90	2·77	Orange yellow
	Dimethylaniline	0·0806	2·20	2·04	Orange
Titanium tetrachloride	Quinoline	0·0875	3·05	3·15	Orange red
	α-Picoline	0·0875	5·50	5·41	Orange yellow
	Dimethylaniline	0·0875	3·50	3·55	Orange yellow

The appearance of different colours at the theoretical neutralization point of different pairs of acids and bases suggests that the orders of relative strength in acetyl chloride are: stannic chloride > titanium tetrachloride; quinoline > α-picoline > dimethylaniline. Surprisingly, the order of strength of the bases is different in aqueous solutions as the following pK_a values [6] show: dimethylaniline 5·06, α-picoline 5·05, quinoline 4·85. This anomaly can, however, be explained by comparison of the steric requirements of the acetylium ion and the proton.

Benzanthrone differs from Crystal Violet in that it does not show a gradation of colour. It cannot therefore be used to arrange acids and bases according to their strengths. This may be due to a large value of the transition interval of benzanthrone or to benzanthrone's showing only two colours, one in acidic and one in basic solutions in acetyl chloride.

Attempts to use carbon tetrachloride in these titrations were unsuccessful.

The colour changes of these indicators can be explained on the basis of the existence (already postulated [1]) of ionic species in acetyl chloride solutions. The solvoacids stannic chloride and titanium tetrachloride dissolve in acetyl chloride and increase the concentration of acetylium ions (which correspond to the hydrogen ions of aqueous solutions), *e.g.*,

$$SnCl_4 + 2AcCl \rightleftharpoons 2Ac^+ + SnCl_6^{2-}$$

Solvobases ionize in acetyl chloride and similarly bring about an increase in the concentration of chloride ions.

Experimental.—A burette equipped with reservoir for stock solution of the titrant connected to a titration bottle and an arrangement for magnetic stirring was employed. The apparatus was guarded from moisture by freshly prepared calcium chloride.

The acids and bases were weighed by difference and care was taken to avoid the contact of moisture. 20 ml. of the solvent were taken in the titration bottle and a weighed amount of the substance to be titrated was added. The indicator (3—5 mg.) was added, and the

[6] Braude and Nachod, "Determination of organic structures by physical methods," Academic Press Inc., New York, N.Y., 1955, pp. 600, 613.

mixture was stirred magnetically. The titrant solutions were prepared in a 100-ml. measuring flask in a dry box. Burette readings were noted corresponding to changes in colour of the indicator; the results are given in Table 2. The volume of titrant recorded is that of the colour change nearest the expected end-point.

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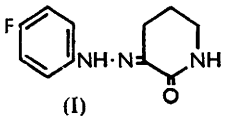
170. 5-*Fluorotryptamine.*

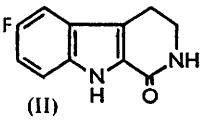
By Z. PELCHOWICZ and ERNST D. BERGMANN.

THE interesting biological properties of 5-fluorotryptophan made it desirable to prepare 5-fluorotryptamine (IV) both as analogue of tryptamine and serotonine and as starting material for further syntheses. The synthesis was based on previous observations.[1]

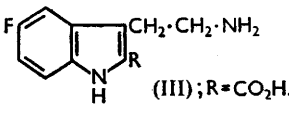
Ethyl 2-oxopiperidine-3-carboxylate and *p*-fluorobenzenediazonium chloride gave in 56% yield 2 : 3-dioxopiperidine *p*-fluorophenylhydrazone (I), which was cyclized by acid to the carboline II (yield, 71%). This was hydrolyzed to 5-fluorotryptamine-2-carboxylic acid (III) in 85% yield and the latter decarboxylated to the tryptamine (IV) (best isolated in form of its stable hydrochloride). The overall yield was 29%.



(I)



(II)



(III); R = CO_2H. (IV); R = H

Given subcutaneously to mice, 5-fluorotryptamine (LD_{50} 439 mg./kg.) is more toxic than serotonine (>868 mg./kg.),[2] whilst intracerebrally the tryptamine induced central effects similar to 10—30 μg. of serotonin [3] only in doses above 250 μg. per mouse. A full report on the toxicological properties of 5-fluorotryptamine will be published elsewhere by Dr. H. Edery.

Experimental.—2 : 3-*Dioxopiperidine* 3-*p-fluorophenylhydrazone* (I). To a well-agitated solution of ethyl 2-oxopiperidine-3-carboxylate [4] (47 g.) and potassium hydroxide (16·5 g.) in water (550 ml.), which had been kept at room temperature for 24 hr., filtered, and cooled to 0°, was added a solution of *p*-fluorobenzenediazonium chloride [from 4-fluoroaniline [5] (32·1 g.). After 5 min., the product was adjusted to pH 3—4 (acetic acid) and then stirred for 5 hr. at 5°. Filtration gave the *derivative* (I) (37 g.; 56%), which crystallized from methanol in yellow needles, m. p. 214·5—215° (Found: C, 59·9; H, 5·3; F, 8·9. $C_{11}H_{12}ON_3F$ requires C, 59·7; H, 5·5; F, 8·6%).

6-*Fluoro*-1 : 2 : 3 : 4-*tetrahydro*-1-*oxo*-β-*carboline* (II).—A mixture of (I) (26 g.), concentrated hydrochloric acid (60 ml.), and acetic acid (120 ml.) was refluxed for 3 hr. The crystals which separated upon cooling, and a second crop which was precipitated by addition of water to the filtrate, were recrystallized from aqueous alcohol; the *crystals* (17 g.; 71%) had m. p. 236—237° (Found: C, 64·8; H, 4·7; F, 9·7. $C_{11}H_9ON_2F$ requires C, 64·6; H, 4·5; F, 9·3%).

5-*Fluorotryptamine*-2-*carboxylic acid* (III). A mixture of the carboline (II) (15 g.), dissolved in alcohol (150 ml.), and potassium hydroxide (33·5 g.), dissolved in water (150 ml.), was refluxed for 1 hr. Then 150 ml. of the liquid were distilled off and replaced by the same quantity of water. The solution was cooled, decolorized with active charcoal, filtered, and acidified with acetic acid. After recrystallization from water, the crystals (14 g.; 85%) melted at 285—287° (decomp.) (Found: C, 59·3; H, 5·2; F, 8·6. $C_{11}H_{11}O_2N_2F$ requires C, 59·4; H, 5·0; F, 8·6%).

[1] Japp and Klingemann, *Ber.*, 1887, **20**, 2942, 3284, 3398; *Annalen*, 1888, **247**, 218; Shapiro and Abramovitch, *Chem. and Ind.*, 1955, 1255; *J. Amer. Chem. Soc.*, 1955, **77**, 6690; *J.*, 1956, 4589; Henecka, Timmler, Lorenz, and Geiger, *Ber.*, 1957, **90**, 1060; Quadbeck and Rohm, *Z. physiol Chem.*, 1954, **297**, 229.

[2] Freyburger, *J. Pharm. Exp. Ther.*, 1952, **105**, 80.

[3] Haley, *Acta Pharmacol. Toxicol.*, 1957, **13**, 107.

[4] Albertson and Fillman, *J. Amer. Chem. Soc.*, 1949, **71**, 2819.

[5] Bradlow and VanderWerf, *ibid.*, 1948, **70**, 654.

5-*Fluorotryptamine hydrochloride* (IV). A mixture of the carboxylic acid (6 g.) and 10% hydrochloric acid (180 ml.) was refluxed until the evolution of gas ceased and a clear solution had formed. Upon cooling, crystals (5 g.; 86%) separated, which were recrystallized by adding ether to their alcoholic solution; they melted at 282° (Found: C, 56·0; H, 5·6. $C_{10}H_{12}N_2ClF$ requires C, 56·1; H, 5·6%).

SCIENTIFIC DEPARTMENT, MINISTRY OF DEFENCE, TEL-AVIV. [*Received, July 7th,* 1958.]

171. *The Extractives of* Quintinnia serrata.

By R. C. CAMBIE.

Quintinnia serrata A. Cunn. (New Zealand "Tawheowheo") is a tree which is endemic and common in forests of the North Island of New Zealand. Extraction of the dried bark with aqueous methanol gave a crystalline phenolic glucoside (12·5% yield), circular R_F 0·17, with traces of a further phenolic non-glycosidic constituent, circular R_F 0·74. The latter was identified by paper chromatography as dihydroquercetin, after separation from the total solid by ether-extraction. The ether-insoluble glycoside was a dextrorotatory rhamnoside of (±)-dihydroquercetin, the melting point of which (179·5°) agreed with that recorded for the 3-rhamnoside, astilbin.[1,2] The position of the rhamnose moiety was confirmed by complete methylation of the phenolic hydroxyl groups and hydrolysis to dihydro-3′ : 4′ : 5 : 7-tetra-*O*-methylquercetin.

Astilbin has previously been isolated only from the rhizomes of *Astilbe odontophylla* (var. congesta),[1] *Astilbe thunbergi*,[3] and the leaves of *Litsea glauca*.[4] Neither astilbin nor dihydroquercetin was found in the leaves of *Quintinnia serrata* when a methanolic extract was examined by paper chromatography.

Experimental.—Microanalyses are by Dr. A. D. Campbell, University of Otago, N.Z. Infrared spectra were measured for KBr discs and ultraviolet spectra were measured for EtOH solutions. Circular paper chromatography was carried out on Whatman's No. 1 paper, with the following solvent systems: (A) chloroform–ethanol–water (8 : 2 : 5; lower phase); (B) 60% aqueous acetic acid; (C) phenol saturated with water at 22° (5% aqueous ferric chloride as spray reagent).

Extraction. Aerial bark (1·2 kg.) was extracted (Soxhlet) with 85% aqueous methanol for 24 hr., and the dark red extract concentrated, *in vacuo*, to 2 l. Addition of water (1 l.) and removal of further methanol, *in vacuo*, precipitated discoloured crystals (135 g.). Repetition of the process with the addition of a suitable volume of water gave further yields (15·5 g.). After removal of wax with light petroleum and repeated extraction with ether the solid consisted of a single phenolic compound, R_F 0·17 (A), 0·85 (B), 0·66 (C). Paper chromatography of the final syrupy residue from the extract and of dihydroquercetin gave identical spots, R_F 0·74 (A), 0·77 (B), 0·69 (C).

Astilbin. The solid, crystallised repeatedly from 40% ethanol, gave astilbin monohydrate, needles, m. p. 179·5° (decomp.) (lit.,[1] m. p. 179—180°) (total yield, 150 g.), $[\alpha]_D^{25}$ +4° [*c* 1·3 in Me_2CO–H_2O (1 : 1)] (Found, for sample dried at room temperature: C, 54·0; H, 5·6. Calc. for $C_{21}H_{22}O_{11}$,H_2O: C, 53·9; H, 5·2%). Found, for sample dried at 100° to constant weight: C, 56·4; H, 5·0. Calc. for $C_{21}H_{22}O_{11}$: C, 56·0; H, 4·9%), $\nu_{max.}$ 3448 (OH), 2959 (C-H), 2732 (shoulder) (C-H), 1650 (conjugated CO) cm.$^{-1}$, $\lambda_{max.}$ 292 mμ (log ε 4·21), 330 (shoulder) mμ (log ε 3·66). The hepta-acetate, prepared by the use of pyridine and acetic anhydride (1 hr.; 90°), formed needles, m. p. 107°, from 50% aqueous ethanol (Found: C, 56·2, 56·0; H, 4·3, 4·7; Ac, 38·8. $C_{35}H_{36}O_{18}$ requires C, 56·4; H, 4·9; 7Ac, 40·4%), $\nu_{max.}$ 2976 (C-H), 1776 (acetate), 1761 (acetate), 1684 (conjugated CO) cm.$^{-1}$. The ferric reaction was negative and the compound was insoluble in dilute alkali.

[1] Hayashi and Ouchi, *Misc. Reports Res. Inst. Nat. Resources, Japan*, 1950, No. 17—18, 19; *Chem. Abs.*, 1953, **47**, 705.
[2] *Idem, ibid.*, 1953, No. 32, 1; *Chem. Abs.*, 1954, **48**, 13841.
[3] Shimada, Sawada, and Fukuda, *J. Pharm. Soc. Japan*, 1952, **72**, 578; *Chem. Abs.*, 1952, **46**, 8810.
[4] Nakabayashi, *J. Agr. Chem. Soc. Japan*, 1952, **26**, 469; *Chem. Abs.*, 1954, **48**, 5942.

Methylation of astilbin in methanol–ether (1 : 1) with diazomethane at 0°, or with dimethyl sulphate and anhydrous potassium carbonate in dry acetone for 60 hr., gave the tetramethyl ether, needles (from aqueous dimethylformamide–methanol), m. p. 225—227° (lit.,[2] m. p. 226—227°) (Found: C, 57·8; H, 6·0; OMe, 23·7. Calc. for $C_{25}H_{30}O_{11},H_2O$: C, 57·2; H, 6·15; 4OMe, 23·7%), $\nu_{max.}$ 3509 (OMe), 3333 (OH), 2941 (C-H), 1672 (conjugated CO) cm.$^{-1}$. Hydrolysis with 2N-hydrochloric acid for 1 hr. and extraction with ether gave dihydro-3′ : 4′ : 5 : 7-tetra-*O*-methylquercetin (needles from 90% ethanol), m. p. and mixed m. p. 168—169°.

Hydrolysis of astilbin. Astilbin monohydrate (6·52 g.), hydrolysed with 7% sulphuric acid (150 c.c.) for 2 hr., yielded the aglycone (4·03 g.) (Found: aglycone, 64·5. $C_{21}H_{22}O_{10},H_2O$ requires aglycone, 64·9%). Repeated crystallisation from hot water (charcoal) gave optically inactive, hexagonal rods, m. p. and mixed m. p. 239—240° (decomp.) with (±)-dihydroquercetin, prepared by racemisation of authentic (+)-dihydroquercetin, $[\alpha]_D^{25}$ +48° [*c* 1·0 in Me_2CO–H_2O (1 : 1)], by Pew's method [5] (Found: C, 59·5; H, 4·0. Calc. for $C_{15}H_{12}O_7$: C, 59·2; H, 4·0%), $\nu_{max.}$ 3410 (OH), 3289 (OH), 3195 (sh) (OH), 2959 (C-H), 1640 (conjugated CO) cm.$^{-1}$, $\lambda_{max.}$ 292 mμ (log ε 4·35), 330 (sh) mμ (log ε 3·72) [penta-acetate (needles from methanol), m. p. 152—153° (lit.,[6] m. p. 150—152°) (Found: C, 58·7; H, 4·3; Ac, 41·3. Calc. for $C_{25}H_{22}O_{12}$: C, 58·4; H, 4·3; 5Ac, 41·8%), $\nu_{max.}$ 1777 (acetate), 1740 (sh) (acetate), 1705 (conjugated CO), cm.$^{-1}$, $\lambda_{max.}$ 264 mμ (log ε 4·12), 313 mμ (log ε 3·61); tetrabenzoate (needles from ethanol), m. p. 188—189° (lit.,[7] m. p. 192°) (Found: C, 71·9; H, 4·2. Calc. for $C_{43}H_{28}O_{11}$: C, 71·6; H, 3·9%)]. The tetramethyl ether, prepared by the method of Hergert *et al.*,[8] formed granular crystals m. p. 169°, from ethyl acetate–ligroin (lit.,[8] m. p. 169—170°) [monoacetate (needles from methanol), m. p. 171—172° (lit.,[8] m. p. 171—172°)].

Comparative paper chromatography of the neutralised and concentrated hydrolysate and of rhamnose gave identical spots. The rhamnose was isolated as the *p*-nitrophenylhydrazone, m. p. and mixed m. p. 187—188°.

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University of Auckland, New Zealand. [*Received, August 18th*, 1958.]

[5] Pew, *J. Amer. Chem. Soc.*, 1948, **70**, 3031.
[6] Nishida, Ito, and Kondo, *J. Japan Tech. Assoc. Pulp Paper Ind.*, 1952, **6**, 261, 332; *Chem. Abs.*, 1952, **46**, 11343.
[7] Kondo, *J. Fac. Agr. Kyushi Univ., Japan*, 1951, **10**, 79; *Chem. Abs.*, 1953, **47**, 4602.
[8] Hergert, Coad, and Logan, *J. Org. Chem.*, 1956, **21**, 304.

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172. *Molecular-orbital Treatment of Compounds containing Intramolecular Hydrogen Bonds.*

By S. Marcinkiewicz and J. Green.

Hunsberger *et al.*,[1] studying the infrared spectra of a number of aromatic compounds containing vicinal hydroxy- and carbonyl groups, found that the strength of the intramolecular hydrogen-bond varies with the amount of double-bond character exhibited by the ring bond between the carbon atoms bearing the chelated substituents. A linear relation was observed between Δν(C=O) and Pauling's percentage double-bond character for the ring bonds in benzene, naphthalene, and phenanthrene. The linear relation was not perfect, since Δν(C=O) values for the isomeric 1 : 2- and 2 : 1-derivatives of naphthalene were appreciably different. Also the linearity did not extend to aliphatic compounds, since the double bond in propene was found to correspond to approximately the same Δν(C=O) value as the 9 : 10-bond in phenanthrene. To account for these phenomena, Hunsberger *et al.*[1d] postulated a novel concept of steric facilitation of chelation.

The study of the chelated hydrogen bond may become a valuable method in the study

[1] (*a*) Hunsberger, *J. Amer. Chem. Soc.*, 1950, **72**, 5626; (*b*) Hunsberger, Ketcham, and Gutowsky, *ibid.*, 1952, **74**, 4839; (*c*) Hunsberger, Lednicer, Gutowsky, Bunker, and Taussig, *ibid.*, 1955, **77**, 2466; (*d*) Hunsberger, Gutowsky, Powell, Morin, and Bandurco, *ibid.*, 1958, **80**, 3294.

of aromatic character and related problems and, therefore, it was of interest to consider the data reported by Hunsberger *et al.* from the point of view of the molecular-orbital theory.[2]

It may be assumed that the strength of the intramolecular hydrogen bond in *o*-hydroxy-ketones, -aldehydes, and -esters depends not only on the bond order of the bonds between the carbon atoms bearing the chelated substituents, but also on the tendency of the carbonyl-oxygen atom to form a hydrogen bond, and hence on the free valence of the ring-carbon atom bearing the carbonyl group.[3] If it is further assumed that $\Delta\nu$(C=O) is a linear function of bond order and free valence in the parent hydrocarbon, the general expression correlating $\Delta\nu$(C=O) with the wave-mechanical quantities will be:

$$\Delta\nu(\text{C=O}) = K \cdot p_{rs} + L(N_{\max.} - \sum_s p_{rs}) + M \quad . \quad . \quad . \quad . \quad (1)$$

where p_{rs} stands for the mobile bond order of the bond bearing the chelated substituents and s in summation applies to all ring-carbon atoms adjacent to the carbon atom r that bears the carbonyl group. $N_{\max.}$ is the highest value the bond number may take, and is equal to $\sqrt{3}$ for tertiary, $\sqrt{2}$ for secondary, and 1 for primary carbon atoms, all in conjugated systems.[4] K, L, M are parameters characteristic for the type of the carbonyl group forming the chelated hydrogen bond with the hydroxyl group.

Substituting the values of $\Delta\nu$(C=O), representing the average values of $\Delta\nu$(C=O) of esters, ketones, and aldehydes reported by Hunsberger *et al.* for the aromatic compounds studied by them, we obtain a set of five equations:

$$43\ (\pm 1) = 0{\cdot}667K + 0{\cdot}080L + M \text{ (for 1-hydroxy-2-Y*-benzene)}$$
$$59\ (\pm 1) = 0{\cdot}725K + 0{\cdot}134L + M \text{ (for 2-hydroxy-1-Y*-naphthalene)}$$
$$54\ (\pm 1) = 0{\cdot}725K + 0{\cdot}086L + M \text{ (for 1-hydroxy-2-Y*-naphthalene)}$$
$$29\ (\pm 1) = 0{\cdot}603K + 0{\cdot}086L + M \text{ (for 2-hydroxy-3-Y*-naphthalene)}$$
$$70\ (\pm 1) = 0{\cdot}775K + 0{\cdot}133L + M \text{ (for 9-hydroxy-10-Y*-phenanthrene)}$$

Y* = Carbonyl substituent.

The equations are consistent for values of K, L, and M of 205, 104, and −103, respectively. While the data from the experiments of Hunsberger *et al.* are scanty, it is unlikely that the agreement is fortuitous, and it appears that the infrared spectra of the chelated compounds can be interpreted without postulating other than electronic effects. Equation (1) explains also the apparently anomalous value of $\Delta\nu$(C=O) for methyl acetoacetate (Hunsberger *et al.*). The free valence at the end of the double bond in propene distant from the methyl group is $1 - p_{rs}$. Substituting this in equation (1) and solving it leads to the values for the bond order and free valence at the end of the double bond in propene as 0·85 and 0·15, respectively. These figures, which are of the right order, reflect delocalisation of π-electrons in propene owing to hyperconjugation.

In two recent papers, Hunsberger *et al.*[1c,d] have applied the concept of steric facilitation of chelation to the study of the Mills–Nixon effect in tetrahydronaphthalene and indane derivatives. The available results are insufficient for the application of equation (1) to this problem, since results for at least 3 isomers in each case are required, but the results of Hunsberger *et al.* suggest greater effects of saturated rings or vicinal methyl groups on the bond orders than was calculated by Berthier and Pullman.[5]

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[2] Coulson, " Valence," Oxford, 1954.
[3] Pullman and Pullman, " Progress in Organic Chemistry," Butterworths, London, 1958, Vol. IV, p. 31.
[4] Moffit, footnote to Coulson, *J. Chim. phys.*, 1948, **45**, 243.
[5] Berthier and Pullman, *Bull. Soc. chim. France*, 1950, **17**, 88.

173. *Pyrrolidine- and 1-Methylpyrrolidine-3-carboxylic Acid.*

By J. F. Cavalla.

In other work it was necessary to prepare esters of the hitherto unknown pyrrolidine- and 1-methylpyrrolidine-3-carboxylic acid. Miyamoto's recent work [1] on the synthesis of pyrrolidine-3-carboxylic acid prompts us to publish our results before the completion of the main work.

For the synthesis of ethyl 1-methylpyrrolidine-3-carboxylate the method described by Bergel and his co-workers [2] for the preparation of the analogous ethyl 1-methyl-3-phenylpyrrolidine-3-carboxylate proved satisfactory. This involved catalytic reduction of ethyl γ-benzylmethylamino-α-cyanobutyrate with palladised charcoal, both the cyano- and the benzylmethylamino-group being reduced and the molecule cyclised with elimination of toluene and ammonia.

Many methods were tried before a satisfactory synthesis was evolved for the unsubstituted pyrrolidine-3-carboxylic acid. Bergel *et al.*[2] prepared 3-phenylpyrrolidine-3-carboxylic acid in small yield by catalytic reduction of ethyl αβ-dicyano-α-phenylpropionate; reduction of the simpler ethyl αβ-dicyanopropionate in our hands, however, did not give the required product. Bergel, Morrison, and Rinderknecht later reported [3] the preparation of ethyl 3-phenylpiperidine-3-carboxylate by catalytic reduction of ethyl 5-dibenzylamino-2-cyano-3-phenylpentanoate. Reduction of ethyl γ-dibenzylamino-α-cyanobutyrate gave the required compound on one occasion in low yield, but the experiment could not be repeated. Other methods were tried, depending on the reduction of γ-substituted α-cyanobutyric esters, amongst them the γγ-diethoxy-, the γ-hydroxy- (as the γ-lactone), the γ-benzyloxy-, the γ-ethoxy- and the γ-diethylamino-ester, but in each case reduction of the cyano-group proved unsatisfactory, ammonia being formed. The final satisfactory method started from ethane-1 : 1 : 2-tricarboxylic acid. A Mannich-type reaction with this acid, benzylamine, and formaldehyde gave α-benzylaminomethylsuccinic acid which, on esterification and distillation, gave its lactam, ethyl 1-benzylpyrrolid-5-one-3-carboxylate. Reduction by lithium aluminium hydride gave 1-benzyl-3-hydroxymethylpyrrolidine which was oxidised to the corresponding acid and debenzylated to the required pyrrolidine-3-carboxylic acid.

Experimental.—Ethyl γ-benzylmethylamino-α-cyanobutyrate. The sodio-derivative of ethyl cyanoacetate (prepared from 26·6 g. of the ester) in absolute ethanol (50 ml.) was treated slowly at room temperature with a solution of *N*-benzyl-2-chloro-*N*-methylethylamine [4] (48·8 g.) in toluene (100 ml.). The mixture was stirred for 30 min., then refluxed with stirring for 1½ hr., cooled, filtered, and concentrated. Isolation with ether and distillation *in vacuo* gave the *product* (20·7 g.), b. p. 154°/0·6 mm., n_D^{20} 1·5026 (Found: C, 69·4; H, 7·7; N, 10·6. $C_{15}H_{20}O_2N_2$ requires C, 69·2; H, 7·7; N, 10·8%). This compound was prepared in the crude state by Schmutz and Kunzle [5] who reported that it decomposed on distillation.

Ethyl 1-methylpyrrolidine-3-carboxylate. The preceding ester (19·5 g.) in ethanol (150 ml.) was treated with 6·7N-hydrochloric acid (22·4 ml., 2 equiv.) and hydrogenated with 10% palladised charcoal (3·5 g.), the theoretical volume of hydrogen being absorbed in 4 hr. After removal of the solvent and treatment with 2N-sodium carbonate the base was isolated with ether and distilled *in vacuo*, to give the *pyrrolidine* (2·84 g.), b. p. 99°/25 mm., n_D^{20} 1·4454 (Found: C, 61·4; H, 9·4; N, 9·0. $C_8H_{15}O_2N$ requires C, 61·1; H, 9·6; N, 8·9%).

Ethyl γ-dibenzylamino-α-cyanobutyrate. Ethyl sodiocyanoacetate (34 g., 1·5 mol.) in ethyl cyanoacetate (100 ml.) was stirred at 100° with 2-dibenzylaminoethyl chloride [6] (43·5 g.) in toluene (40 ml.) for 1½ hr., then left overnight at room temperature. Water (300 ml.) was added

[1] Miyamoto, *Yakugaku Zasshi*, 1957, **77**, 568; *Chem. Abs.*, 1957, **51**, 16,422.
[2] Bergel, Hindley, Morrison, and Rinderknecht, *J.*, 1944, 269.
[3] Bergel, Morrison, and Rinderknecht, U.S.P. 2,446,804; *Chem. Abs.*, 1949, **43**, 695.
[4] Wilson, *J.*, 1952, 3524.
[5] Schmutz and Kunzle, *Helv. Chim. Acta*, 1955, **38**, 925.
[6] U.S.P., 1,949,247; *Chem. Abs.*, 1934, **28**, 2850.

and the mixture extracted with benzene (3 × 75 ml.), and the bulked organic layers were dried (Na_2SO_4) and concentrated to a red oil. (An aliquot part of this decomposed on distillation in a high vacuum.) The oil was suspended in 6N-hydrochloric acid (250 ml.), and the insoluble portion extracted with ether and benzene; basification and isolation with benzene then gave the crude product as a cherry-red oil (17·5 g.).

Ethyl pyrrolidine-3-carboxylate. The preceding oil (13·1 g.) in ethanol (120 ml.) containing 6N-hydrobromic acid (13·1 ml., 2 equiv.) was hydrogenated with 10% palladised charcoal (2 g.) at atmospheric pressure. Absorption of hydrogen was rapid at first but became slow. Isolation as for the methyl analogue gave ethyl pyrrolidine-3-carboxylate (1·05 g.), b. p. 99—100°/14 mm., n_D^{20} 1·4568 (Found: C, 59·1; H, 8·8; N, 9·5. $C_7H_{13}O_2N$ requires C, 58·7; H, 9·2; N, 9·8%). Repetition of this reduction failed.

α-Benzylaminomethylsuccinic acid. Ethane-1 : 1 : 2-tricarboxylic acid (95 g.) in water (180 ml.) was treated with benzylamine (62 g.), then, at −2°, with aqueous 40% formaldehyde (49 ml.) and left at 0° for 3 days. The solution, containing a slimy solid, was treated with acetone and scratched, to give a white powder (120 g.), m. p. 76—115° (decomp.). This was heated in water (125 ml.) at 95° for 20 min., then cooled, and acetone was added to give the *product* (65 g.) as needles, m. p. 141—142° (Found: C, 60·7; H, 6·4; N, 5·7. $C_{12}H_{15}O_4N$ requires C, 60·8; H, 6·4; N, 5·9%).

Ethyl 1-benzyl-5-pyrrolidone-3-carboxylate. The foregoing acid (65 g.) in absolute ethanol (500 ml.) was treated with dry hydrogen chloride (40 g.) and the mixture refluxed for 8 hr. Isolation with ether and dilute potassium carbonate gave the amino-ester which lactamised on distillation *in vacuo* to give the *pyrrolidone* (56·9 g.), b. p. 175°/1·0 mm., n_D^{20} 1·5278 (Found: C, 68·6; H, 6·9; N, 5·5. $C_{14}H_{17}O_3N$ requires C, 68·0; H, 6·9; N, 5·7%).

1-Benzyl-3-hydroxymethylpyrrolidine. The pyrrolidone (56·8 g.) in dry ether (300 ml.) was added dropwise with stirring to a cooled suspension of lithium aluminium hydride (30 g.) in dry ether (500 ml.), and the mixture refluxed with stirring for 16 hr. The solution was cooled strongly, treated cautiously with water (50 ml.), and filtered, and the solid was washed with ether. The ethereal solution was concentrated to an oil and distilled *in vacuo*, to give the *alcohol* (40·6 g.), b. p. 129°/0·9 mm., n_D^{20} 1·5414 (Found: C, 75·2; H, 8·8; N, 7·3. $C_{12}H_{17}ON$ requires C, 75·4; H, 9·0; N, 7·3%). Its *oxalate* formed needles, m. p. 99—100°, from methanol–ether (Found: C, 60·2; H, 7·3; N, 5·0. $C_{12}H_{17}ON,C_2H_2O_4$ requires C, 59·8; H, 6·8; N, 5·0%).

1-Benzylpyrrolidine-3-carboxylic acid. 1-Benzyl-3-hydroxymethylpyrrolidine (25·85 g.) in 2N-sulphuric acid (150 ml.) was added dropwise with stirring to a solution of chromium trioxide (30 g.) in 2N-sulphuric acid (200 ml.) and left at room temperature overnight. The resulting dark brown solution was treated with a solution of barium hydroxide octahydrate (205 g.) in warm water (500 ml.) and filtered, and the solid washed with water. The combined filtrate and washings were extracted with ether (200 ml.), then treated with a stream of carbon dioxide, filtered, and concentrated *in vacuo*. Addition of acetone then gave the *acid* (13·9 g.), m. p. 105—107°, which crystallised from methanol–acetone as hygroscopic rods, m. p. 106—108° (Found: C, 70·0; H, 7·6; N, 6·4. $C_{12}H_{15}O_2N$ requires C, 70·2; H, 7·4; N, 6·8%).

Pyrrolidine-3-carboxylic acid. The preceding acid (1·05 g.) in ethanol (100 ml.) was hydrogenated with 10% palladised charcoal (0·25 g.) at atmospheric pressure and the solution was filtered and concentrated to a mixture of crystals and oil. Crystallisation from methanol–acetone gave the *amino-acid* (0·45 g.) as hygroscopic needles, m. p. 183—185°, pK 3·38 and 10·72 (Found: C, 51·8; H, 8·0; N, 11·7. $C_5H_9O_2N$ requires C, 52·2; H, 7·9; N, 12·2%), ν (in Nujol) 722, 725, 790, 839, 864, 895, 912, 940, 967, 1015, 1048, 1060, 1110, 1171, 1195, 1295, 1307, 1352, 1565, 1656, 2366, 2764, and 3444 cm.$^{-1}$.

Methyl 1-benzylpyrrolidine-3-carboxylate. The acid (13·3 g.) in methanol (200 ml.) containing dry hydrogen chloride (15 g.) was refluxed for 5 hr. Removal of the solvent, basification, and isolation with ether gave the *ester* (8·7 g.), b. p. 122°/0·8 mm., n_D^{20} 1·5207 (Found: C, 71·5; H, 8·0; N, 6·3. $C_{13}H_{17}O_2N$ requires C, 71·2; H, 7·8; N, 6·4%).

Methyl pyrrolidine-3-carboxylate. The preceding ester (8·5 g.) was hydrogenated as for the corresponding acid, to give the *amino-ester* (3·8 g.), b. p. 92°/17 mm., n_D^{20} 1·4590 (Found: C, 56·4; H, 8·6; N, 10·7. $C_6H_{11}O_2N$ requires C, 55·8; H, 8·6; N, 10·9%).

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174. *Di*-O-cyclo*hexylidene*-D-*mannose*.

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Di-*O-cyclo*hexylidene-D-mannose has been prepared by condensation of D-mannose with *cyclo*hexanone in the presence of sulphuric acid. The *cyclo*hexylidene groups have been shown to occupy the 2 : 3-5 : 6-positions, as do the *iso*propylidene groups in the corresponding derivative from acetone. This is in agreement with work on D-glucose,[1,2] L-sorbose,[3,4] dulcitol,[3,5] and D-mannitol,[6] where *cyclo*hexanone has been found to react with the same positions as acetone. The compound was similar to the corresponding acetone derivative in not reducing Fehling's solution in spite of having a free 1-position.

Di-*O-cyclo*hexylidene-D-mannose was characterised by oxidation with alkaline potassium permanganate to potassium di-*O-cyclo*hexylidene-D-mannonate, whose lactone absorbed strongly at 1779 cm.$^{-1}$ in the infrared region (saturated γ-lactones[7,8] absorb at 1780—1760 cm.$^{-1}$). The lactone yielded the known 2-(D-*manno*pentahydroxypentyl)benzimidazole on reaction with *o*-phenylenediamine in the presence of hydrochloric acid to remove the ketal groups. This proved that the above oxidation occurred at the reducing centre of the mannose derivative.

Reaction with benzoyl chloride gave a monobenzoate, and reduction with sodium borohydride gave a new di-*O-cyclo*hexylidene-D-mannitol, further characterised as its dibenzoate.

Experimental.—The infrared spectra were determined for Nujol mulls. Light petroleum was the fraction of b. p. 60—80°. Alumina was type H, mesh 100/200, supplied by Peter Spence Ltd.

Di-O-cyclo*hexylidene*-D-*mannose*. D-Mannose (9 g.) was shaken for 16 hr. at room temperature with *cyclo*hexanone (20 ml.) containing sulphuric acid (1 ml.). The solid reaction mixture was warmed with *n*-heptane until two liquid layers were formed. The *n*-heptane phase was decanted and kept overnight at −40°. The resulting colourless needles (12·2 g.), m. p. 120—121°, after two recrystallisations from *n*-heptane, gave 2 : 3-5 : 6-*di*-O-cyclo*hexylidene*-D-*mannose* (11·2 g., 66%), m. p. 122°, $[\alpha]_D^{21}$ +13·4° (*c* 0·92 in chloroform), $[\alpha]_D^{20}$ +7·8° (*c* 1·29 in ethanol) (Found: C, 63·4; H, 8·0. $C_{18}H_{28}O_6$ requires C, 63·5; H, 8·3%). The product did not reduce Fehling's solution and absorbed at 3559 cm.$^{-1}$ in the OH stretching region of the infrared spectrum.

Benzoyl chloride (0·14 ml.) in pyridine (1 ml.) was added to a solution of this derivative (0·34 g.) in pyridine (1 ml.) at 0°. After 15 hr. at room temperature, the excess of benzoyl chloride was decomposed and the mixture poured into ice-water, to give yellow oil. Chloroform-extraction, concentration, chromatography of the extract on alumina, and elution with benzene gave white needles (0·15 g., 34%). Two recrystallisations from light petroleum yielded 2 : 3-5 : 6-*di*-O-cyclo*hexylidene*-D-*mannose* 1-*benzoate*, m. p. 138—139°, $[\alpha]_D^{20}$ +36·6° (*c* 1·12 in chloroform) (Found: C, 67·1; H, 7·6. $C_{25}H_{32}O_7$ requires C, 67·6; H, 7·2%).

Oxidation. Di-*O-cyclo*hexylidene-D-mannose was oxidised by alkaline potassium permanganate by Ohle and Behrend's method[9] to yield *potassium* 2 : 3-5 : 6-*di*-O-cyclo*hexylidene*-D-*mannonate* (60%), $[\alpha]_D^{15}$ −30·1° (*c* 1·08 in water). The product absorbed strongly at 1605 cm.$^{-1}$ (characteristic of the CO_2^- group) and gave a yellow precipitate with sodium cobaltinitrite. (The corresponding *iso*propylidene compound,[9] prepared similarly, absorbed strongly at 1613 cm.$^{-1}$.)

Ether was added to a solution of the potassium salt (0·95 g.) in water (40 ml.). The

[1] Hockett, Miller, and Scattergood, *J. Amer. Chem. Soc.*, 1949, **71**, 3072.
[2] Gluzman and Klyushink, *Zhur. obshchei Khim.*, 1955, **25**, 2118.
[3] Kazimirova, *ibid.*, 1954, **24**, 626.
[4] *Idem, ibid.*, 1955, **25**, 1601.
[5] *Idem, ibid.*, 1957, **27**, 981.
[6] Bourne, Corbett, and Erilinne, *J.*, 1950, 786.
[7] Bellamy, " The Infra-Red Spectra of Complex Molecules," Methuen & Co., London, 1954.
[8] Barker, Bourne, Prinkard, and Whiffen, *Chem. and Ind.*, 1958, 658.
[9] Ohle and Behrend, *Ber.*, 1925, **58**, 2590.

theoretical quantity of N-sulphuric acid was added, and the mixture was shaken to dissolve the solid precipitate in the aqueous layer. The ether layer was separated, dried, and evaporated to a white solid, which, after two recrystallisations from light petroleum containing a little benzene, gave 2 : 3-5 : 6-*di*-O-cyclo*hexylidene*-D-*mannono*-γ-*lactone*, m. p. 108—110°, $[\alpha]_D^{23}$ +43·9° (*c* 1·51 in chloroform) (Found: C, 63·7; H, 7·8. $C_{18}H_{26}O_6$ requires C, 63·9; H, 7·7%).

The γ-lactone (0·27 g.) and *o*-phenylenediamine (0·1 g.) were heated in water (1 ml.) and hydrochloric acid (0·2 ml.) for 7 hr. in a steam-bath. After water (4 ml.) had been added, the dark solution was filtered through charcoal and neutralised with aqueous ammonia. Recrystallisation of the precipitated white solid from 30% aqueous ethanol gave 2-(D-*manno*pentahydroxypentyl)benzimidazole, m. p. 219—221° (decomp.), identified by comparison with an authentic sample, m. p. 220—221° (decomp.), $[\alpha]_D^{16}$ −23·2° (*c* 0·88 in N-hydrochloric acid), prepared by the same method from potassium 2 : 3-5 : 6-di-*O*-*iso*propylidene-D-mannonate. Haskins and Hudson [10] record m. p. 224° (decomp.), $[\alpha]_D^{20}$ −23·7° (*c* 5 in N-hydrochloric acid).

Reduction. Sodium borohydride (0·6 g.) was added to a stirred suspension of di-*O*-*cyclo*hexylidene-D-mannose (3·4 g.) in water (200 ml.) and methanol (100 ml.). After 3 hours' stirring, sodium borohydride (0·2 g.) was added. Stirring was continued for 16 hr. more, a trace of solid then remaining. After the filtered solution had been adjusted to pH 4 with dilute hydrochloric acid, the resulting white solid (3 g.), m. p. 115—120°, was collected, washed with water, and recrystallised three times from light petroleum–ethanol to give colourless needles of 1 : 2-4 : 5(or 2 : 3-5 : 6)-*di*-O-cyclo*hexylidene*-D-*mannitol*, m. p. 133—134°, $[\alpha]_D^{19}$ −11·7° (*c* 0·96 in chloroform) (Found: C, 63·6; H, 8·9. $C_{18}H_{30}O_6$ requires C, 63·1; H, 8·8%).

Complete hydrolysis was achieved by leaving a solution of the product (0·81 g.) in ethanol (60 ml.) and hydrochloric acid (20 ml.) for 14 hr. at room temperature. The solution was neutralised with lead carbonate, filtered, and concentrated to give D-mannitol (0·35 g., 78%), m. p. 160—167°, characterised as its hexa-acetate, m. p. 122—123°.

Benzoylation of the D-*mannitol derivative.* The reduced compound (0·5 g.) was benzoylated by the procedure outlined above to yield a white solid (0·47 g., 60%), m. p. 139—141°. One recrystallisation from light petroleum, followed by two from aqueous ethanol, gave 2 : 3-5 : 6-*di*-O-cyclo*hexylidene*-D-*mannitol* 1 : 4-*dibenzoate*, m. p. 141—142°, $[\alpha]_D^{19}$ −9·2° (*c* 1·63 in chloroform) (Found: C, 69·9; H, 6·9. $C_{32}H_{38}O_8$ requires C, 69·8; H, 6·9%).

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[10] Haskins and Hudson, *J. Amer. Chem. Soc.*, 1939, **61**, 1266.